The National Academy of Clinical Biochemistry

Presents

LABORATORY MEDICINE PRACTICE GUIDELINES

EVIDENCE-BASED PRACTICE FOR POINT-OF-CARE TESTING

AACCPress

Evidence-Based Practice for Point-of-Care Testing

Editor

James H. Nichols, Ph.D., FACB
Baystate Health
Springfield, Massachusetts
USA

The preparation of this revised monograph was achieved with the expert input of the editors, members of the guidelines committee, experts who submitted manuscripts for each section, and many expert reviewers, who are listed at the end of the document. The material in this monograph represents the opinions of the editors and does not represent the official position of the National Academy of Clinical Biochemistry or any of the cosponsoring organizations. The National Academy of Clinical Biochemistry is the official Academy of the American Association for Clinical Chemistry.

Contents

Preface

This is the 11th in the series of Laboratory Medicine Practice Guidelines (LMPG) sponsored by the National Academy of Clinical Biochemistry (NACB). The field of point-of-care testing (POCT), diagnostic testing conducted close to the site of patient care, was divided into disease- and test-specific focus areas. Groups of expert physicians, laboratorians, and diagnostic manufacturers in each focus area were assembled to conduct systematic reviews of the scientific literature and prepare guidelines based on the strength of scientific evidence linking the use of POCT to patient outcome. To our knowledge, this is the most comprehensive review of the point-of-care literature to date.

It is hoped that these guidelines will be useful for those implementing new testing, as well as those reviewing the basis of current practice. These guidelines should help sort fact from conjecture when testing is applied to different patient populations and establish proven applications from off-label and alternative uses of POCT. These guidelines will also be useful in defining mechanisms for optimizing patient outcome and identify areas lacking in the current literature that are needed for future research.

The guidelines were presented in open forum at the AACC Annual Meeting (Los Angeles, CA, USA) in July 2004. Portions of these guidelines were also presented at several meetings between 2003 and 2005: CLMA Breakout Session (Salt Lake City, UT, USA) in June 2003, 37th Brazilian Congress of Pathology and Clinical Laboratory Medicine (Rio de Janiero, Brazil) in September 2003, Maine Society for Clinical Laboratory Science Northeast Regional Joint Fall Conference (Portland, ME, USA) in October 2003, Association of Clinical Biochemists (Dublin Ireland) in November 2003, LabMed2003 Alliance of Northeast AACC Local Sections (Providence, RI, USA) in November 2003, CLMA Breakout Session and ASCP simulcast audioconference (Atlanta, GA, USA) in March 2004, the Northern California American Association for Clinical Chemistry (AACC) local section (San Jose, CA, USA) in April 2004, Teleconference Network of Texas (San Antonio, TX, USA) in May 2004, the Beckman Conference (Boston, MA, USA) in May 2004, the AACC Critical and Point of Care Testing Division/IFCC meeting (Wurzburg, Germany) in June 2004, AACC Workshop (Los Angeles CA, USA) in July 2004, 23rd Annual Southwest Association of Clinical Microbiologists (San Antonio, TX) in September 2004, Mid-Atlantic Point of Care Coordinators Fall Symposium (Baltimore, MD, USA) in October 2004, East Coast Central Florida POCT Conference (Cocoa Beach, FL, USA) in October 2004, Northwest Medical Laboratory Symposium (Portland, OR, USA) in October 2004, Quality 2005 (Antwerp, Belgium) in March 2005, EuroMedLab (Glasgow, Scotland) in May 2005, AACC Upstate New York Local Section Spring Meeting (Rochester, NY, USA) in May 2005, American Society for Microbiology symposium (Atlanta, GA, USA) in June 2005, AACC workshop (Orlando, FL, USA) in July 2005, College of American Pathologists workshop (Chicago, IL, USA), Dade Microbiology Symposia (Harrisburg, PA, USA) in September 2005, and the 8th Annual Fall Clinical Pathology Symposium (Louisville, KY, USA) in November 2005. Participants at each meeting had the ability to discuss the merits of the guidelines and submit comments to the NACB Web site for formal response by the NACB during the open comment period from January 2004 through October 2005. A summary of these comments and revisions is presented at the end of each section of the guidelines when applicable.

Introduction

Ellis Jacobs, Barbara Goldsmith, Lasse Larrson, Harold Richardson, and Patrick St. Louis

In these Laboratory Medicine Practice Guidelines (LMPG), the National Academy of Clinical Biochemistry (NACB) is examining the application of evidence-based medicine (EBM) to the form of diagnostic testing known as point-of-care testing (POCT). For the purpose of this document, POCT is defined as "clinical laboratory testing conducted close to the site of patient care, typically by clinical personnel whose primary training is not in the clinical laboratory sciences or by patients (self-testing). POCT refers to any testing performed outside of the traditional, core or central laboratory." According to this definition, there are many synonyms for this form of testing:

- POCT
- Ancillary testing
- Satellite testing
- Bedside testing
- Near patient testing
- Home testing
- Self-management
- Patient self-management
- Remote testing
- Physician's office laboratories

EBM is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients *(1)* (Table I-1). It is the integration of best research evidence with clinical expertise and patient values. Best research evidence is composed of both clinically relevant research and basic science. Additionally, it is patient-centered research that evaluates the accuracy and precision of diagnostic tests, the power of prognostic markers, and the efficacy/safety of therapeutic, rehabilitative, and preventive regimens. Clinical expertise encompasses the ability to use clinical skills and experience to identify a patient's unique health state, to make diagnosis, and to evaluate the risks and benefits of interventions, taking into account the patient's personal values and expectations. The patient's unique preferences, concerns, and expectations need to be integrated into the clinical decision process.

There is a need for establishing an evidence-based practice for POCT. POCT is an increasingly popular means of delivering laboratory testing. When used appropriately, POCT can improve patient outcome by providing a faster result and a shorter timeframe to therapeutic intervention. However, when overused or incorrectly performed, POCT presents a patient risk. POCT may seem deceptively simple, but the test is not freely interchangeable with traditional core laboratory instrumentation in all patient-care situations. POCT may seem inexpensive, but overuse and inappropriate test use leads to significant increases in cost of care. The value of POCT really needs to be demonstrated through well-designed randomized controlled trials.

This LMPG will systematically review the existing scientific evidence relating POCT to patient outcome, grade the literature, and draft guidelines about the optimal use of POCT devices in patient care. The objective of this EBM of the practice of POCT is to systematically review and synthesize the available evidence on the effectiveness of POCT, with specific focus on outcomes in the areas of:

1. Patient/health
2. Operational/management
3. Economic benefit

Table I-1 Terminology Associated With Evidence-Based Medicine

Consensus recommendations	Advice on an aspect of patient care based on peer opinion
Clinical protocols	Guidance covering an aspect of clinical care; standardizes practice, minimizes variation
Outcome study	Scientific research defining the end result or effect of a change in patient management.
Systematic review	Synthesis and grading of the quality of research literature, conducted in a predefined manner
Practice guidelines	Systematically developed statement based on scientific evidence that guides patient management decisions for specific clinical conditions and decreases variation in clinical practice
Critical pathway	Evidence-based multidisciplinary plans of care, defining the optimal timing and sequences of clinical processes. Improves care by standardizing clinical practice and communication

In the planning for this LMPG, the practice of POCT was organized according to disease groups, with an introductory section for quality-assurance concepts that cross all disciplines. Focus groups were formed with clinician, laboratorian, and industry representation. For a specific clinical use, pertinent clinical questions were formulated and a systematic review of the clinical literature was conducted to develop practice guidelines. In this document, the evidence for the application of POCT in the following clinical areas will be examined:

- Bilirubin
- Cardiac markers
- Coagulation
- Critical care
- Diabetes
- Drug testing
- Infectious disease
- Occult blood
- Parathyroid testing
- pH
- Renal
- Reproduction

When one examines the scientific literature for evidence for the efficacy of POCT, it is quickly ascertained that there are few randomized case-controlled studies. The majority of publications described method comparisons. POCT is compared to a core laboratory method, and it is assumed that the similar results generate similar clinical outcomes. However, this is not necessarily true for all patients and devices. When the scientific literature is generalized, various characteristics have to be examined:

1. Does the study population compare to the real world?
2. Is there a recruitment and randomization bias associated with the sampling methodology?
3. Will there be compliance issues with the personnel performing POCT?
4. Will staff perform POCT correctly and with the same emphasis as in the study?
5. What is the true benefit of the convenience of POCT—is there any harm with delay because of laboratory confirmation?

Clinical and analytical specificity and sensitivity are other factors that need to be evaluated.

An evidence-based review of POCT must include (1) an assessment of patient outcome associated with obtaining a "quality" test result; (2) an understanding of how the testing system is integrated into the overall healthcare management; and (3) an understanding of the process or processes that lead to the desired outcome. The laboratory is quantitative and quality focused and therefore uniquely positioned to consult on critical pathways of care.

The basic procedures used by the various workgroups for the systematic review of the POCT literature are outlined in the following tables. The strength/level of evidence was based on effect on the outcome surrogate and the type of trial/study. Determination of the cohesiveness/consistency of the various studies, i.e., does the body of evidence make sense and the study conclusions lead to the same result, was one of the factors for the final guidelines given for or against POCT in a particular environment? To achieve these objectives, focus groups developed pertinent clinical questions for how the test was being used in various clinical settings. It was understood that some settings might raise different questions for the same test when compared to other settings, e.g., in-patient vs. emergency room vs. coronary care. Thus, the same POCT may be used differently in clinical decision-making and patient management in different settings. The format for the questions was:

- What is the effect on *Outcome* when comparing *POCT to Core Lab Testing* (identify comparison) for *screening patient for Disease X* (cite clinical application) in the *Emergency Room* (list patient population)?
- Does POCT for *Disease X* (clinical application/assay/disease) improve *Outcome* (list outcome of interest) in *Patients* (describe population or setting) compared to core lab testing (identify comparison being measured)?

The key components of the question are:

1. How—Clinical application (screening, diagnosis, management)
2. What—Comparison being measured (core vs POCT)
3. Where—Patient population or clinical setting (ED, home, clinic)
4. Why—Outcome (clinical, operational, economical)

Once the questions were developed, key search terms were ascertained for the literature search. Searches were conducted on MEDLINE or PubMed and were supplemented with the use of the National Guideline Clearinghouse, the Cochrane Group, or EBM reviews. Additionally, authors' personal article collections were used. Acceptable citations were limited to peer-reviewed articles with abstracts, those published in English, and those involving human subjects.

Abstracts identified by the literature searches were reviewed by 2 individuals to determine initial eligibility or ineligibility for full-text review, using Form 1 (Appendix A). If there was not consensus, then a third individual reviewed the abstract(s). To be included in the full systematic review of the clinical question, articles selected for full text review were examined for at least 1 relevant outcomes measurement. The systematic review consisted of creating evidence tables Form 2 (Appendix A) that incorporated the following characteristics:

1. Study design—Prospective or retrospective, randomized, and controlled, patient inclusion/exclusion criteria, blinding, number of subjects, etc.
2. Appropriateness of controls
3. Potential for bias (consecutive or nonconsecutive enrollment)

4. Depth of method description—full-length report or technical brief
5. Clinical application—screening, diagnosis, management
6. Specific key outcomes and how they were measured
7. Conclusions are logically supported

For the assessment of study quality, the general approach to grading evidence developed by the US Preventive Services Task Force *(2)* was applied (Table I-2). Once that was done, an assessment of study quality was performed, looking at the individual and aggregate data at 3 different levels (Forms 3 and 4) (Appendix A). At the first level, the individual study design was evaluated, as well as internal and external validity. Internal validity is the degree to which the study provides valid evidence for the populations and setting in which it was conducted. External validity is the extent to which the evidence is relevant and can be generalized to populations and conditions of other patient populations and POCT settings.

The synthesis of the volume of literature constitutes the second level, Form 5 (Appendix A). Aggregate internal and external validity was evaluated, as well as the coherence/consistency of the body of data. How well does the evidence fit together in an understandable model of how POCT leads to improved clinical outcome? Ultimately, the weight of the evidence about the linkage of POCT to outcomes is determined by assessing the degree to which the various bodies of evidence (linkages) "fit" together. To what degree is the testing in the same population and condition in the various linkages? Is the evidence that connects POCT to outcome direct or indirect? Evidence is direct when a single linkage exists but is indirect when multiple linkages are required to reach the same conclusion.

Final guidelines were made according to AHRQ classification (Table I-3) (3). The guidelines are evidence based and require scientific evidence that the recipients of POCT experience better health outcomes than those who did not and that the benefits are large enough to outweigh the risks. Consensus documents are not research evidence and represent guidelines for clinical practice, and inclusion of consensus documents was based on the linkages to outcomes, the reputation of the peer organization, and the consensus process used to develop the document. Health outcomes, e.g., benefit/harm, are the most significant outcomes in weighing the evidence and drafting guidelines.

POCT is an expanding delivery option because of increased pressure for faster results. However, POCT should not be used as a core laboratory replacement in all patient populations without consideration of the test limitations and evaluation of the effect of a faster result on patient care. There is a need for quality POCT outcomes studies to be conducted. Laboratories should require evidence of outcomes for new tests and question clinical utility of ongoing tests.

Table I-2 Levels of Evidence

I	Evidence includes consistent results from well-designed, well-conducted studies in representative populations
II	Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
III	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Table I-3 Strength of Recommendations

A	The NACB strongly recommend adoption; there is good evidence that it improves important health outcomes and concludes that benefits substantially outweigh harms
B	The NACB recommends adoption; there is at least fair evidence that it improves important health outcomes and concludes that benefits outweigh harms.
C	The NACB recommends against adoption; there is evidence that it is ineffective or that harms outweigh benefits.
I	The NACB concludes that the evidence is insufficient to make recommendations; evidence that it is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

REFERENCES

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71–2.
2. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21–35.
3. US Department of Health & Human Services. Agency for Healthcare Research and Quality. Systems to rate the strength of scientific evidence. Publication 02-E016. Bethesda, MD: AHRQ, 2002:11pp. Available at: http://www.ahrq.gov (Accessed March 2006.)

Guidelines Committee

We gratefully acknowledge the following individuals who contributed the original manuscripts upon which this monograph is based:

Robert H. Christenson, Ph.D., FACB
University of Maryland School of Medicine
Baltimore, Maryland
USA

William Clarke, Ph.D.
Johns Hopkins Medical Institutions
Baltimore, Maryland
USA

Ann Gronowski, Ph.D., FACB
Washington University
St. Louis, Missouri
USA

Catherine A. Hammett-Stabler, Ph.D., FACB
University of North Carolina Chapel Hill
Chapel Hill, North Carolina
USA

Ellis Jacobs, Ph.D., FACB
New York State Department of Health
Albany, New York
USA

Steve Kazmierczak, Ph.D., FACB
Oregon Health and Science University
Portland, Oregon
USA

Kent Lewandrowski, M.D.
Massachusetts General Hospital
Boston, Massachusetts
USA

Christopher Price, Ph.D., FACB
University of Oxford
Oxford
UK

David Sacks, M.D., FACB
Brigham and Women's Hospital
Boston, Massachusetts
USA

Robert Sautter, Ph.D.
Carolinas Medical Center
Charlotte, North Carolina
USA

Greg Shipp, M.D.
Nanosphere
Northbrook, Illinois
USA

Lori Sokoll, Ph.D., FACB
Johns Hopkins Medical Institutions
Baltimore, Maryland
USA

Ian Watson, Ph.D., FACB
University Hospital Aintree
Liverpool
UK

William Winter, M.D., FACB
University of Florida
Gainesville, Florida
USA

Marcia L. Zucker, Ph.D., FACB
International Technidyne Corporation (ITC)
Edison, New Jersey
USA

NACB Committees

This publication is produced with the assistance of:

NACB Publications Committee (2006)

KT Jerry Yeo, Ph.D., FACB *(Chair)*
Dartmouth-Hitchcock Medical Center
and Dartmouth Medical School
Lebanon, New Hampshire
USA

Charlie Hawker, Ph.D., FACB
ARUP Laboratories, Inc.
Salt Lake City, Utah
USA

Stanley Lo, Ph.D., FACB
Children Hospital of Wisconsin
Wauwatosa, Wisconsin
USA

Gwen McMillin, FACB
ARUP Laboratories and University of Utah
Salt Lake City, Utah
USA

Richard Mullins, Ph.D., FACB
St. Jude Children's Research Hospital
Memphis, Tennessee
USA

James Ritchie, Ph.D., FACB
Emory University Hospital
Atlanta, Georgia
USA

Sayed Sadrzadeh, Ph.D., FACB
University of Washington School of Medicine
Seattle, Washington
USA

NACB Education and Scientific Affairs Committee (2006)

Shirley Welch, Ph.D., FACB *(Chair)*
Kaiser Permanente NW Regional Laboratory
Portland, Oregon
USA

Michael Bennett, Ph.D., FACB
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
USA

Eleftherios Diamandis, M.D., Ph.D., FACB
Mount Sinai Hospital
Toronto, Ontario
Canada

Gary Meyers, Ph.D., FACB
Centers for Disease Control and Prevention
Atlanta, Georgia
USA

Salvador Sena, Ph.D., FACB
Danbury Hospital
Danbury, Connecticut
USA

Lori Sokoll, Ph.D., FACB
Johns Hopkins Medical Institutions
Baltimore, Maryland
USA

Roland Valdes Jr., Ph.D., FACB
University of Louisville
Louisville, Kentucky
USA

Contributors

Aasne Karine Aarsand, M.D.
Haukeland University Hospital
Bergen
Norway
Chapter 6

David Alter, M.D.
Spectrum Health
Grand Rapids, Michigan
USA
Chapter 6

Fred S. Apple, Ph.D.
Hennepin County Medical Center
University of Minnesota School of Medicine
Minneapolis, Minnesota
USA
Chapter 3

Roger Bertholf, Ph.D., DABCC, FACB
University of Florida
Jacksonville, Florida
USA
Chapter 7

Vinod Bhutani, M.D.
Stanford University
Palo Alto, California
USA
Chapter 2

Valerie Bush, Ph.D., FACB
Bassett Healthcare
Cooperstown, New York
USA
Chapter 4

Sheldon Campbell, M.D., Ph.D.
Yale University
New Haven, Connecticut
USA
Chapter 8

Joseph Campos, Ph.D.
Children's National Medical Center
Washington, DC
USA
Chapter 8

Robert H. Christenson, Ph.D., FACB
University of Maryland School of Medicine
Baltimore, Maryland
USA
Chapter 3

William Clarke, Ph.D., DABCC
Johns Hopkins School of Medicine
Baltimore, Maryland
USA
Chapter 12

Laurence M. Demers, Ph.D., FACB (Consultant)
Milton S. Hershey Medical Center
Hershey, Pennsylvania
USA
Chapter 13

Paul D'Orazio, Ph.D.
Instrumentation Laboratory
Lexington, Massachusetts
USA
Chapter 5

Karen Dyer, MT(ASCP), DLM
Johns Hopkins Hospital
Baltimore, Maryland
USA
Chapter 12

Maria Ferris, M.D.
University of North Carolina
Chapel Hill, North Carolina
USA
Chapter 12

Niels Fogh-Andersen, M.D., D.M.Sc., FACB
Copenhagen University Hospital
Herlev
Denmark
Chapter 5

Stacy Foran Melanson, M.D., Ph.D.
Brigham and Women's Hospital
Boston, Massachusetts
USA
Chapter 9

Gary Francis, M.D.
Cleveland Clinic Foundation
Cleveland, Ohio
USA
Chapter 3

Stephen J. Frost, PhD, MCB, MRSC, FRCPath
Princess Royal Hospital
Haywards Heath
UK
Chapters 6 and 12

Katie Gallagher, MT(ASCP)
Johns Hopkins Hospital
Baltimore, Maryland
USA
Chapter 12

Steve George, Ph.D. MRCPath
Birmingham City Hospital
Birmingham
UK
Chapter 7

Bruce Goldberger, Ph.D., FACB
University of Florida
Gainesville, Florida
USA
Chapter 7 (Consultant)

Barbara Goldsmith, Ph.D, FACB
St. Elizabeth's Medical Center
Boston, Massachusetts
USA
Chapter 1

Glenn Gourley, M.D.
Oregon Health & Science University
Portland, Oregon
USA
Chapter 2

Wallace Greene, Ph.D.
Pennsylvania State University
Hershey Medical Center
Hershey, Pennsylvania
USA
Chapter 8

David G. Grenache, Ph.D., FACB
University of North Carolina School of Medicine
Chapel Hill, North Carolina
USA
Chapter 13

Ann M. Gronowski, Ph.D., FACB
Washington University School of Medicine
St. Louis, Missouri
USA
Chapter 13

Gerri S. Hall, Ph.D.
Cleveland Clinic Foundation
Cleveland, Ohio
USA
Chapter 8

Catherine Hammett-Stabler, Ph.D., DABCC, FACB
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina
USA
Chapter 7

Sandra Humbertson, MT(ASCP)
Johns Hopkins Hospital
Baltimore, Maryland
USA
Chapter 12

Bernard Jaar, M.D.
Johns Hopkins Medical Institutions
Baltimore, Maryland
USA
Chapter 12

Ellis Jacobs, Ph.D, FACB
Wadsworth Center
New York State Department of Health
Albany, New York
USA
Chapter 1

Robert Jesse, M.D., Ph.D.
Medical College of Virginia
Richmond, Virginia
USA
Chapter 3

Vandita Johari, M.D.
Baystate Medical Center
Springfield, Massachusetts
USA
Chapter 4

Bob Kaplanis
Laboratory Sciences of Arizona
Temple, Arizona
USA
Chapter 6

Steven Kazmierczak, Ph.D., FACB
Oregon Health & Science University
Portland, Oregon
USA
Chapter 2

Scott Kerr
Respironics
Murrysville, Pennsylvania
USA
Chapter 2

Atle Klovning, M.D.
University of Bergen
Bergen
Norway
Chapter 6

Edward Kraus, M.D.
Johns Hopkins Medical Institutions
Baltimore, Maryland
USA
Chapter 12

Lasse Larrson, M.D., Ph.D.
University of Linkoping
Linkoping
Sweden
Chapter 1

William D. LeBar, M.S.
Hospital Consolidated Laboratories-Providence Hospital
Southfield, Michigan
USA
Chapter 8

Kent B. Lewandrowski, M.D.
Massachusetts General Hospital
Boston, Massachusetts
USA
Chapter 9

Steven K. Libutti, M.D.
National Cancer Institute
Bethesda, Maryland
USA
Chapter 10 (Consultant)

Stanley Lo, Ph.D., FACB
Medical College of Wisconsin
Milwaukee, Wisconsin
USA
Chapter 2

Glenn Markenson, M.D.
Baystate Health System
Springfield, Massachusetts
USA
Chapter 13

Brenda Nicholes, Ph.D., FACB
Metro Health Medical Center
Case Western Reserve University
Cleveland, Ohio
USA
Chapter 7

James H. Nichols, Ph.D., FACB
Baystate Health
Springfield, Massachusetts
USA
Chapter 11

Anthony Okorodudu, Ph.D., FACB
University of Texas Medical Branch
Galveston, Texas
USA
Chapter 5

John Petersen, Ph.D., FACB
University of Texas Medical Branch Hospitals
Galveston, Texas
USA
Chapter 9

Christopher P. Price, Ph.D., FRSC, FRCPath, FACB
Bayer HealthCare
Newbury
UK
Chapter 6

Srikantha Rao, M.D.
Penn State College of Medicine
Hershey, Pennsylvania
USA
Chapter 4

Alan T. Remaley, M.D., Ph.D.
National Institutes of Health
Bethesda, Maryland
USA
Chapter 10

Harold Richardson, M.D., FCCM, FRCPC
Ontario Medical Association
Ontario
Canada
Chapter 1

Alex Robertson, M.D.
Brody School of Medicine
East Carolina University
Greenville, North Carolina
USA
Chapter 2

Donna Roush, MLT (ASCP) PA
Lancaster General Hospital
Lancaster, Pennsylvania
USA
Chapter 8

James T. Rudrik, Ph.D.
Michigan Department of Community Health
Lansing, Michigan
USA
Chapter 8

Barbara Russell, MHE, MT(ASCP) SH
Medical College of Georgia
Augusta, Georgia
USA
Chapter 8

David B. Sacks, MB, ChB, FRCPath, FACB
Brigham and Women's Hospital
and Harvard Medical School
Boston, Massachusetts
USA
Chapter 6

Sverre Sandberg, M.D., Ph.D.
Haukeland University Hospital
Bergen
Norway
Chapter 6

Robert Sautter, Ph.D.
Carolinas Pathology Group
Carolinas HealthCare System
Charlotte, North Carolina
USA
Chapter 8

Eric Schmith, MT(ASCP)
Johns Hopkins Hospital
Baltimore, Maryland
USA
Chapter 12

Salvador F. Sena, Ph.D., FACB
Danbury Hospital
Danbury, Connecticut
USA
Chapters 2 and 10

Greg Shipp, M.D.
Abbott Point-of-Care
East Windsor, New Jersey
and Nanosphere
Northbrook, Illinois
USA
Chapter 5

Terry Shirey, Ph.D., FACB
Nova Biomedical
Waltham, Massachusetts
USA
Chapter 5

Brian Smith MSc, MRCPath
Maudesley Hospital
London
UK
Chapter 7

Lori J. Sokoll, Ph.D., FACB
Johns Hopkins Medical Institutions
Baltimore, Maryland
USA
Chapter 10

Andrew St John, Ph.D., MAACB
ARC Consulting
Perth
Western Australia
Chapter 6

Patrick St. Louis, Ph.D.
Sainte-Justine Hospital
Montreal, Quebec
Canada
Chapter 1 and 13 (Consultant)

Alan B. Storrow, M.D.
Vanderbilt University
Nashville, Tennessee
USA
Chapter 3

Ramasamyiyer Swaminathan, MB BS, Ph.D., FRCPath, FRCPA, FACB
Guy's and St Thomas' Hospital
London
UK
Chapter 6

Dawn Taylor, MT(ASCP)
St. John Health Labs
Detroit, Michigan
USA
Chapter 11

John Toffaletti, Ph.D.
Duke University Medical Center
Durham, North Carolina
USA
Chapter 5

Robert Udelsman, M.D., M.B.A.
Yale University
New Haven, Connecticut
USA
Chapter 10 (Consultant)

Heike Varnholt, M.D.
Baystate Health System
Springfield, Massachusetts
USA
Chapter 11

Alain Verstraete, M.D., Ph.D.
Ghent University
Belgium
Chapter 7 (Consultant)

Ian D. Watson, Ph.D., FRCPath, FACB
University Hospital Aintree
Liverpool
UK
Chapter 7

Robin Weiner
Quidel Corporation
San Diego, California
USA
Chapter 13 (Consultant)

Shirley Welch, Ph.D., FACB
Kaiser Permanente NW Regional Laboratory
Portland, Oregon
USA
Chapter 7

Frank H. Wians, Jr., Ph.D., FACB
University of Texas Southwestern Medical Center
Dallas, Texas
USA
Chapter 10

Leslie Williams, MT(ASCP)
Bayer Diagnostics
Tarrytown, New York
USA
Chapter 11

William E. Winter, M.D., FACB
University of Florida
Gainesville, Florida
USA
Chapter 6

Alan H.B. Wu, Ph.D., FACB
University of California San Francisco
San Francisco, California
USA
Chapter 3

Jean Wu, M.D.
Johns Hopkins Medical Institutions
Baltimore, Maryland
USA
Chapter 12

Jiaxi Wu, Ph.D., M.D.
University of Texas Southwestern Medical Center
Dallas, Texas
USA
Chapter 10

Marcia L. Zucker, Ph.D.
International Technidyne Corporation
Edison, New Jersey
USA
Chapter 4

Nonstandard Abbreviations

AACC, American Association for Clinical Chemistry; ABG, arterial blood gases; AcAc, acetoacetate; ACE, acetone; ACS, acute coronary syndrome; ACT, activated clotting time; ADA, American Diabetes Association; AFDC, aid to families with dependent children; AGA, American Gastroenterological Association; AHRQ, Agency for Healthcare Research and Quality; AIDS, acquired immune deficiency syndrome; AMI, acute myocardial infarction; aPTT, activated partial thromboplastin time; ART, anti-retroviral therapy; ASCP, American Society of Clinical Pathologists, BBT, basal body temperature monitoring; BOHB, β-hydroxybutyrate; BUN, blood urea nitrogen; CABG, coronary arterial bypass grafting; CCU, critical care unit; CDC, Centers for Disease Control and Prevention; CICU, cardiac intensive care unit; CLIA, Clinical Laboratory Improvement Amendments; CLMA, Clinical Laboratory Management Association; CLT, central laboratory testing; COC, cocaine; CR, creatinine; CRC, colorectal cancer; CVD, cardiovascular disease; CVDL, cardiovascular diagnostics laboratory or cardiac catheterization laboratory; DCCT, Diabetes Control and Complications Trial; DDW, Digestive Diseases of the Week; DHHS, Department of Health and Human Services; DKA, diabetic ketoacidosis; DM, diabetes mellitus; DRE, digital rectal examination; DUA, dipstick urinalysis; EBM, evidence-based medicine; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; ED, emergency department; EIA, enzyme immunoassay; EQA, external quality assessment; ESRD, end-stage renal disease; FDA, US Food and Drug Administration; fFN, fetal fibronectin; FOBT, fecal occult blood testing; GAS, group A streptococcus; GBM, glomerular basement membrane; GBS, group B streptococcus; GC-MS, gas chromatography mass spectrometry; GER, gastroesophageal reflux; GFR, glomerular filtration rate; GI, gastrointestinal; HA, heterophilic antibodies; HAART, highly active antiretroviral therapy; hCG, human chorionic gonadotropin hormone; HFOV, high-frequency oscillatory ventilation; HIV, human immunodeficiency virus; HO, Hemoccult; HOS, HPLC, high-pressure liquid chromatography; HQ, HemoQuant; Hemoccult Sensa; Hsel, HemeSelect; IFA, immunofluorescence assay; IM, infectious mononucleosis; INR, international normalized ratio; IQC, internal quality control; ISO, International Organization for Standardization; LH, luteinizing hormone; LMPG, Laboratory Medicine Practice Guidelines; LOS, length of stay; MDA, Medical Devices Agency; MDMA, 3,4-methylenedioxymethamphetamine;[1] MI, myocardial infarction; MIP, minimally invasive parathyroidectomy; MIRP, minimally invasive radioguided parathyroidectomy; NACB, National Academy of Clinical Biochemistry; NICU, neonatal intensive care unit; NIDA, National Institute on Drug Abuse; NPV, negative predictive value; NSAID, nonsteroidal anti-inflammatory drug; OPI, opiates; OR, operating room; PCP, phencyclidine; PCR, polymerase chain reaction; P/Cr, protein/creatinine ratio; PICU, pediatric intensive care unit; PID, pelvic inflammatory disease; POC, point of care; POCT, point of care testing; PPV, positive predictive value; PROM, premature rupture of the membranes; PPROM, preterm premature rupture of the membranes; PSM, patient self-management; PST, patient self-testing; PT, prothrombin time; PTCA, percutaneous transluminal coronary angioplasty; PTH, parathyroid hormone; QA, quality assurance; QC, quality control; QI, quality improvement; QM, quality management; RCT, randomized controlled trials; RSV, respiratory syncytial virus; SAMSHA, Substance Abuse and Mental Health Services Administration; SICU, surgical intensive care unit; SMBG, self-monitoring blood glucose; STD, sexually transmitted disease; SUDS, single-use diagnostic system; TAT, turnaround time; TEG, thromboelastography; THC, delta-9-tetrahydrocannabinol; THCCOOH, Δ-9-tetrahydrocannabinol carboxylic acid; TTAT, therapeutic turnaround time; UA, unstable angina; UAE, urinary albumin excretion; UKB, urine ketone body; UKPDS, United Kingdom Prospective Diabetes Study; VAP, video-assisted parathyroidectomy.

Chapter 1

Management

Ellis Jacobs, Barbara Goldsmith, Lasse Larrson, Harold Richardson, and Patrick St. Louis

QUALITY ASSURANCE AND MEDICAL ERROR

This chapter is an evidence-based review and assessment of quality assurance practices associated with point-of-care testing (POCT). The literature about quality assurance (QA) and quality management (QM) of POCT is by and large not evidence based *(1–6),* due, in large part, to the difficulty of assessing the causal impact of POCT on medical errors. Even in the traditional clinical laboratory setting, the scientific basis of QA and QM is the last area to have the concepts of evidence-based medicine (EBM) applied.

Does the application of QA to POCT reduce medical errors? (Literature Search 1)

Guideline 1. *We recommend that a formal process of QA of POCT be developed in support of risk management and a reduction in medical errors.*

Strength/consensus of recommendation: B

Level of evidence: III (expert opinion)

Quality control (QC) and QA are integral components forming the basis of the QM hierarchy of the clinical laboratory *(7)*. The performance goals of POCT are no different from those of the traditional clinical laboratory, namely, to:

- provide accurate and timely analyses
- provide reports that are useful to the clinician treating the patient
- make epidemiological information available to public health authorities
- make the best possible use of people, equipment, and reagents in the interests of efficiency
- manage use

The justification and benefits of QA when applied to POCT would seem to be self-evident.

QA goes beyond QC and focuses on the impact of laboratory testing on patient care. A QA program for laboratory services should establish:

- performance expectations that cover preanalytical, analytical and postanalytical components of the service;
- performance expectations after consultation with user-physicians and other healthcare workers;
- periodic audit to determine that the service is meeting its established performance expectations;
- a program of performance comparisons to that of the central or core laboratory;
- periodic review of the service patterns of practice against established, validated, external benchmarks;
- review of the QA program findings by a management team.

Although much has been written in recent years about the use of POCT, including the health cost benefits, there remains a paucity of evidence on which to base conclusions or make recommendations. Existing documents *(1–7)* appear to be consensus statements by expert groups based on collective insight and experience but with no clear indication of the underlying evidence, although it likely falls mainly into category III (as defined in the introduction).

The recent evolution of POCT has focused on small user-friendly devices with limited but robust analytical capabilities. Users tend to identify with a particular device for a particular purpose and, thus, see that device in isolation. In reality, each device is serving a function that traditionally belonged in the central or core laboratory, with its established QM processes and procedures supported by technical and professional expertise. Frequently, persons who lack the training and insight in laboratory-based testing carry out POCT in a clinical setting. Because POCT results are treated comparably to those generated by the central laboratory for patient care, it follows that the quality requirements are the same regardless of the testing site, process, or procedure. At the same time, the unique characteristics (location, operators, distribution, etc) add special requirements to QA/QM. Because most instruments themselves are robust in their analytical performance, the QA program should specifically address pre- and postanalytical concerns.

Requirements for QA, internal QC, and external quality assessment (EQA) of POCT have been stated in many publications *(3–7)*. The recommendations are consensus based and include the following:

- QA is an essential component of POCT and includes all the measures taken to ensure that investigations are reliable:
  - Correct identification of the patient
  - Appropriate test selection
  - Obtaining a satisfactory specimen
  - Analyzing it and recording the results promptly and correctly
  - Interpreting the result accurately
  - Taking appropriate action
  - Documenting all procedures for reference
- IQC requirements:
  - Procedure established for IQC at appropriate frequency
  - QC material procurement
  - Correction of nonconformities
- Users of POCT have a duty to participate in an EQA scheme and perform adequately as part of clinical governance. Questions to consider are:
  - What is the role of the central laboratory in providing or recommending EQA schemes for POCT?
  - Who is responsible for coordination of EQA within POCT; are necessary procedures in place?
  - Who will review performance?
  - Is support available for inadequate performance?
  - Can the central laboratory assist by providing parallel testing?

The international standard, ISO 22870 Point-of-Care (POCT)—Requirements for quality and competence *(8)*, was recently published. This document was prepared by Working Group #1 of the International Organization for Standardization (ISO) Technical Committee TC 212. The introduction states that risk to the patient and to the facility can be managed by a well-designed, fully implemented, QM system that provides for:

- Evaluation of new or alternative POCT instruments and systems
- Evaluation and approval of end-user proposals and protocols
- Purchase and installation of equipment
- Maintenance of consumable supplies and reagents
- Training, certification, and recertification of POCT system operators
- QC and QA

The technical requirements part of the international standard details those relating to personnel, accommodation and environmental conditions, equipment, preexamination procedures, examination procedures, ensuring the quality of the examination procedures, postexamination procedures, and the reporting of results.

DOES MANAGEMENT IMPROVE THE QUALITY OF POCT?

The term *management* as used here identifies 2 major parts. The first encompasses personnel responsible for oversight of the institutional POCT program. Personnel can variously be an individual (director, coordinator) or a team (interdisciplinary committee, management committee). The second deals with the activities related to the regulation of all the processes needed to generate reliable POCT results. Processes should be defined to cover all aspects of the POCT project. Falling partly within this second section and partly as an independent adjunct to POCT processes is the field of data management. Here, data from the testing process, including QC and patient results, as well as related information such as error types and frequencies and operator certification and competency, are collected and manipulated to provide information useful in monitoring and improving the total process.

Guideline 2. *We strongly recommend the use of an interdisciplinary committee to manage POCT* (Literature Search 2)

Strength/consensus of recommendation: A

Level of evidence: II and III (time-controlled studies, descriptive studies, and expert opinion–consensus documents)

In smaller sites, an individual coordinator or director may be responsible for POCT, but a committee structure is preferable, especially for larger sites or institutions. The management structure must have official standing, with the explicit support of the institutional administration. Committees should be interdisciplinary to ensure input from stakeholders, leading to a broader perspective on the POCT project and enhancing chances of success. Published studies have described improvements in many aspects of the POCT programs after the implementation of a management committee *(3, 9, 10)*. Generally, there was no preexisting structure. In addition, and lending weight to our recommendations, documents published by various accreditation and regulatory agencies propose, with varying degrees of insistence, that a management (interdisciplinary) committee be operational at any site performing POC testing *(11–13)*. These documents take various forms, including guidelines, position statements, and consensus statements.

The interdisciplinary team structure, by providing a forum for discussion of different ideas and approaches, permits more universally acceptable solutions to project activities. There is no consensus about the actual composition of the committee, and indications are that this may vary project to project. Also, the frequency with which meetings are held should be flexible enough to minimize impact on time demands of committee members while maintaining maximum benefit. Thus, the committee approach should provide adequate oversight with sufficient flexibility.

With respect to its mandate, the committee is responsible for the development, implementation, and monitoring of processes and related protocols that shall cover all aspects of the institution's POCT program, which may include testing performed away from the principal site but that falls under the institutional jurisdiction. The UK Medical Devices Agency (MDA) *(12)* states that clinical governance is the responsibility of the institution and this responsibility also devolves onto the POCT committee. Clinical governance is defined as a framework through which organizations are accountable for continually improving the quality of their services and safeguarding high standards of care by creating in environment in which excellence in clinical care will flourish.

Processes should be defined to cover all aspects of the POCT project, including consideration of requests for POCT (needs evaluation), evaluation and selection of a device or test appropriate for the identified use, and all aspects of the testing process. This latter will include all phases of the analytical process (preanalytical, analytical and postanalytical), as well as QA aspects of the project, including ongoing QM and quality improvement initiatives. With respect to needs evaluation, the literature suggests that although identifying a clinical need before proceeding with a POCT project is desirable, events sometimes overtake process *(14)*. Regardless, post facto monitoring of cost-effectiveness is important and can redress this problem.

Guideline 3. *We strongly recommend training programs to improve the quality of POCT.*

Strength/consensus of recommendation: A

Level of evidence: II (cohort/case-controlled study and time-controlled study)

Studies have shown directly *(7, 15)* and indirectly *(2)* that training and ongoing certification of operators should be one of the major priorities for effective POCT. Also, organizations such as the ISO *(8)* and the UK MDA *(12)* recognize and stress the importance of training for effective POCT, which relates to the fact that POCT usually involves many tests and devices, as well as multiple operators, most of whom are not laboratory-trained personnel. This lack of training implies a lack of understanding of the principles of laboratory assays and good laboratory practices for ensuring the reliability of test results. Also, there will be a lack of knowledge of the particular test method or system.

Training needs to cover all phases of the testing process, including appropriate responses to unusual test results. Important preanalytical steps include proper identification of the patient and sample acquisition, whereas postanalytical issues include charting of results, verification of unanticipated results, and notification of responsible persons. In this context, data from studies on laboratory-related errors indicate that the majority of incidents relate to the preanalytical phase *(16, 17)*. There is reason to believe that similar issues exist with POCT *(10, 18)*. Finally, training, including the description of analytic procedural steps, as well as proper material handling, is best addressed by clearly written testing protocols that follow manufacturer's instructions.

Guideline 4. *We recommend data management as a mechanism to improve the quality of POCT.*

Strength/consensus of recommendation: B

Level of evidence: II and III (time-controlled study and expert opinion)

In any enterprise, data management is fundamental to quality and performance improvement, and documentation of quality relies on data *(2)*. Depending on the questions asked, analyzing data can show quality trends, thereby permitting decisions on actions to remedy or to improve the quality of the process *(19)*. POCT, whether manual or instrumented, generates significant amounts of data, including identifiers associated with the patient-testing process; results of all QC and patient tests, as well as other data, including reagent and material handling information such as lot numbers and expiry dates; unusual test results; and specific responses to results. There is, for example, a wealth of evidence, particularly Class III, showing that evaluating POCT QC data permits responses for improvement in test quality. This improvement may be by identifying inappropriately performing lots of reagents, trends resulting from improper material storage and handling, or operators who are using improper testing technique. Thus, overall data management can monitor compliance with the requirements for quality in POCT. Dyer et al *(19)*, for example, showed that compliance problems with dating reagents, uncapped bottles, and operational errors in POCT could be followed up by a nursing unit and corrective action taken. It is clear that data management per se does not improve the POCT process. It is the monitoring of the data for events and trends, along with the existence and implementation of response protocols, that ensures success *(15)*.

Manual POCT has the significant disadvantage that all information, including test results, material handling data, and result reporting and comments, has to be manually entered into the database, which is not only time consuming but also prone to errors of omission and commission, and so extra care must be taken in verifying the entry of these data. Instrumented POCT devices have a variable amount of data storage and transfer capability, certainly improving the situation. However, the lack of uniformity among these devices has led to the description of a connectivity standard for POCT devices *(20)*. It is anticipated that this standard will eventually be adopted across the in vitro diagnostics (IVD) industry.

Guideline 5. *We strongly recommend the use of Continuous Quality Improvement with Quality Indicator.*

Strength/consensus of recommendation: A

Level of evidence: II (time-controlled studies)

The POCT Management Committee is empowered to put QA programs in place and is responsible for monitoring and follow-up. Two traditional components of QA, internal QC and EQA, monitor primarily the analytical process. However, as implied in the sections above, problems at any phase of the total process can influence the reliability of the test result. Thus, the identification of specific, measurable indicators related to the quality of a POCT project or test permits monitoring and evaluation of the data. In turn, this allows for the implementation of corrective measures or of measures to enhance the process, which is supported by longitudinal studies *(9*, *10*, *19*, *21)*, publications from standards organizations (ISO, MDA, Clinical and Laboratory Standards Institute, [CLSI, formerly NCCLS]) *(1*, *5*, *8)*, and expert opinion *(11*, *22)*.

REFERENCES

1. Kost GJ. Preventing medical errors in point-of-care testing: security, validation, safeguards, and connectivity. Arch Pathol Lab Med 2001;125:1307–15.
2. Nichols JH. Quality in point-of-care testing. Expert Rev Mol Diagn 2003;3:563–72.
3. Jansen RT, Blaton V, Burnett D, Huisman W, Queralto JM, Allman B. European Communities Confederation of Clinical Chemistry: essential criteria for quality systems of medical laboratories. Working Group on Harmonisation of Quality Systems and Accreditation. Eur J Clin Chem Clin Biochem 1997;35:123–32.
4. Medical Devices Agency. Management of in vitro diagnostic medical devices. Document MDA DB2002(02). London, UK: MDA, 2002:40pp.
5. Clinical and Laboratory Standards Institute. Application of a quality management system model for laboratory services; Approved guideline—3rd ed. Document GP26-A3. Wayne, PA: CLSI, 2004:60pp.
6. Clinical and Laboratory Standards Institute. Wellness testing using IVD devices; Approved guideline. Document AST3-A. Wayne, PA: CLSI, 1999:18pp.
7. Clinical and Laboratory Standards Institute. Continuous quality improvement: integrating five key quality system components; Approved guideline—2nd ed. Document GP22-A2. Wayne, PA: CLSI, 2004:68pp.
8. International Organization of Standardization. Point-of-care testing (POCT)—requirements for quality and competence. Document ISO 22870:2006. Geneva, Switzerland: ISO, 2006:11pp.
9. Jacobs E, Hinson KA, Tolnai J, Simson E. Implementation, management and continuous quality improvement of point-of-care testing in an academic health care setting. Clin Chim Acta 2001;307:49–59.
10. Nichols JH, Poe SS. Quality assurance, practical management, and outcomes of point-of-care testing: laboratory perspectives, part I. Clin Lab Manage Rev 1999;13:341–50.
11. Jansen RT, Blaton V, Burnett D, Huisman W, Queralto JM, Zerah S, et al. Additional essential criteria for quality systems of medical laboratories. European Community Confederation of Clinical Chemistry (EC4) Working Group on Harmonisation of Quality Systems and Accreditation. Clin Chem Lab Med 1998;36:249–52.
12. Medical Devices Agency. Management and use of IVD point of care test devices. Document MDA DB2002(03). London, UK: MDA 2002:31pp.
13. Clinical and Laboratory Standards Institute. Point-of-care in vitro diagnostic (IVD) testing; Approved guideline. Document AST2-A. Wayne, PA: CLSI, 1999:86pp.
14. Kost GJ, Hague C. The current and future status of critical care testing and patient monitoring. Am J Clin Pathol 1995;104(Suppl 1): S2–17.
15. Tighe P. Laboratory-based quality assurance programme for near-patient urine dipstick testing, 1990–1997: development, management and results. Br J Biomed Sci 1999:56:6–15.
16. Bonini P, Plebani M, Ceriotti F, Rubboli F. Errors in laboratory medicine. Clin Chem 2002;48:691–8.
17. Astion ML, Shojians KG, Hamill TR, et al. Classifying laboratory incident reports to identify problems that jeopardize patient safety. Am J Clin Pathol 2003;120:18–26.
18. Hopkins S. Do no harm: the lab's role in improving patient safety. Advance Administrators Lab 2004;13:50–57.
19. Dyer K, Nichols JH, Taylor M, Miller R, Saltz J. Development of a universal connectivity and data management system. Crit Care Nurs Q 2001;24:25–38.
20. Clinical and Laboratory Standards Institute. Point-of-care connectivity; Approved standard. Document POCT1-A2. Wayne, PA: CLSI, 2006:306pp.
21. Connelly LM. Past, present, future: a continuous cycle of improvement for ancillary glucose testing. Clin Lab Manage Rev 1997;11:171–80.
22. Kost GJ. Guidelines for point-of-care testing. Am J Clin Pathol 1995;104(Suppl 1):S111–2.

PUBLIC COMMENTS

No public comments were received on the guidelines.

Chapter **2**

Transcutaneous Bilirubin Testing

Steven Kazmierczak, Vinod Bhutani, Glenn Gourley, Scott Kerr, Stanley Lo, Alex Robertson, and Salvador F. Sena

INTRODUCTION

The management of jaundice in neonates continues to be a challenging clinical problem. More recently, it has taken on increased importance because of factors such as early hospital discharge, increased prevalence of breastfeeding, and lack of adherence to prompt postdischarge follow-up testing of newborns *(1, 2)*. Jaundice in near-term and term newborns is clinically evident in more than 60% of newborns during the first week after birth; it is usually benign but may lead to kernicterus if unmonitored or untreated *(3)*. Because of the limitations on visual assessment of jaundice, especially in infants of darker skin color, physicians have been advised to confirm suspected hyperbilirubinemia. Neonatal hyperbilirubinemia, defined as serum bilirubin concentrations >221 μmol/L (>12.9 mg/dL, conversion from mg/dL × 17.1 = μmol/L), has been estimated to occur in up to 10% of newborns *(3–6)*. A number of proposals have been made that would reduce the risk of kernicterus among these infants, including screening of newborns by measurement of total serum bilirubin, transcutaneous bilirubin concentrations *(3, 7, 8)*, end-expiratory carbon monoxide, or a combination of bilirubin and carbon monoxide measurements *(9)*. This guideline will focus on the use of transcutaneous bilirubin measurements for the evaluation of hyperbilirubinemia in healthy, term infants.

The ability to measure bilirubin simply, rapidly, and accurately and in a variety of settings is important for assessing hyperbilirubinemia and evaluating the risk of kernicterus. Laboratory-based measurement of bilirubin in serum or plasma using diazo-based chemical methods is the technique most often used to determine the concentration of bilirubin in newborns. However, bilirubin measured with chemical-based methods is often inaccurate because of interference from hemoglobin as a result of hemolysis. Visual inspection of the skin, sclera, and mucous membranes is a rapid and inexpensive technique for estimating bilirubin concentrations. In addition, documentation of the cephalocaudal progression of jaundice can provide an indication of the increase in hyperbilirubinemia. Unfortunately, these methods are frequently inaccurate, especially when applied to newborns of mixed ethnicity or of diverse racial backgrounds *(7)*. Another rapid noninvasive technique to assess bilirubin concentration is by transcutaneous spectrophotometric measurement. Transcutaneous bilirubin concentrations have been found to correlate extremely well with laboratory-based measurements. The purpose of this guideline is to evaluate the available literature and identify those studies that clearly demonstrate the utility of transcutaneous point-of-care bilirubin testing compared with traditional clinical laboratory–based measurement.

Does transcutaneous bilirubin measurement improve clinical outcome, shorten length of stay, or decrease readmission rate for newborns with hyperbilirubinemia, compared with measurement of bilirubin in serum? (Literature Search 3)

Guideline 6. *Assessment of hyperbilirubinemia with use of transcutaneous bilirubin measurements may have utility in decreasing readmission rate of newborns with hyperbilirubinemia and monitoring bilirubin concentrations in newborns. To date, only 1 study has been published that addresses this issue. Further evidence is needed to evaluate whether transcutaneous bilirubin measurements improve clinical outcome, shorten length of stay, or decrease the readmission rate for newborns with hyperbilirubinemia.*

Strength/consensus of recommendation: I

Level of evidence: III (clinical experience, descriptive studies, and opinion)

Literature Search 3 summarizes the results of our literature search of MEDLINE OVID for peer-reviewed articles that address the effect of transcutaneous bilirubin measurements on clinical outcome, length of stay, or readmission rates for newborns who have been previously discharged. The literature addressing transcutaneous bilirubin testing and these concerns is limited. The majority of studies that have been published compare transcutaneous bilirubin measurements with chemical measurements performed in the clinical laboratory. Generally, good agreement has been reported between transcutaneous bilirubin measurements and measurements performed using blood. This finding has led many investigators to speculate that

transcutaneous bilirubin measurements will influence length of stay, clinical outcome, and readmission rates *(10)*. Unfortunately, well-designed prospective studies that address these issues are lacking. One study found that the mean time savings associated with performing a transcutaneous bilirubin measurement compared with measurement of serum bilirubin in a central laboratory was 2 h 22 min *(11)*. It is not clear whether this time savings had any impact on length of stay or clinical outcome.

A recently published study by Petersen et al. *(12)* compared readmission rates for hyperbilirubinemia, length of stay, days of treatment with phototherapy, and the number of bilirubin measurements performed within the clinical laboratory before and after the implementation of transcutaneous bilirubin measurements. They retrospectively studied 6603 newborns for 8 months before implementation of transcutaneous bilirubin measurements and for 8 months after transcutaneous bilirubin measurements. Implementation of transcutaneous bilirubin measurements was not associated with any change in the mean length of stay for normal newborns, newborns with hyperbilirubinemia requiring phototherapy before discharge, or the number of days of treatment with phototherapy. However, these investigators did find a significant reduction in the number of hospital readmissions per 1000 newborns for clinically significant hyperbilirubinemia, from a mean (SD) of 4.5 (2.4) to 1.8 (1.7) and a statistically significant increase in the monthly incidence of phototherapy treatment before discharge from 5.9% (1.3) to 7.7% (1.3) after implementation of transcutaneous bilirubin measurements. They speculated that the convenience and rapid turnaround time of transcutaneous bilirubin testing may have encouraged more effective screening and identification of newborns with clinically significant hyperbilirubinemia.

Is there an optimum frequency, timing, or site of transcutaneous bilirubin measurements that results in best agreement with bilirubin measurements performed using serum? (Literature Search 4)

Guideline 7. *Transcutaneous bilirubin measurements performed on the forehead or sternum are preferable to other sites and provide similar correlation with bilirubin measurements performed in serum when infants have not been exposed to sunlight or phototherapy. Bilirubin concentrations should be assessed by measurement of total bilirubin in serum or transcutaneous bilirubin measurements within the first 24 h after birth in all infants who are jaundiced. The need for and timing of repeated transcutaneous or serum bilirubin measurements should be assessed with nomograms according to the postnatal age and bilirubin concentration.*

Strength/consensus of recommendation: B

Level of evidence: II and III (well-designed correlation trials, clinical experience, and consensus opinion)

The forehead and sternum have been the sites most frequently used for transcutaneous bilirubin measurements and have been shown to correlate reasonably well with bilirubin measured in serum *(10, 13–16)*. The majority of studies that compared sites of transcutaneous bilirubin measurements have been performed with the Air-Shields (Air-Shields, Hatboro, PA) meter, with fewer reports involving the BiliChek (Respironics Inc., Murrysville, PA) meter. Five studies with the Air-Shields meter found the sternum to provide the best agreement with serum bilirubin *(17–21)*, 6 studies found no difference between readings taken from the forehead or sternum *(13, 22–26)*, and 2 studies reported that forehead readings became less reliable in infants older than 3 days *(27, 28)*. The decrease in correlation between forehead readings and bilirubin measured in serum was presumably due to exposure of the head to sunlight. Two studies performed with the BiliChek meter found the forehead to be the preferred site for transcutaneous measurements *(29, 30)*. Two studies found that transcutaneous bilirubin measurements taken at the forehead are lower in newborns who are crying, especially at higher concentrations of serum bilirubin *(22, 31)*.

One study of 336 Japanese newborns not receiving phototherapy evaluated 8 sites where transcutaneous measurements were made and compared these with serum bilirubin concentrations *(13)*. Readings taken from the forehead, chest, and sternum provided the best agreement ($r = 0.910–0.922$) with serum bilirubin measurements. Measurements taken from the abdomen and upper and lower back showed less agreement ($r = 0.89–0.888$), and measurements taken from the sole and heel demonstrated the poorest agreement with serum bilirubin ($r = 0.763–0.771$). A more recent study by Randeberg et al. *(32)* found that transcutaneous readings taken from the forehead correlated best with bilirubin measured in serum compared with transcutaneous measurements taken from the heel, back, or thigh. Other studies have found that the mean of individual readings taken from the forehead, chest, and sternum correlated best with serum bilirubin concentrations *(24, 33)*. Maisels et al. *(34)* found better correlation between transcutaneous measurements and serum bilirubin concentrations when transcutaneous measurements were performed on the sternum ($r = 0.953$) compared with the forehead ($r = 0.914$). They suggested that measurements from the sternum are less likely to be influenced by the effects of ambient light, particularly sunlight, and may be more desirable when measurements are taken after infants have been discharged.

The suggestion that capillary blood bilirubin concentrations are less than those of bilirubin found in arterial blood because of penetration of light through the vascular bed of infantile skin *(35)* has led some to speculate that the agreement between transcutaneous bilirubin concentrations and serum bilirubin concentrations may be affected by the site of blood collection. Amato et al. *(36)* compared transcutaneous bilirubin measurements with serum bilirubin concentrations measured in capillary blood and arterial blood. They found that the site where the blood sample was collected did not influence the agreement between transcutaneous bilirubin values and serum bilirubin concentrations.

Recommendations have been made by the American Academy of Pediatrics Clinical Practice Guidelines for the frequency of performing serum or transcutaneous bilirubin measurements *(7)*. These recommendations suggest that transcutaneous bilirubin or total serum bilirubin measurements be performed within the first 24 h after birth on every infant who is jaundiced. Furthermore, the need for and timing of repeated transcutaneous or serum bilirubin measurements depends on the postnatal age and bilirubin concentration. An hour-specific nomogram has been developed for determining the need for repeated measurements *(3, 4)*. However, an age-specific nomogram for newborns who addresses clinical risk factors for hyperbilirubinemia still needs to be developed *(7)*. Guidelines have also been established recommending that, before discharge, all newborns be assessed for the risk of developing severe hyperbilirubinemia. Predischarge assessment should be performed by measurement of bilirubin concentrations with total serum bilirubin or transcutaneous bilirubin or assessment of clinical risk factors.

Is the measurement of bilirubin by use of a transcutaneous method contraindicated for use in newborns who are undergoing phototherapy, premature infants, or newborns who are ill? (Literature Search 5)

Guideline 8. *Transcutaneous bilirubin measurements should not be performed on infants undergoing phototherapy. We also note that light exposure of infants who are discharged may also adversely affect the utility of transcutaneous measurements. The effect of gestational age on transcutaneous bilirubin measurements is less clear. Some reports suggest limiting the use of transcutaneous bilirubin measurements to newborns <30, 32 or 34 weeks' gestation, whereas others suggest no effect of gestational age. There are too few studies available that address the effect of underlying illness in newborns and its effect on use of transcutaneous bilirubin measurements.*

Strength/consensus of phototherapy recommendation: C

Level of evidence: II and III (well-designed clinical trials, descriptive studies, and consensus opinion)

Strength/consensus of premature/gestational age recommendation: C

Level of evidence: II (well-designed clinical trials, descriptive studies)

Strength/consensus of underlying illness recommendation: I

Literature Search 5 summarizes the results of our literature search of MEDLINE0 OVID for peer-reviewed articles that address the use of transcutaneous bilirubin measurements in newborns who are undergoing phototherapy, premature infants, or newborns who are ill. Although transcutaneous bilirubin measurements have been shown to correlate well with bilirubin concentrations measured in serum, there have been reports suggesting that transcutaneous measurements can be affected by a variety of factors, including use of phototherapy, birth weight, gestational age, and postnatal age *(17, 22, 27, 37–41)*.

Phototherapy has been reported by numerous investigators to adversely effect the correlation between transcutaneous bilirubin measurements and bilirubin measured in serum, and none recommend use of transcutaneous bilirubinometry in infants undergoing phototherapy *(17, 21, 30, 38, 40, 42–45)*. Phototherapy results in a blanching of the skin. Values obtained with transcutaneous bilirubin measurements have been shown to decrease rapidly after the implementation of phototherapy. The average decrease in transcutaneous measurements observed in 1 study of 9 neonates was 30% after 150 min of phototherapy, with much smaller decreases of 4% seen in the subsequent 150 min *(46)*. Another study reported a decrease in transcutaneous bilirubin measurements of 25% after 2 h of phototherapy and a 50% decrease after 12 h. The decrease in transcutaneous bilirubin measurements is much greater than that seen in serum bilirubin concentrations *(43)*. Exposure of infants to sunlight also has been found to adversely affect the correlation between transcutaneous and serum bilirubin measurements *(22, 27)*. This finding may limit the utility of transcutaneous bilirubin measurements on infants who are discharged and exposed to sunlight.

There is a lack of agreement on the effect of gestational age on the correlation between transcutaneous bilirubin measurements and bilirubin measured in serum. Two studies performed with the BiliChek meter suggested that this device be used only for infants >30 weeks' *(38)* or 32 weeks' *(30)* gestational age. However, another study that compared the BiliChek meter vs serum bilirubin measured using high-performance liquid chromatography (HPLC) found that gestational age did not affect the correlation between these 2 methods *(29)*. One study, performed with the Air-Shields meter, found that infants <34 weeks' gestational age had poorer agreement between transcutaneous bilirubin measurements and bilirubin measured in serum *(47)*.

One study used the BiliChek to evaluate the effect of newborn illness on transcutaneous measurements *(30)*. These authors found that the presence of hypoxia, hypoglycemia, infection, respiratory distress syndrome, or severity of illness did not adversely affect transcutaneous bilirubin measurements. Another study, also performed using the BiliChek meter, found that infants with bleeding or abdominal problems had similar agreement between transcutaneous bilirubin and serum bilirubin measurements compared with healthy newborns *(38)*.

Are transcutaneous bilirubin measurements associated with decreased blood sampling compared with serum bilirubin measurements? Do transcutaneous bilirubin measurements decrease the incidence of complications associated with blood collection such as infection or osteomyelitis? (Literature Search 6)

Continued on next page

Continued from previous page

Guideline 9. *There is insufficient evidence available to judge the impact of transcutaneous bilirubin measurements on number of blood samples collected from newborns. Whether there is any effect on complications of blood collection such as infection or osteomyelitis has not been adequately studied.*

Strength/consensus of recommendation: I

Measurement of serum bilirubin concentrations is one of the most frequent causes for collection of blood from newborn infants *(48)*. Blood sampling involves pain for newborn infants, and infant stress may have long-term adverse consequences *(49*, *50)*. In addition, there are other potential complications associated with blood collection from neonates, including the risk of infection and osteomyelitis *(51)*.

One aspect of transcutaneous bilirubin measurements that has been reported and should theoretically help improve clinical outcomes is the reduction in neonatal blood loss because of decreased blood sampling *(10*, *14*, *23*, *30*, *52*, *53)*. These studies suggest that a 20% to 34% reduction in samples collected for bilirubin analysis could be achieved after implementation of transcutaneous bilirubin measurements. However, not all investigators report any decrease in serum bilirubin measurements after the implementation of transcutaneous measurements. Bourchier et al. *(18)* found no difference in the number of serum bilirubin measurements performed after the introduction of transcutaneous bilirubin meter, and 1 study actually found an increase in the total number of bilirubin tests performed. Petersen et al. *(12)* found that the mean number of laboratory measurements of serum bilirubin did not change after the introduction of transcutaneous bilirubin testing. However, the total number of bilirubin measurements (serum bilirubin plus transcutaneous bilirubin) increased from a mean (SD) per newborn of 0.37 (0.08) to 0.61 (0.13).

The implementation of transcutaneous bilirubin measurements and its impact on lessening the risk of infection or osteomyelitis have not been addressed. However, one would not expect any decrease in these complications if the implementation of transcutaneous bilirubin determinations does not decrease the number of samples collected for biochemical analyses.

How does the accuracy of transcutaneous bilirubin measurements compare with total bilirubin measured in serum? (Literature Search 7)

Guideline 10. *We cannot recommend use of the ColorMate III (Chromatics Color Sciences International Inc., New York, NY) bilirubinometer, because of the limited number of published articles describing the performance of this instrument. Evaluation of jaundice with the Air-Shields or BiliChek seems to provide accuracy similar to that of serum bilirubin measurements. The BiliChek and Air-Shield have the advantage, compared with the ColorMate III, of not requiring a baseline measurement. Finally, we do not recommend assessment of bilirubin with use of the Ingram icterometer (Thomas A. Ingram and Co, Birmingham, England; distributed in the United States by Cascade Health Care Products, Salem, OR), because of its reliance on observer visualization of depth of yellow color of the skin.*

Strength/consensus of recommendation: B

Level of evidence: II (well-designed correlation trials, clinical experience, descriptive studies, and opinion)

Literature Search 7 summarizes the results of our literature search of MEDLINE OVID for peer-reviewed articles that address the accuracy of transcutaneous bilirubin measurements compared with bilirubin measured in serum. The literature addressing transcutaneous bilirubin testing and how it compares with serum bilirubin measurements is complicated by the fact that there are different instruments available for measuring transcutaneous bilirubin. Another important factor, often overlooked, is that the majority of studies that evaluate transcutaneous bilirubin measurements compare these measurements with bilirubin measured in serum by laboratory instruments that use diazo-based chemical methods. There is a recognized need to improve the precision and accuracy of bilirubin measurements performed in the clinical laboratory, especially in samples collected from neonates *(54*, *55)*. Collection of blood from newborns is often hemolyzed, and in vitro hemolysis is recognized as a source of error in bilirubin measurements because of release of hemoglobin and other intracellular compounds that can interfere with chemical-based measurement of bilirubin. In vitro hemolysis also represents the most common cause for rejection of specimens within the clinical laboratory *(56*, *57)*. There are several studies that have evaluated the accuracy and precision of transcutaneous bilirubin measurements compared with bilirubin measurements performed by HPLC *(3*, *29*, *58)*. These studies suggest that transcutaneous bilirubin measurements may be used not only as a screening device but also as a reliable substitute for standard serum bilirubin measurements. Evaluations of the accuracy of transcutaneous bilirubin measurements should be conducted with the most accurate methods available for determination of serum bilirubin.

A factor needing to be considered when transcutaneous bilirubin measurements and bilirubin measured in serum are compared is that bilirubin measured by a transcutaneous method and bilirubin measured in serum may represent different physiological characteristics. Rubaltelli et al. *(29)* suggested that bilirubin measured in serum and transcutaneous bilirubin measurements do not measure the same characteristic because laboratory-based methods measure bilirubin that is circulating in the blood, whereas transcutaneous methods measure the amount of bilirubin that has moved from the serum into the

tissues. Whether or not transcutaneous bilirubin methods offer additional information not provided by serum bilirubin measurements remains to be determined *(59)*.

The ColorMate III (Chromatics Color Sciences International Inc, New York, NY) transcutaneous bilirubinometer uses a xenon flash tube and light sensors to measure wavelengths from 400 to 700 nm, with filters to assess the reflectance of light at specific wavelengths. One drawback to use of this device is that a baseline reading, obtained shortly after birth, is required for infants. One article described the use of this device on 2441 infants *(10)*. Transcutaneous bilirubin results showed good correlation with bilirubin measured in serum ($r = 0.956$), and accuracy was not affected by race or weight. Repeated measurements of the same individual during 30 min showed a coefficient of variation of 3.1% at a bilirubin concentration of 144 μmol/L (8.4 mg/dL).

The Minolta/Air-Shields Jaundice Meter uses 2 wavelengths (460 nm and 550 nm) and a dual-optical-path system to measure bilirubin transcutaneously. The original Jaundice Meter and the JM-102 model generated readings as a unitless numerical index that had to be correlated to the total serum bilirubin measured in each population subset because race and gestational age significantly altered the results. Several studies reported better agreement between bilirubin measured with the Air-Shields transcutaneous bilirubin meter and serum bilirubin concentrations when baseline readings were performed *(37, 47, 60, 61)*. There is a lack of agreement concerning the correlation between transcutaneous bilirubin measurements and total bilirubin concentrations measured in serum. Some studies have reported that agreement between transcutaneous bilirubin measurements and bilirubin measured in serum are worse when serum bilirubin concentrations were >205 μmol/L (12 mg/dL) *(11, 62)*, whereas others reported poorer agreement when serum bilirubin concentrations were <205 μmol/L (12 mg/dL) *(25)*. Finally, others suggested that agreement between transcutaneous and serum bilirubin is independent of bilirubin concentrations *(24)*.

A number of studies have been performed comparing transcutaneous bilirubin measurements by the Air-Shields meter to serum bilirubin measured in the clinical laboratory. Correlation coefficients range from $r = 0.52$ to 0.96, with the majority of studies reporting correlation coefficients between $r = 0.70$ and 0.80 *(1, 13, 16, 18, 33, 34, 42, 60, 63–66)*. Differences in study design, the particular model of Air-Shields meter that was used, study population tested, site where transcutaneous measurements were performed, and method used to measure serum bilirubin concentrations probably account for the variability in the reported results. Studies performed with the most recent version of the Air-Shields meter, JM-103, show much better correlation with serum bilirubin compared with the earlier JM-101 and JM-102 models *(34)*. Many studies report that the Air-Shields meter performs better in infants with lighter skin compared with darker skin *(37, 15, 47, 60, 62, 67)*, although 1 study reported skin color to have no effect *(23)*. A single study reported that the correlation between transcutaneous bilirubin measured with the Air-Shields device and serum bilirubin concentrations was adversely affected by the presence of hemolytic disease *(68)*.

A recent transcutaneous meter that has been developed, BiliChek, uses reflectance data obtained from multiple wavelength readings from 400 nm to 760 nm. The use of multiple wavelength readings enables the instrument to correct for differences in skin pigmentation, thereby eliminating the need for performing a baseline reading. When evaluated against measurement of serum bilirubin with HPLC as a reference method, the BiliChek device has been shown to be more accurate compared with bilirubin measured using laboratory-based diazo techniques *(3, 29)*. Two studies performed a direct comparison between the BiliChek and Air-Shields meters. One study of 64 newborns found no difference in accuracy between the BiliChek and Air-Shields meters *(69)*. The 95th percentile confidence interval for both meters was ±65 μmol/L (3.8 mg/dL) compared with bilirubin measured in serum. Another study of 101 infants found the 95th percentile confidence interval of the Air-Shields meter to be ±68 μmol/L (4.0 mg/dL) vs ±34 μmol/L (2.0 mg/dL) for the BiliChek compared with bilirubin measured in serum *(70)*. Two studies found that, although the BiliChek meter showed good correlation with serum bilirubin measurements, the meter underestimated serum bilirubin concentrations by ~4 μmol/L (2.0 mg/dL), with the effect being more prevalent at increased concentrations of bilirubin *(1, 71)*.

In addition to assessment of bilirubin with use of transcutaneous meters, the Ingram Icterometer is also considered by some to be a type of transcutaneous bilirubin monitor. The Ingram icterometer consists of transparent Plexiglas (Altuglas International, Philadelphia, PA) containing stripes of differing yellow hue. The accuracy of this semiquantitative method depends on the ability of the user to visualize the degree of yellow color of the skin. A limited number of published articles describe the use of the icterometer. Comparison of bilirubin estimated with the icterometer with bilirubin concentrations measured in serum shows correlation coefficients ranging from $r = 0.63$ to greater than $r = 0.90$ *(16, 72–74)*.

Is measurement of bilirubin with a transcutaneous device more cost-effective compared with bilirubin measurements performed in the clinical laboratory? (Literature Search 8)

Guideline 11. *There is insufficient evidence to evaluate the cost-effectiveness of transcutaneous bilirubin measurements.*

Strength/consensus of recommendation: I

Level of Evidence: III (descriptive studies, opinion)

Literature Search 8 summarizes the results of our literature search of MEDLINE OVID for peer-reviewed articles that address the cost-effectiveness of transcutaneous bilirubin measurements. No studies have been performed to evaluate the actual costs associated with implementation of transcutaneous bilirubin measurements. Some studies suggest that the increased cost of transcutaneous bilirubin measurements is

offset by a decrease in the need for serum bilirubin measurements *(5*, *11*, *38)*. Petersen et al. *(12)* attempted to evaluate the costs associated with transcutaneous bilirubin measurements by estimating the impact of transcutaneous bilirubin measurements on hospital charges. They found that there were decreased charges as a result of fewer readmissions of newborns because of hyperbilirubinemia. However, the decrease in readmissions was offset by increased charges associated with transcutaneous bilirubin measurements and an increased number of newborns treated with phototherapy before discharge after the introduction of transcutaneous measurements. The net result was a small but statistically insignificant increase in charges after the introduction of transcutaneous bilirubin measurements. Because these authors report charges associated with implementation of transcutaneous bilirubin measurements, it is still not clear what the implementation of transcutaneous measurements does to actual costs.

Measurement of total bilirubin in serum remains the standard of care for the assessment of newborn jaundice. Replacement of serum bilirubin measurements by a transcutaneous method will require substantial investigation to understand its limitations and benefits. Clinical practice guidelines recently published by the American Academy of Pediatrics recommend that transcutaneous bilirubin measurement or a total serum bilirubin measurement be performed on every infant who is jaundiced, with repeated measurements performed according to the degree of the initial hyperbilirubinemia, the age of the infant, and the evolution of the hyperbilirubinemia *(7)*.

REFERENCES

1. Engle WD, Jackson GL, Sendelbach D, Manning D, Frawley WH. Assessment of a transcutaneous device in the evaluation of neonatal hyperbilirubinemia in a primary Hispanic population. Pediatrics 2002;110:61–7.
2. Maisels MJ, Newman TB. Jaundice in full-term and near-term babies who leave the hospital within 36 hours. Clin Perinatol 1998;25:295–302.
3. Bhutani VK, Gourley GR, Adler S, Kreamer B, Dalin C, Johnson LH. Noninvasive measurement of total serum bilirubin in a multiracial predischarge newborn population to assess the risk of severe hyperbilirubinemia. Pediatrics 2000;106:11. http://www.pediatrics.org/cgi/content/ full/106/2/e17 (Accessed March 2006).
4. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999;103:6–14.
5. Maisels MJ, Kring E. Length of stay, jaundice, and hospital admissions. Pediatrics 1998;101:995–8.
6. Lee KS, Perlman M, Ballantyne M, Elliott I, To T. Association between duration of neonatal hospital stay and readmission rate. J Pediatr 1995;127:758–66.
7. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114: 297–316.
8. Ip S, Chung M, Kulig J, O'Brien R, Sege R, Glicken S, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics 2004;114:130–53. http://www.pediatrics.org/cgi/content/full/114/1/e130 (Accessed March 2006).
9. Stevenson D, Fanaroff A, Maisels J, Young B, Wong R, Vreman H, et al. Prediction of hyperbilirubinemia in near-term and term infants. Pediatrics 2001;108:31–9.
10. Tayaba R, Gribetz D, Gribetz I, Holtzman IR. Noninvasive estimation of serum bilirubin. Pediatrics 1998;102:7. http://www.pediatrics.org/cgi/content/full/102/3/e28 (Accessed March 2006).
11. Suckling RJ, Laing IA, Kirk JM. Transcutaneous bilirubinometry as a screening tool for neonatal jaundice. Scot Med J 1995;40: 14–5.
12. Petersen JR, Okorodudu AO, Mohammad AA, Fernando A, Shattuck KE. Association of transcutaneous bilirubin testing in hospital with decreased readmission rate for hyperbilirubinemia. Clin Chem 2005;51:540–4.
13. Yamauchi Y, Yamanouchi I. Transcutaneous bilirubinometry: evaluation of accuracy and reliability in a large population. Acta Paediatr Scand 1988;77:791–5.
14. Maisels MJ, Kring E. Transcutaneous bilirubinometry (TcB) decreases the need for serum bilirubin measurements (SB) and save money [abstract]. Pediatr Res 1994;35:239A.
15. Tan KL, Chia HP, Koh BC. Transcutaneous bilirubinometry in Chinese, Malay and Indian infants. Acta Paediatr 1996;85:986–90.
16. Bilgen H, Ince Z, Ozek E, Bekiroglu N, Ors R. Transcutaneous measurement of hyperbilirubinemia: comparison of the Minolta jaundice and the Ingram icterometer. Ann Trop Paediatr 1998;18:325–8.
17. Tan KL, Dong F. Transcutaneous bilirubinometry during and after phototherapy. Acta Paediatr 2003;92:327–31.
18. Bourchier D, Cull AB, Oettli PE. Transcutaneous bilirubinometry: 22 months experience at Waikato Women's Hospital. N Z Med J 1987;100:599–600.
19. Carbonell X, Botet F, Figueras J, Riu-Godo A. Prediction of hyperbilirubinemia in the healthy term newborn. Acta Paediatr 2001;90:166–70.
20. Lin YJ, Ju SH, Lin CH. The clinical application of transcutaneous bilirubinometry in full-term Chinese infants. Acta Paediatr Singapore 1993;34:69–76.
21. Fok TF, Lau SP, Jui CW, Wan CW. Transcutaneous bilirubinometer: its use in Chinese term infants and the effect of haematocrit and phototherapy on the TcB index. Aust Paediatr J 1986;22: 107–9.
22. Yamauchi Y, Yamanouchi I. Transcutaneous bilirubinometry: variability of TcB measurements on the forehead with crying. Acta Paediatr Jpn 1991;33:655–7.
23. Dai J, Krahn J, Parry DM. Clinical impact of transcutaneous bilirubinometry as an adjunctive screen for hyperbilirubinemia. Clin Biochem 1996;29:581–6.
24. Maisels MJ, Conrad S. Transcutaneous bilirubin measurements in full term infants. Pediatrics 1982;70:464–7.
25. Tan KL, Mylvaganam A. Transcutaneous bilirubinometry in preterm very low birth weight infants. Acta Paediatr Scand 1988; 77:796–801.
26. Yamauchi Y, Yamanouchi I. Transcutaneous bilirubinometry in normal Japanese infants. Acta Paediatr Jpn 1989;31:65–72.
27. Yamauchi Y, Yamanouchi I. Transcutaneous bilirubinometry: effect of postnatal age. Acta Paediatr Jpn 1991;33:663–7.
28. Yamauchi Y, Yamanouchi I. Factors affecting transcutaneous bilirubin measurement: effect of daylight. Acta Paediatr Jpn 1991;33:658–62.

29. Rubaltelli FF, Gourley GR, Loskamp N, Modi N, Roth-Kleiner AM, Sender A, et al. Transcutaneous bilirubin measurement: a multicenter evaluation of a new device. Pediatrics 2004;107:1264–71.
30. Ebbesen F, Rasmussen LM, Wimberley PD. A new transcutaneous bilirubinometer, BiliCheck, used in the neonatal intensive care unit and the maternity ward. Acta Paediatr 2002;91:203–11.
31. Yamauchi Y, Yamanouchi I. Transcutaneous bilirubinometry: interinstrumental variability of TcB instruments. Acta Paediatr Scand 1989;78:844–7.
32. Randeberg LL, Roll EB, Nilsen LTN, Christensen T, Svaasand LO. In vivo spectroscopy of jaundiced newborn skin reveals more than a bilirubin index. Acta Paediatr 2005;94:65–71.
33. Laeeq A, Yasin M, Chaudhry AR. Transcutaneous bilirubinometry: clinical application. J Pak Med Assoc 1993;43:28–30.
34. Maisels MJ, Ostrea EM Jr, Touch S, Clune SE, Cepeda E, Kring E, et al. Evaluation of a new transcutaneous bilirubinometer. Pediatrics 2004;113:1628–35.
35. Sisson TRC, Wickler M. Transmission of light through living tissue [abstract]. Pediatr Res 1973;7:316.
36. Amato M, Huppi P, Markus D. Assessment of neonatal jaundice in low birth weight infants comparing transcutaneous, capillary, and arterial bilirubin levels. Eur J Pediatr 1990;150:59–61.
37. Onks D, Silverman L, Robertson A. Effect of melanin, oxyhemoglobin, and bilirubin on transcutaneous bilirubinometry. Acta Paediatr 1993;82:19–22.
38. Knupfer M, Pulzer F, Braun L, Heilmann A, Robel-Tillig E, Vogtmann C. Transcutaneous bilirubinometry in preterm infants. Acta Paediatr 2001;90:899–903.
39. Ozkan H, Oren H, Duman N, Duman M. Derman bilirubin kinetics during phototherapy in term neonates. Acta Paediatr 2003; 92:577–81.
40. Yamauchi Y, Yamanouchi I. Transcutaneous bilirubinometry: effect of irradiation on the skin bilirubin index. Biol Neonate 1988;54:314–9.
41. Amit Y, Jabour S, Arad ID. Effect of skinfold thickness on transcutaneous bilirubin measurements. Biol Neonate 1993;63:209–14.
42. Kumar A, Faridi MMA, Singh N, Ahmad SH. Transcutaneous bilirubinometry in the management of bilirubinemia in term neonates. Indian J Med Res 1994;99:227–30.
43. Hegyi T, Hiatt IM, Indyk L. Transcutaneous bilirubinometry I: correlations in term infants. J Pediatr 1981;98:454–7.
44. Yamauchi Y, Yamanouchi I. Transcutaneous bilirubinometry: bilirubin kinetics of the skin and serum during and after phototherapy. Biol Neonate 1989;56:263–9.
45. Tudehope DI, Chang A. Non-invasive method of measuring bilirubin levels in newborn infants. Med J Aust 1982;1:165–8.
46. Shinwell ES, Sciaky Y, Karplus M. Effect of position changing on bilirubin levels during phototherapy. J Perinatol 2002;22:226–9.
47. Knudsen A, Ebbesen F. Transcutaneous bilirubinometry in neonatal intensive care units. Arch Dis Child 1996;75:F53–6.
48. Madsen LP, Rasmussen MK, Bjerregaard LL, Nøhr SB, Ebbesen F. Impact of blood sampling in very preterm infants. Scand J Clin Lab Invest 2000;60:125–32.
49. Brown L. Physiologic response to cutaneous pain in neonates. Neonatal Netw 1987;5:18–21.
50. Owens ME, Todt EH. Pain in infancy: reaction to heel lance. Pain 1984;20:77–86.
51. Wimberley PD, Lou HC, Pedersen H, Hejl M, Lassen NA, Friis-Hansen B. Hypertensive peaks in the pathogenesis of intraventricular haemorrhage in the newborn: abolition by phenobarbitone sedation. Acta Paediatr Scand 1982;71:537–42.
52. Briscoe L, Clark S, Yoxall CW. Can transcutaneous bilirubinometry reduce the need for blood tests in jaundiced full term babies? Arch Dis Child Fetal Neonatal Ed 2002;86:F190–2.
53. Stevenson DK, Wong RJ, Vreman HJ, McDonagh AF, Maisels MJ, Lightner DA. NICHD conference on kernicterus: research on prevention of bilirubin-induced brain injury and kernicterus: bench-to-bedside: diagnostic methods and prevention and treatment strategies. J Perinatol 2004;24:521–5.
54. Vreman HJ, Verter J, Oh W, Fanaroff AA, Wright LL, Lemons JA, et al. Interlaboratory variability of bilirubin measurements. Clin Chem 1996;42:869–73.
55. Lo S, Doumas BT, Ashwood E. Performance of bilirubin determinations in US laboratories: revisited. Clin Chem 2004;50:190–4.
56. Jones BA, Calam RR, Howanitz PJ. Chemistry specimen acceptability: a College of American Pathologists Q-Probes study of 435 laboratories. Arch Pathol Lab Med 1997;121:19–26.
57. Kazmierczak SC, Robertson AF, Briley KP. Comparison of hemolysis in blood samples collected using an automatic incision device and a manual lance. Arch Pediatr Adolesc Med 2002; 156:1072–4.
58. Kazmierczak SC, Robertson AF, Briley KP, Kreamer B, Gourley GR. Transcutaneous measurement of bilirubin in newborns: comparison with an automated Jendrassik-Grof procedure and HPLC. Clin Chem 2004;50:433–5.
59. Stevenson DK, Wong RJ, Vreman HJ. Reduction in hospital readmission rates for hyperbilirubinemia is associated with use of transcutaneous bilirubin measurements [editorial]. Clin Chem 2005;51:481–2.
60. Linder N, Regev A, Gazit G, Carplus M, Mandelberg A, Tamir I, et al. Noninvasive determination of neonatal hyperbilirubinemia: standardization for variation in skin color. Am J Perinatol 1994;11:223–5.
61. Knudsen A. Predicting the need for phototherapy in healthy mature neonates using transcutaneous bilirubinometry on the first postnatal day. Biol Neonate 1995;68:398–403.
62. Tan KL. Transcutaneous bilirubinometry in Chinese and Malay infants. Ann Acad Med Singapore 1985;14:591–4.
63. Bhat V, Srinivasan S, Usha TS, Puri RK. Correlation of transcutaneous bilirubinometry with serum bilirubin in south Indian neonates. Indian J Med Res 1987;86:49–52.
64. Bhutta ZA, Yusuf K. Transcutaneous bilirubinometry in Pakistani newborns: a preliminary report. J Pakistan Med Assoc 1991; 41:155–6.
65. Brown LP, Arnold L, Allison D, Jacobsen B, Klein ME, Charsha D. Transcutaneous bilirubinometer: intermeter reliability. J Perinatol 1990;10:167–9.
66. Kivlahan C, James EJP. The natural history of neonatal jaundice. Pediatrics 1984;74:364–70.
67. Karrar Z, Al Habib S, Al Basit OB, Ashong F, Osundwa V. Transcutaneous bilirubin measurements in Saudi infants: the use of the jaundice meter to identify significant jaundice. Ann Trop Paediatr 1989;9:59–61.
68. Sheridan-Pereira M, Gorman W. Transcutaneous bilirubinometry: an evaluation. Arch Dis Child 1982;57:708–20.
69. Wong CM, Van Dijk PJE, Laing IA. A comparison of transcutaneous bilirubinometers: SpectRx BiliCheck versus Minolta AirShields. Arch Dis Child Fetal Neonatal Ed 2002;87:F137–40.
70. Robertson A, Kazmierczak S, Vos P. Improved transcutaneous bilirubinometry: comparison of SpectRx, BiliCheck, and Minolta jaundice meter JM-102 for estimating total serum bilirubin in a normal newborn population. J Perinatol 2002;22:12–4.

71. Yap SH, Mohammad I, Ryan CA. Avoiding painful blood sampling in neonates by transcutaneous bilirubinometry. Irish J Med Sci 2002;171:188–90.
72. Schumacher RE, Thornberry JM, Gutcher GR. Transcutaneous bilirubinometry: a comparison of old and new methods. Pediatrics 1985;76:10–14.
73. Chaibva NT, Fenner A, Wolfsdorf J. Reliability of an icterometer in black neonates with hyperbilirubinemia. S Afr Med J 1974; 48:1533–4.
74. Gupta PC, Kumari S, Mullick DN, Lal UB. Icterometer: a useful screening tool for neonatal jaundice. Indian Pediatr 1991;285: 473–6.

PUBLIC COMMENTS

No public comments were received on the guidelines.

Chapter **3**

Use of Cardiac Biomarkers for Acute Coronary Syndromes

Alan B. Storrow, Fred S. Apple, Alan H.B. Wu, Robert Jesse, Gary Francis, and Robert H. Christenson

INTRODUCTION

The disposition of patients with chest pain from the emergency department (ED) is one of the most difficult challenges that face caregivers. Admission of patients with a low probability of acute coronary syndrome (ACS) often leads to excessive hospital costs *(1)*. A strategy that is too liberal with regard to ED discharges may lead to higher numbers of patients released with acute myocardial infarction (AMI). Inappropriate discharge of ED patients who have AMI has been estimated to occur in 2%–5% of patients and is the single most common cause of malpractice lawsuits against ED physicians *(2, 3)*.

The scope of the recommendations presented here involves use of biomarkers of cardiac injury in the ED. The clinical questions addressed include administrative issues and cost-effectiveness, as well as clinical and technical performance of cardiac biomarkers. Search strategies were used to examine PubMed and EMBASE databases. Only articles in the English language were included.

Who are the stakeholders who should be involved in developing an accelerated protocol for use of biomarkers for evaluation of patients with possible ACS?

Guideline 12. *Members of EDs, primary care physicians, divisions of cardiology, hospital administrations, and clinical laboratories should work collectively to develop an accelerated protocol for the use of biochemical markers in the evaluation of patients with possible ACS.*

Strength/consensus of recommendation: A

Level of evidence: III

No clinical trials have examined the outcome of collaborative development of accelerated protocols vs development of such protocols by one specific group. Although the recommendation that laboratorians should work with ED physicians, primary care physicians, cardiologists, and hospital administration may appear obvious *(4)*, in actual practice decisions on testing protocols are often made without input from the laboratory. Laboratory directors must be aggressive in requesting that qualified personnel be part of organizational and operating committees when such discussions are being conducted or should initiate the discussions themselves.

Many hospitals today have a dedicated area within the ED for the rapid evaluation of patients with potential ACS. These areas are frequently designated as "chest pain centers," "heart emergency rooms," or some other term to indicate that the efficient evaluation and management of patients with chest pain or other signs and symptoms of ACS is a major objective of that center *(5–8)*. Essential for early AMI rule-out is frequent electrocardiographic testing and blood collections for the measurement of cardiac biomarkers. Patients with negative results for these tests on a serial basis most likely do not have an AMI. They may, however, have UA or other forms of acute cardiovascular disease. For these patients, it is appropriate to perform additional studies such as a stress test, echocardiogram, or radionuclide myocardial perfusion imaging for risk stratification *(5–10)*. Establishment of a clinical practice guideline for the evaluation of patients with chest pain will reduce the variability of practices among physicians and institutions and at the same time improve the accuracy of disposition decisions *(11)*. Consensus on the merits of this approach was overwhelmingly favorable.

Where should accelerated protocols for diagnosis or the rule-out of AMI be implemented?

Guideline 13. *For simplicity, this protocol should apply to either the facilitated diagnosis or the rule-out of AMI in the ED or to routine diagnosis from other areas of the hospital, should a patient develop symptoms consistent with ACS while hospitalized.*

Strength/consensus of recommendation: B

Level of evidence: III

No clinical trials have been performed to examine the outcome of accelerated protocols in the ED vs other patient care

locations. Consensus from the committee and feedback from conferences is that for "routine AMI diagnosis" of patients who are already hospitalized for other reasons, the same criteria should apply as are used in the ED. Some physicians or administrators may believe that rapid AMI rule-out of hospitalized patients is less important than rapid evaluation and disposition of ED patients. Nevertheless, the committee felt that the same protocol used in the ED is appropriate for routine AMI diagnosis because new therapies for ACS are available and, when appropriate, should be delivered rapidly *(2, 12)*. The use of a rapid AMI rule-out protocol will simplify the steps needed from the laboratory's perspective and provide physicians optimum diagnostic measures for all patients. Consensus on the merits of this approach was favorable overall.

How should the effectiveness of accelerated protocols for diagnosis or the rule-out of AMI be assessed and measured?

Guideline 14. *Members of EDs, divisions of cardiology, primary care physicians, hospital administrations, and clinical laboratories should work collectively to use quality-assurance measures, evidence-based guidelines, and monitoring to reduce medical error and improve the treatment of patients with possible ACS.*

Strength/consensus of recommendation: A

Level of evidence: III

Registry and other data *(13–17)* have suggested that quality assurance activities improve patient outcomes. Consensus on the merits of this approach was overwhelmingly favorable.

What should be the reference point for reporting the temporal sequence of blood specimens for patients suspected of having ACS?

Guideline 15. *For routine clinical practice, blood collections should be referenced relative to the time of presentation to the ED and (when available) the reported time of chest-pain onset.*

Strength/consensus of recommendation: A

Level of evidence: III

Although the time of chest-pain onset for AMI patients is sometimes known, this information is less available or reliable for those with unstable angina or other cardiac diseases. It is common for these patients to report multiple episodes of chest pain during the hours or days before ED presentation. The pathophysiology of ACS is dynamic and includes intermittent closure and spontaneous reperfusion of coronary arteries with ruptured atherosclerotic plaques. In the elderly or in patients with diabetes mellitus, there may be altered thresholds or a blunted response to pain. Indeed, there are many patients with ACS who experience silent ischemia and infarction (ie, no pain during occlusive episodes) *(18)*. The time of presentation is most reliable as a reference point; however, additional information may be added when the actual time of chest pain (equivalent) is available. Thus, many reviewers felt it important to also note the time of onset of chest pain, especially when there is a history of a single chest-pain event (and not several events during many days) and when the time of onset as reported by the patient or family is deemed to be reliable. It may also provide an explanation as to why some clinical studies fail to document a consistent rise in the concentration of the marker, eg, at 6 h, whereas other studies indicate that the markers were increased at this point in all patients (eg, when the majority of enrolled patients in the study present beyond 6 h of chest pain).

In addition to members of EDs, primary care physicians, divisions of cardiology, hospital administrations, and clinical laboratories, are there others who need to be involved in accelerated pathways for ACS patients?

Guideline 16. *The multidisciplinary team must include personnel knowledgeable about local reimbursement. Vendors should work with customers to help optimize cost-effective provision of biomarker testing.*

Strength/consensus of recommendation: A

Level of evidence: II

Biomarker testing cannot be justified if the laboratory or hospital cannot receive reasonable reimbursement for the service. Thus, an important issue that must be resolved at each institution is reimbursement for testing. For example, the Center for Medicare and Medicaid Services announced that "it is not necessary to use troponin in addition to creatine kinase (CPT codes 82550-82554) (which includes the MB isoenzyme) in the management of patients with myocardial infarctions," suggesting that reimbursement will not be given when both tests are ordered *(19)*. Private insurance companies may also limit reimbursements for cardiac biomarkers. Guidelines recommend use of cardiac troponin as the new standard for myocardial injury, but there is still a role for both CK-MB and cardiac troponin assays (see NACB guidelines on "Cardiac Biomarkers of ACS").

How rapidly are results of cardiac biomarker testing needed by clinicians? What standard for measurement for turnaround time (TAT) should be used?

Guideline 17. *The laboratory should perform cardiac marker testing with a TAT of 1 h, optimally 30 min, or less. The TAT is defined as the time from blood collection to the reporting of results.*

Strength/consensus of recommendation: A

Level of evidence: II

AMI patients with ST-segment elevation on the ECG can be effectively treated with thrombolytic therapy, particularly if therapy is initiated within 12 h after the onset of chest pain. Delays in implementation will reduce the success of this treatment. As such, the National Heart Attack Alert Program has made a recommendation to physicians to treat all AMI patients within 60 min of their arrival in the ED *(20)*. However, results for serum cardiac markers are not needed in making this therapeutic decision.

Rapid testing and reporting of cardiac marker concentrations may produce other benefits for cardiac patients. Identification of high-risk patients by rapid troponin testing has been suggested to improve outcome in those patients eligible for advanced therapies *(2, 12, 21)*. Patients with non–ST-elevation AMI have been shown to benefit from early percutaneous intervention *(5, 21, 22)* or glycoprotein IIb/IIIa inhibitors *(23)*. Rapid cardiac marker testing may lead to earlier detection and use of these therapies. Most (75%) of the 1352 ED physicians surveyed in a recent Q-probes study by the College of American Pathologists believed that the results of tests measuring myocardial injury should be reported back to them in 45 min or less, using as the reference point the ordering time of the tests *(4)*. Consensus of the committee and feedback on draft documents are that providing rapid testing will lead to more time-efficient disposition decisions.

The factors that affect TATs include the delay in the delivery of the sample to the laboratory, the preanalytical steps necessary to prepare the sample, the analysis time, and delivery of results to the ordering physician. The committee acknowledges that the time taken for the delivery of samples to the laboratory is not always under the control of the laboratory. Nevertheless, laboratory personnel should work closely with hospital administrators, specimen couriers, and nursing staff to minimize delays. TATs can be improved with the implementation of pneumatic tubes that deliver samples directly and rapidly to the central laboratory. The use of satellite laboratories is another mechanism to reduce delivery time reporting TATs, improve clinician satisfaction, and decrease length of patient stay in the ED *(24)*.

It is complicated for laboratories to consistently (>90%) deliver cardiac biomarker results in <30 min with laboratory-based serum or plasma assays. Results of cardiac marker testing are not used to guide thrombolytic therapy, and there is no clear evidence that availability of rapid biomarker results leads to better patient outcomes. Moreover, rule-out of AMI from the ED requires results of serial sampling, which does not support need for a very rapid TAT on any single sample. The committee recognizes the controversy surrounding time from, as well as the need for, a standard definition of TAT (Figure 1). Nonetheless, caregiver consensus clearly indicates that rapid availability of results is desirable and that time to patient disposition is expedited by rapid availability of cardiac biomarkers.

Is there a recommended strategy for laboratories that are unable to deliver cardiac biomarker results in a time frame of 1 h from time of collection to result reporting?

Guideline 18. *Institutions that cannot consistently deliver cardiac marker TATs of ~1 h should implement POC testing devices.*

Strength/consensus of recommendation: B

Level of evidence: II

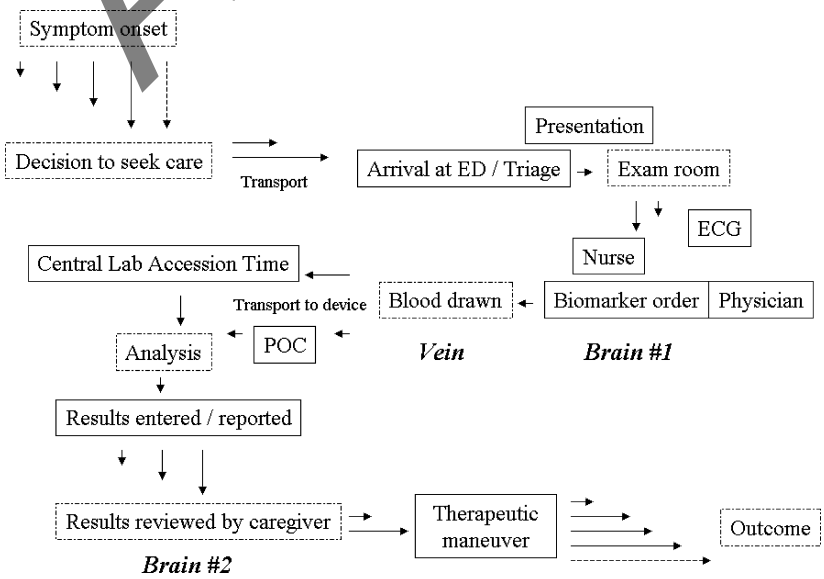

Figure 3-1 Time-point options available to define turnaround time (TAT). Solid boxes indicate times generally recorded or known (hard times), whereas dashed boxes indicate times generally not, or variably, recorded (soft times). Arrow length grossly represents time duration; dashed arrows indicate times with large variability.

Some laboratories do not have automated immunoassay analyzers, rapid-tube delivery systems, or staffing to deliver results within 1 h on a continual or consistent basis. It has been suggested that laboratory-based TATs for myocardial injury do not meet the expectations of either laboratory personnel or emergency physicians *(4)*.

Qualitative, as well as quantitative, POC testing devices are now available for myoglobin, CK-MB, cTnT, and cTnI *(25–41)*, many in multimarker formats. These assays make use of anticoagulated whole blood and have analyzer times of <20 min. Eliminating the need to deliver samples to the central laboratory and centrifugation enables TATs of <30 min. Results obtained with POC cardiac marker testing, compared with central laboratories, have universally suggested significant decreases in TAT *(24, 35, 37, 39, 40, 42–50)*. In addition, the introduction of POC testing has been reported to reduce total ED length of stay *(49, 51)*.

The committee recognizes the lack of evidence supporting cardiac POC testing in the prehospital setting, although this use has shown some promise *(52, 53)*. Likewise, remote location testing, such as on cruise ships, may offer unique advantages but needs further investigation *(54, 55)*.

Although outcome studies have shown that rapid availability of testing and reporting of results for cardiac markers, as well as b-type natriuretic peptide, reduces hospital length of stay and laboratory costs for cardiac patients *(33, 35, 51, 56–58)*, there are no outcome studies to validate the specific need for a 1-h TAT.

However, there is some limited evidence that earlier treatment of high-risk ACS with GP IIb/IIIa inhibitors improves outcome *(15, 21, 22)*, as well as early intervention with PCI *(22, 59–65)*. With the development of new therapeutic strategies for unstable angina and non–Q-wave AMI *(12)*, the committee anticipates that early detection of any myocardial injury will also be beneficial in the treatment of these patients. For those patients who are ruled out for ACS, it is expected that fast TATs for laboratory data will lead to expedited patient discharge and a reduction in overall hospital costs. The NACB Committee encourages prospective outcome studies to examine the putative advantage of reporting TATs within 1 h.

In addition, it is not clear what impact POC cardiac marker testing might have on patient satisfaction, a notoriously multifactorial issue *(66–80)*. However, consensus indicates that a shorter ED length of stay clearly improves patient satisfaction. Whether such satisfaction is a function of POC testing remains to be investigated.

What should be the performance specifications and characteristics of POC technology for measurement of cardiac biomarkers?

Guideline 19. *Performance specifications and characteristics for central laboratory and POC platforms should not differ.*

Strength/consensus of recommendation: A

Level of evidence: III

Consensus of the committee and that from various conferences indicate that the cardiac biomarker criteria for AMI will not differ according to what type of assays are used or performance location. Thus, it is obvious that specifications and performance characteristics for assays must be consistent, regardless of performance platform. Current specifications and performance characteristics for cardiac biomarker assays can be found in the NACB Laboratory Medicine Practice Guideline for Biomarkers of Acute Coronary Syndromes and Heart Failure, Analytical Considerations Section.

What stakeholder(s) should be involved in device and platform selection, training, operator competency assessment, maintenance of POC equipment, and compliance with regulatory requirements?

Guideline 20. *Laboratory personnel must be involved in selection of devices, the training of individuals to perform the analysis, the maintenance of POC equipment, the verification of the proficiency of operators on a regular basis, and the compliance of documentation with requirements by regulatory agencies.*

Strength/consensus of recommendation: A

Level of evidence: III

POC devices are designed for testing to be performed at or near the bedside by primary caregivers. However, the responsibility for such testing must reside with the laboratory; involvement must include selection of POC devices, education, training, maintenance, and quality assurance *(43, 52)*. The success of POC testing programs will depend on cooperation and the acknowledgment of the laboratory's responsibility by hospital administrations, nursing staff, and the appropriate units within the institution.

When the laboratory staff recognizes a situation of noncompliance, they must have the authority to remove POC testing devices and suspend testing from the area where the testing was conducted until the deficiencies have been satisfactorily corrected.

Are qualitative (positive/negative) devices appropriate for assessment of cardiac biomarker results?

Guideline 21. *Although it is recognized that qualitative systems do provide useful information, it is recommended that POC systems provide quantitative results.*

Strength/consensus of recommendation: B

Level of evidence: II

The committee recognizes the lack of evidence suggesting improved outcomes using quantitative systems vs qualitative. However, quantitative results offer particular strengths in risk stratification and low-end sensitivity *(81–83)*.

What is the process that should be used as new boimarkers are developed and introduced into clinical use?

Guideline 22. *Early in the process, manufacturers are encouraged to seek assistance and provide support to professional organizations such as the AACC and IFCC to develop committees for standardizing and establishing performance specifications for new analytes. These organizations will determine the need for analyte standardization according to the potential clinical importance of the marker and gather the necessary scientific expertise for the formation of a standardization committee.*

Strength/consensus of recommendation: A

Level of evidence: III

New markers will continue to be developed and examined for patients with ACS. When a marker such as cardiac troponin demonstrates major advantages over existing markers, there is an urgency for manufacturers to develop and market commercial assays. In the specific cases of CK-MB mass and cTnI assays, there were no cooperative attempts to develop reference materials or to standardize results.

The NACB Committee acknowledges that the exclusive release of new markers may be in the manufacturer's best interests in terms of profitability, and therefore, they may be reluctant to share ideas and needs with their colleagues. Nevertheless, the implementation of new tests is more easily integrated into the laboratory when these markers are available on a wide spectrum of analyzers, and it is in the best interests of the medical community and the in vitro diagnostic industry that assays correlate to one another.

Assays for cardiac markers for early diagnosis, rule-out, triaging of patients from the ED, or for determination of successful reperfusion require markers that have a short assay TAT. Irrespective of how the testing is performed (ie, laboratory-based or POC testing), assays must meet minimum precision requirements. Imprecise assays at or near cutoff concentrations will adversely affect the clinical performance of the test. The committee understands the importance of establishing objective analytical goals for assays for new cardiac markers, which will assist manufacturers in the construction of new assays.

REFERENCES

1. Tierney WM, Fitzgerald J, McHenry R, Roth BJ, Psaty B, Stump DL, et al. Physicians' estimates of the probability of myocardial infarction in emergency room patients with chest pain. Med Decis Making 1986;6:12–7.
2. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. American College of Cardiology, American Heart Association Task Force on Practice Guidelines, Canadian Cardiovascular Society. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110:e82–292.
3. Rusnak RA, Stair TO, Hansen K, Fastow JS. Litigation against the emergency physician: common features in cases of missed myocardial infarction. Ann Emerg Med 1989;18:1029–34.
4. Novis DA, Jones BA, Dale JC, Walsh MK. Biochemical markers of myocardial injury test turnaround time: a College of American Pathologists Q-Probes study of 7020 troponin and 4368 creatine kinase-MB determinations in 159 institutions. Arch Pathol Lab Med 2004;128:158–64.
5. Storrow AB, Gibler WB. Chest pain centers: diagnosis of acute coronary syndromes. Ann Emerg Med 2000;35:449–61.
6. Tatum JL, Jesse RL, Kontos MC, Nicholson CS, Schmidt KL, Roberts CS, Ornato JP. Comprehensive strategy for the evaluation and triage of the chest pain patient. Ann Emerg Med 1997;29:116–25.
7. Gibler WB, Runyon JP, Levy RC, Sayre MR, Kacich R, Hattemer CR, A rapid diagnostic and treatment center for patients with chest pain in the emergency department. Ann Emerg Med 1995;25:1–8.
8. Farkouh ME, Smars PA, Reeder GS, Zinsmeister AR, Evans RW, Meloy TD, et al. A clinical trial of a chest-pain observation unit for patients with unstable angina: Chest Pain Evaluation in the Emergency Room (CHEER) Investigators. N Engl J Med 1998;339:1882–8.
9. Fesmire FM. A rapid protocol to identify and exclude acute myocardial infarction: continuous 12-lead ECG monitoring with 2-hour delta CK-MB. Am J Emerg Med 2000;18:698–702.
10. Fesmire FM, Hughes AD, Fody EP, Jackson AP, Fesmire CE, Gilbert MA, et al. The Erlanger chest pain evaluation protocol: a one-year experience with serial 12-lead ECG monitoring, two-hour delta serum marker measurements, and selective nuclear stress testing to identify and exclude acute coronary syndromes. Ann Emerg Med 2002;40:584–94.
11. Lewis S. Paradox, process and perception: the role of organizations in clinical practice guidelines development. CMAJ 1995; 153:1073–7.
12. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. American College of Cardiology; American Heart Association, Committee on the Management of Patients with Unstable Angina. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). J Am Coll Cardiol 2002;40:1366–74.
13. Mehta RH, Newby LK, Patel Y, Hoekstra JW, Miller CD, Chen AY, et al. The impact of emergency department structure and care processes in delivering care for non-ST-segment elevation acute coronary syndromes. Am Heart J 2006;152:648–60.
14. Peterson ED, Roe MT, Mulgund J, DeLong ER, Lytle BL, Brindis RG, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. JAMA 2006;295:1912–20.
15. Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA 2004;292:2096–104.
16. Hoekstra JW, Pollack CV Jr, Roe MT, Peterson ED, Brindis R, Harrington RA, et al. Improving the care of patients with non-ST-elevation acute coronary syndromes in the emergency department: the CRUSADE initiative. Acad Emerg Med 2002;9:1146–55.

17. Roe MT, Ohman EM, Pollack CV Jr, Peterson ED, Brindis RG, Harrington RA, et al. Changing the model of care for patients with acute coronary syndromes. Am Heart J 2003;146:605–12.
18. Cohn PF. Silent myocardial ischemia: an update. Adv Intern Med 1989;34:377–92.
19. Health Care Financing Administration (HCFA). Revision of Troponin Policy: Medicare Part A. Dallas, TX: HCFA, 1998:6–7.
20. National Heart Attack Alert Program Coordinating Committee. Emergency department: rapid identification and treatment of patients with acute myocardial infarction: National Heart Attack Alert Program Coordinating Committee, 60 Minutes to Treatment Working Group. Ann Emerg Med 1994;23:311–29.
21. Bhatt DL, Topol EJ. Current role of platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. JAMA 2000;284:1549–58.
22. Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy: Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. N Engl J Med 1998; 338:1785–92.
23. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)-Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879–87.
24. Lee-Lewandrowski E, Corboy D, Lewandrowski K, Sinclair J, McDermot S, Benzer T. Implementation of a point-of-care satellite laboratory in the emergency department of an academic medical center. Arch Pathol Lab Med 2004;127:456–60.
25. Agewall S. Evaluation of point-of-care test systems using the new definition of myocardial infarction. Clin Biochem 2003;36:27–30.
26. Antman EM, Grudzien C, Sacks DB. Evaluation of a rapid bedside assay for detection of serum cardiac troponin T. JAMA 1995; 273:1279–82.
27. Apple FS, Anderson FP, Collinson P, Jesse RL, Kontos MC, Levitt MA, et al. Clinical evaluation of the first medical whole blood, point-of-care testing device for detection of myocardial infarction. Clin Chem 2000;46:1604–9.
28. Apple FS, Christenson RH, Valdes R Jr, Andriak AJ, Berg A, Duh SH, et al. Simultaneous rapid measurement of whole blood myoglobin, creatine kinase MB, and cardiac troponin I by the triage cardiac panel for detection of myocardial infarction. Clin Chem 1999;45:199–205.
29. Apple FS, Ler R, Chung AY, Berger MJ, Murakami MM. Point-of-care i-STAT cardiac troponin I for assessment of patients with symptoms suggestive of acute coronary syndrome. Clin Chem 2006;52:322–5.
30. Brogan GX Jr, Bock JL, McCuskey CF, Hollander JE, Thode H Jr, Gawad Y, et al. Evaluation of cardiac STATus CK-MB/myoglobin device for rapidly ruling out acute myocardial infarction. Clin Lab Med 1997;17:655–68.
31. Brogan GX Jr, Friedman S, McCuskey C, Cooling DS, Berrutti L, Thode HC Jr, et al. Evaluation of a new rapid quantitative immunoassay for serum myoglobin versus CK-MB for ruling out acute myocardial infarction in the emergency department. Ann Emerg Med 1994;24:665–71.
32. Collinson PO, Gerhardt W, Katus HA, Muller-Bardoff M, Braun S, Schricke U, et al. Multicentre evaluation of an immunological rapid test for the detection of troponin T in whole blood samples. Eur J Clin Chem Clin Biochem 1996;34:591–8.
33. Collinson PO, John C, Lynch S, Rao A, Canepa-Anson R, Carson E, et al. A prospective randomized controlled trial of point-of-care testing on the coronary care unit. Ann Clin Biochem 2004;41(Pt 5):397–404.
34. Heeschen C, Goldmann BU, Moeller RH, Hamm CW. Analytical performance and clinical application of a new rapid bedside assay for the detection of serum cardiac troponin I. Clin Chem 1998; 44:1925–30.
35. Kost GJ, Tran NK. Point-of-care testing and cardiac biomarkers: the standard of care and vision for chest pain centers. Cardiol Clin 2005;23:467–90, vi.
36. Muller-Bardorff M, Sylven C, Rasmanis G, Jorgenson B, Collinson PO, Waldenhofer U, et al. Evaluation of a point-of-care system for quantitative determination of troponin T and myoglobin. Clin Chem Lab Med 2000;38:567–74.
37. Stubbs P, Collinson PO. Point-of-care testing: a cardiologist's view. Clin Chim Acta 2001;311:57–61.
38. Wu AH, Smith A, Christenson RH, Murakami MM, Apple FS. Evaluation of a point-of-care assay for cardiac markers for patients suspected of acute myocardial infarction. Clin Chim Acta 2004; 346:211–9.
39. Yang Z, Min Zhou D. Cardiac markers and their point-of-care testing for diagnosis of acute myocardial infarction. Clin Biochem 2006;39:771–80.
40. Storrow AB, Lindsell CJ, Collins SP, Fermann GJ, Blomkalns AL, Williams JM, et al. Emergency department multimarker point-of-care testing reduces time to cardiac marker results without loss of diagnostic accuracy. Point of Care 2006;5:132–6.
41. REACTT. Evaluation of a bedside whole-blood rapid troponin T assay in the emergency department. Rapid Evaluation by Assay of Cardiac Troponin T (REACTT) Investigators Study Group. Acad Emerg Med 1997;4:1018–24.
42. Altinier S, Zaninotto M, Mion M, Carraro P, Rocco S, Tosato F, Point-of-care testing of cardiac markers: results from an experience in an emergency department. Clin Chim Acta 2001; 311:67–72.
43. Azzazy HM, Christenson RH. Cardiac markers of acute coronary syndromes: is there a case for point-of-care testing? Clin Biochem 2002;35:13–27.
44. Caragher TE, Fernandez BB, Jacobs FL, Barr LA. Evaluation of quantitative cardiac biomarker point-of-care testing in the emergency department. J Emerg Med 2002;22:1–7.
45. Collinson PO. The need for a point of care testing: an evidence-based appraisal. Scand J Clin Lab Invest 1999;230:67–73.
46. McCord J, Nowak RM, McCullough PA, Foreback C, Borzak S, Tokarski G, et al. Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. Circulation 2001;104:1483–8.
47. Newby LK, Storrow AB, Gibler WB, Garvey JL, Tucker JF, Kaplan AL, et al. Bedside multimarker testing for risk stratification in chest pain units: the Chest Pain Evaluation by Creatine Kinase-MB, Myoglobin, and Troponin I (CHECKMATE) Study. Circulation 2001;103:1832–7.
48. Di Serio F, Antonelli G, Trerotoli P, Tampoia M, Matarrese A, Pansini N. Appropriateness of point-of-care testing (POCT) in an emergency department. Clin Chim Acta 2003;333:185–9.
49. Sieck S. The evolution of a new standard of hospital care: paradigm shift to the emergency department and the role of point-of-care testing. Point of Care 2006;5:2–5.

50. Apple FS, Chung AY, Kogut ME, Bubany S, Murakami MM. Decreased patient charges following implementation of point-of-care cardiac troponin monitoring in acute coronary syndrome patients in a community hospital cardiology unit. Clin Chim Acta 2006;370:191–5.
51. Singer AJ, Ardise J, Gulla J, Cangro J. Point-of-care testing reduces length of stay in emergency department chest pain patients. Ann Emerg Med 2005;45:587–91.
52. Di Serio F, Lovero R, Leone M, De Sario R, Ruggieri V, Varraso L, et al. Integration between the tele-cardiology unit and the central laboratory: methodological and clinical evaluation of point-of-care testing cardiac marker in the ambulance. Clin Chem Lab Med 2006;44:768–73.
53. Schuchert A, Hamm C, Scholz J, Klimmeck S, Goldmann B, Meinertz T. Prehospital testing for troponin T in patients with suspected acute myocardial infarction. Am Heart J 1999;138(1 Pt 1):45–8.
54. Cawdery M, Burg MD. Emergency medicine career paths less traveled: cruise ship medicine, Indian health, and critical care medicine. Ann Emerg Med 2004;44:79–83.
55. Kost GJ, Tran NK, Tuntideelert M, Kulrattanamaneeporn S, peungposop N. Katrina, the tsunami, and point-of-care testing: optimizing rapid response diagnosis in disasters. Am J Clin Pathol 2005;126:1–8.
56. Gomez MA, Anderson JL, Karagounis LA, Muhlestein JB, Mooers FB. An emergency department-based protocol for rapidly ruling out myocardial ischemia reduces hospital time and expense: results of a randomized study (ROMIO). J Am Coll Cardiol 1996; 28:25–33.
57. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004; 350:647–54.
58. Wu AH, Clive JM. Impact of CK-MB testing policies on hospital length of stay and laboratory costs for patients with myocardial infarction or chest pain. Clin Chem 1997;43:326–32.
59. Berger PB, Ellis SG, Holmes DR Jr, Granger CB, Criger DA, Betriu A, et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. Circulation 1999;100:14–20.
60. Brodie BR, Stuckey TD, Wall TC, Kissling G, Hansen CJ, Muncy DB, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1998;32:1312–9.
61. Cannon CP, Gibson CM, Lambrew CT, Shoultz DA, Levy D, French WJ, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000; 283:2941–7.
62. Cox DA, Stone GW, Grines CL, Stuckey T, Zimetbaum PJ, Tcheng JE, et al. Comparative early and late outcomes after primary percutaneous coronary intervention in ST-segment elevation and non-ST-segment elevation acute myocardial infarction (from the CADILLAC trial). Am J Cardiol 2006;98:331–7.
63. Diderholm E, Andren B, Frostfeldt G, Genberg M, Jernberg T, Lagerqvist B, et al. ST depression in ECG at entry indicates severe coronary lesions and large benefits of an early invasive treatment strategy in unstable coronary artery disease; the FRISC II ECG substudy. The Fast Revascularisation during InStability in Coronary artery disease. Eur Heart J 2002;23:41–9.
64. Holmvang L, Clemmensen P, Lindahl B, Lagerqvist B, Venge P, Wagner G, et al. Quantitative analysis of the admission electrocardiogram identifies patients with unstable coronary artery disease who benefit the most from early invasive treatment. J Am Coll Cardiol 2003;41:905–15.
65. Tardiff BE, Califf RM, Tcheng JE, Lincoff AM, Sigmon KN, Harrington RA, et al. Clinical outcomes after detection of elevated cardiac enzymes in patients undergoing percutaneous intervention: IMPACT-II Investigators: Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis-II. J Am Coll Cardiol 1999;33:88–96.
66. Arendts G, MacKenzie J, Lee JK. Discharge planning and patient satisfaction in an emergency short-stay unit. Emerg Med Austral 2006;18:7–14.
67. Boudreaux ED, Cruz BL, Baumann BM. The use of performance improvement methods to enhance emergency department patient satisfaction in the United States: a critical review of the literature and suggestions for future research. Acad Emerg Med 2006;13:795–802.
68. Boudreaux ED, D'Autremont S, Wood K, Jones GN. Predictors of emergency department patient satisfaction: stability over 17 months. Acad Emerg Med 2004;11:51–8.
69. Boudreaux ED, Friedman J, Chansky ME, Baumann BM. Emergency department patient satisfaction: examining the role of acuity. Acad Emerg Med 2004;11:162–8.
70. Davis BA, Kiesel CK, McFarland J, Collard A, Coston K, Keeton A. Evaluating instruments for quality: testing convergent validity of the consumer emergency care satisfaction scale. J Nurs Care Qual 2005;20:364–8.
71. Fermann GJ, Suyama J. Point of care testing in the emergency department. J Emerg Med 2002;22:393–404.
72. Goodacre SW, Quinney D, Revill S, Morris F, Capewell S, Nicholl J. Patient and primary care physician satisfaction with chest pain unit and routine care. Acad Emerg Med 2004;11:827–33.
73. Huang JA, Lai CS, Tsai WC, Weng RH, Hu WH, Yang DY. Determining factors of patient satisfaction for frequent users of emergency services in a medical center. J Chin Med Assoc 2004;67:403–10.
74. Muntlin A, Gunningberg L, Carlsson M. Patients' perceptions of quality of care at an emergency department and identification of areas for quality improvement. J Clin Nurs 2006;15:1045–56.
75. Rodi SW, Grau MV, Orsini CM. Evaluation of a fast track unit: alignment of resources and demand results in improved satisfaction and decreased length of stay for emergency department patients. Qual Manag Health Care 2006;15:163–70.
76. Taylor C, Benger JR. Patient satisfaction in emergency medicine. Emerg Med J 2004;21:528–32.
77. Taylor D, Kennedy MP, Virtue E, McDonald G. A multifaceted intervention improves patient satisfaction and perceptions of emergency department care. Int J Qual Health Care 2006;18:238–45.
78. Vukmir RB. Customer satisfaction. Int J Qual Health Care 2006;19:8–31.
79. Yildirim C, Kocoglu H, Goksu S, Gunay N, Savas H. Patient satisfaction in a university hospital emergency department in Turkey. Acta Medica (Hradec Kralove)/Universitas Carolina, Facultas Medica Hradec Kralove 2005;48:59–62.
80. von Lode P. Point-of-care immunotesting: approaching the analytical performance of central laboratory methods. Clin Biochem 2005;38:591–606.

81. Morrow DA. Evidence-based decision limits for cardiac troponin: low-level elevation and prognosis. Am Heart J 2004; 148:739–42.
82. Pham MX, Whooley MA, Evans GT Jr, Liu C, Emadi H, Tong W, et al. Prognostic value of low-level cardiac troponin-I elevations in patients without definite acute coronary syndromes. Am Heart J 2004;148:776–82.
83. Wu AH. Point-of-care testing for conventional cardiac markers. Point of Care 2006;5:20–4.

PUBLIC COMMENTS

Drafts of these recommendations were presented at the 2004 A.O. Beckman Conference, held in Boston, MA, and at the 2004 AACC Annual Meeting and Exposition in Chicago, IL. Feedback was captured by audiotape, and issues were discussed in detail by conference call. The document was reviewed by the IFCC Committee on Evidence Based Laboratory Medicine.

Chapter **4**

Coagulation

Marcia L. Zucker, Vandita Johari, Valerie Bush, and Srikantha Rao

INTRODUCTION

Point-of-care coagulation testing has been termed the most rapidly growing point-of-care application in the hospital setting *(1)*. This rapid growth implies a widespread acceptance of the use of point-of-care coagulation assays, yet it is unclear whether documentation exists showing a clinical advantage to these methodologies. The purpose of this guideline is to evaluate the available literature and identify those studies, if any, that objectively demonstrate the utility of point-of-care coagulation testing compared with more traditional laboratory analyses.

The term "coagulation testing" is used to describe an ever-growing selection of diagnostic tests. These range from the traditional global coagulation assays, i.e., the prothrombin time (PT) and activated partial thromboplastin time (aPTT), to assays specific to individual coagulation factors and their inhibition, e.g., factor VIII, fibrinogen, and anti–factor Xa assays, to technologies designed to evaluate the process of clot formation and the influence of platelets and fibrinolysis on hemostasis, i.e., Sonoclot and thromboelastography (TEG).

This Laboratory Medicine Practice Guideline (LMPG) is targeted to address 2 basic questions:

1. Is there evidence of improved clinical outcome from the use of point-of-care coagulation testing?
2. What is the evidence that the current "standards of care" in point-of-care coagulation are appropriate?

Considering the wide range of clinical applications for these assays, a decision was made to evaluate only the global coagulation assays: the activated clotting time (ACT), the aPTT, and the PT, including the calculation of the international normalized ratio (INR). It will be left to later updates to address the important issues of individualized heparin and protamine dosing for cardiac surgery, thrombin-time-based tests, heparin-level measurement, heparin neutralization verification, and TEG analyses, among others. Also left to later updates are the clinical utility of these assays for monitoring novel anticoagulants such as direct thrombin inhibitors and direct factor Xa inhibitors, as well as the use of available electronic tools for management of anticoagulation therapy.

A critical assumption made in this document is that all point-of-care coagulation monitoring instruments are equally accurate and precise. There are insufficient data to allow recommendations based on specific instrumentation for these tests, and it must be the responsibility of the individual facility to evaluate available systems before implementation in a clinical setting. Although many of the studies described in this document were performed using point-of-care instruments that are no longer available in the marketplace, the value of the studies remains and should not be discounted.

Literature searches were conducted through online databases (PubMed, MEDLINE, BioMedNet) and private libraries maintained by members of the LMPG team. Articles identified from author collections were only included if they are indexed on one of the 3 public search engines. All searches were performed using extremely broad search criteria. These searches were defined by the test name and any of the terms "bedside," "point of care," "near patient," or "whole blood." The majority of the publications identified consisted of correlation analyses, either point of care to laboratory or between different point-of-care systems. Such studies were excluded from further consideration because they do not directly address the clinical utility of these systems. An overview of publications dealing with correlation analyses can be found in Zimmerman *(2)*.

aPTT

Is there evidence of improved clinical outcome using point-of-care aPTT testing? (Literature Search 9)

Guideline 23. *We recommend that the use of point-of-care aPTT be considered a safe and effective alternative to laboratory aPTT testing for anticoagulation and hemostasis monitoring.*

Strength/consensus of recommendation: B

Level of evidence: I and II (at least 1 randomized controlled trial, small randomized controlled trials, nonrandomized controlled trials, and multiple time series without intervention)

Guideline 24. *We strongly recommend that therapeutic ranges, workflow patterns, and cost analysis be evaluated, and where necessary altered, during the implementation of point-of-care aPTT testing to ensure optimization of patient treatment protocols.*

Strength/consensus of recommendation: A

Level of evidence: II (small randomized controlled trials and nonrandomized controlled trials)

The literature about point-of-care aPTT, excluding straightforward analyses of correlation to the clinical laboratory aPTT, falls into 3 categories: evaluations specifically designed to measure turnaround time (TAT) *(3–5)*, evaluations of diagnostic accuracy using laboratory measurement of anti–factor Xa activity as the gold standard *(6–11)*, and outcome studies *(12–16)*. Prospective studies of TAT have evaluated multiple patient populations, laboratory systems, and point-of-care monitors, and all have shown that TAT, defined as time from sample draw to time of result availability, is significantly reduced with point-of-care testing ($P < 0.001$ to $P < 0.05$) *(3–5)*. These authors suggested that this significant reduction in TAT could lead to improved patient care but did not directly address patient outcome questions.

The evaluations of diagnostic accuracy examined use appraisals of clinical decision point agreement to determine whether point-of-care aPTT monitors are as accurate as laboratory aPTT analyses for monitoring anticoagulation. All but 1 of these analyses use the chromogenic determination of anti–factor Xa activity in the patient's blood as the standard for therapeutic decisions. The single investigation without anti–factor Xa values explored the efficacy of an aPTT assay as a preoperative screening tool to predict which patients would exhibit severe bleeding after cardiac surgery. In this trial, Nuttall and colleagues *(7)* concluded that the Biotrack 512 (Ciba Corning; no longer marketed) point-of-care monitor had similar predictive value for bleeding tendency compared with standard laboratory tests, (MLA Electra, Medical Laboratory Automation; no longer marketed). Four articles reviewed evaluated point-of-care aPTT assays for monitoring heparin anticoagulation during continuous intravenous heparin infusion. Therapeutic ranges in these studies were defined as heparin at 0.2–0.4 *(6)*, 0.3–0.7 *(9, 11)*, or 0.36–0.82 *(10)* units/mL as measured by chromogenic laboratory assays. In all reports, the point-of-care system (Biotrack 512 *(6)*; CoaguChek Plus, Roche Diagnostics, Basel, Switzerland *(10)*; Hemochron 8000, ITC, Edison, NJ, USA *(9)*; Hemochron Jr. Signature *(11)*; TAS, Cardiovascular Diagnostics, Inc., no longer marketed *(10)*) showed reasonable agreement with anti-Xa levels, at least equivalent to the levels of agreement seen for the laboratory aPTT. Several authors noted that the oft-quoted target range of 1.5–2.5 times normal was inappropriate for both the point-of-care and laboratory systems *(9, 10)*. Solomon and colleagues drew similar conclusions when the CoaguChek Plus and TAS systems were evaluated for determination of the appropriate time to remove the femoral access sheath after interventional cardiology procedures *(8)*.

Three trials were identified evaluating the use of point-of-care coagulation assays to guide transfusions after cardiac surgery *(12–14)*. All 3 studies identified a subpopulation of patients determined to have bleeding complications after heparin reversal with protamine. Two of the studies defined bleeding by visual inspection of the operative field at the end of procedure and implemented the point-of-care-based transfusion algorithms using PT, aPTT and platelet count *(12)*, or function as measured by the bleeding time *(13)* in the operating room. Both groups found significant reductions in postoperative bleeding and blood product usage in the algorithm group compared with that of patients transfused by routine procedures (central laboratory test results *(12)* or clinician discretion *(13)*). The third trial, conducted by Capraro and colleagues *(14)*, did not introduce point-of-care testing for transfusion until after the patients left the operating suite. Bleeding in this trial was defined as chest-tube drainage exceeding 1.5 mL/kg/15 min after initial draining of the mediastinal tubes. In contrast to the other studies, these investigators found no difference in bleeding or blood-product usage between the 2 groups across the hospital stay. In fact, the algorithm-controlled group received more platelets during the first hour than the control group. The authors suggest that this difference may be due to the use of the bleeding time to define the need for platelet transfusion. An explanation of the contradictory results between the Capraro et al. study *(14)* and those by Despotis et al. *(12)* and Nuttall et al. *(13)* may lie in the time of algorithm initiation. Nuttall et al. *(13)* noted that in both his and the Despotis et al. *(12)* studies, the lower number of coagulation-product transfusions in the operating room in the algorithm group may have led to the significant reduction in bleeding observed in the intensive care unit. One explanation could be that the earlier directed transfusion therapy may have more efficiently corrected the hemostatic problems. If this is true, the lack of improved outcome in the Capraro et al. *(14)* evaluation may be due to the time of algorithm initiation. In any case, all these trials used multiple point-of-care assays so that the precise impact of the aPTT alone cannot be isolated from the other assays involved.

Point-of-care aPTT assays have also been an integral component of 2 large-scale, multicenter, randomized, controlled, pharmaceutical trials. In a subset analysis of patients enrolled in GUSTO-I, Zabel and colleagues *(15)* evaluated bleeding, transfusion requirements, recurrent ischemia, and mortality at 30 days and 1 year for patients monitored using point-of-care aPTT (CoaguChek Plus) compared with those monitored with local laboratory aPTTs. The point-of-care group had a higher percentage of patients in therapeutic range at 12 and 24 h, less severe or moderate bleeding, and fewer transfusions that the laboratory group ($P < 0.01$), although these patients exhibited somewhat higher rates of recurrent ischemia ($P = 0.01$). Mortality at 30 days and 1 year were equivalent in the 2 groups ($P = 0.27$ and $P = 0.38$, respectively).

As part of the PARAGON A clinical trial, investigators were required to use point-of-care aPTT (Hemochron Jr.) assays to maintain clinician blinding to therapeutic regimen *(18)*. A strong statistical trend ($P = 0.08$) was observed between time to therapeutic aPTT and the 30-day death or myocardial infarction combined endpoint. The authors suggest that a change in clinical protocol to include more frequent testing (PARAGON A required testing at 6- to 12-h intervals) might improve patient outcomes by increasing the likelihood of attaining therapeutic levels more

quickly. Becker and colleagues *(16)* arrived at a similar conclusion after a randomized controlled trial evaluating weight-adjusted vs empirical heparin dosing, as well as point-of-care (CoaguChek Plus) vs laboratory aPTT management, of 113 patients with active venous or arterial thromboembolic disease requiring intravenous heparin therapy. Although the time between sample draw and dose adjustment was significantly shorter for the point-of-care group ($P = 0.0001$), no change in test frequency was made and no differences were observed in time to target range or time within range between the point-of-care and laboratory groups.

The need to change procedures to optimize the advantages of point-of-care testing was directly demonstrated by Nichols and coworkers *(17)* in their prospective, nonrandomized analysis of the effect of point-of-care testing on patient wait times before and after elective invasive cardiology and radiology procedures. The authors conclude that point-of-care testing must be integrated into clinical-management pathways if the benefits of the reduced turnaround times are to have positive clinical impact.

PT/INR

Is there evidence of improved clinical outcome using point-of-care PT testing? In the hospital? (Literature Search 10)

Guideline 25. *We recommend that the use of point-of-care PT be considered a safe and effective alternative to laboratory PT testing for hemostasis monitoring.*

Strength/consensus of recommendation: B

Level of evidence: I and II (at least 1 randomized controlled trial, small randomized controlled trials, nonrandomized controlled trials, and multiple time series without intervention)

Guideline 26. *We strongly recommend that critical ranges, workflow patterns, and cost analysis be evaluated, and where necessary altered, during the implementation of point-of-care PT testing to ensure optimization of patient treatment protocols.*

Strength/consensus of recommendation: A

Level of evidence: II (small randomized controlled trials, nonrandomized controlled trials)

As seen for the aPTT, the majority of literature identified in this search consisted of clinical correlation analyses between point-of-care PT/INR monitors and hospital-based laboratory systems. Fewer articles specifically addressed TAT for the PT test, but again, unsurprisingly, all these studies showed statistically significant improvement in TAT with point of care *(4, 5, 19)*. The studies by Despotis et al. *(12)*, Nuttall et al. *(13)*, Capraro et al. *(14)*, and Nichols et al. *(17)* included PT testing in their evaluations. These trials showed improved patient outcomes *(12, 13)* or no effect on outcome *(14)* after cardiac surgery and reduced wait times surrounding interventional cardiology and radiology procedures *(17)*. As with the aPTT discussion, the impact of the PT test itself cannot be isolated from other point-of-care tests used or the procedural changes implemented for these study populations.

Two pharmaceutical treatment evaluations using point-of-care PT monitoring (CoaguChek *(20)*; ProTime, ITC *(21)*) were identified. Although there were no INR-specific endpoints described in these controlled trials, investigators participating in both studies noted that the warfarin anticoagulation arm of the study showed good therapeutic management.

Is there evidence of improved clinical outcome using point-of-care PT testing? In the anticoagulation clinic?

Guideline 27. *We recommend that the use of point-of-care PT be considered a safe and effective alternative to laboratory PT testing for oral anticoagulation monitoring and management.*

Strength/consensus of recommendation: B

Level of evidence: II and III (controlled trials without randomization, cohort or case-control analytic studies, and opinions of respected authorities)

The use of point-of-care PT/INR devices has been shown to be safe and effective in several studies in oral anticoagulation clinic populations *(22–25)*. In addition to evaluating the correlation of the point-of-care system (CoaguChek *(22, 24)*, ProTime *(23)*), patient and clinician satisfaction was assessed by questionnaire. Satisfaction was the only endpoint evaluated in the study by Choudry and colleagues *(26)*. In these studies, both the patients and the clinicians preferred using fingerstick samples on the point-of-care system to venous sampling for laboratory testing. This is a rapidly growing management strategy for patients receiving long-term vitamin K antagonist anticoagulation in which a highly experienced, dedicated staff can help to provide optimal management to this patient population *(25)*.

Is there evidence of improved clinical outcome using point-of-care PT testing? For patient self-testing (PST)/patient self-management (PSM)?

Guideline 28. *We recommend the use of point-of-care PT as a safe and effective method for oral anticoagulation monitoring for appropriately trained and capable individuals.*

Strength/consensus of recommendation: B

Level of evidence: I, II, and III (at least 1 randomized controlled trial, small randomized controlled trials, nonrandomized controlled trials, and opinions of respected authorities)

Another growing management strategy for oral anticoagulation monitoring is PST and its extension, PSM. In either scenario, the patient or caregiver monitors the patient's INR at home with a point-of-care monitor. PST patients then report the result to the clinic or physician responsible for their care who determines any required warfarin dose adjustments. PSM patients generally use an algorithm provided by a medical professional to adjust their own dose according to the INR reading. There have been a large number of studies evaluating the efficacy of PST or PSM compared to routine medical care (testing and dose adjustment by primary care physician) and to oral anticoagulation clinic care. Endpoints include time in therapeutic range, as well as, in some trials, incidence of hemorrhage or thromboembolism. Several recent reviews of these studies have been published *(27–30)*. In each study, PST or PSM has been shown to be superior to routine medical care and at least equivalent to oral anticoagulation clinic management. One confounding factor in these studies is the frequency of PT/INR testing. The inverse correlation of time between tests and time in therapeutic range has been clearly demonstrated *(31)*, and PST/PSM patients routinely monitor their PT/INR at higher frequencies than patients monitored by laboratory-based strategies.

ACT

Is there evidence of improved clinical outcome with ACT testing? Is there evidence for optimal target times to be used with ACT monitoring? In cardiovascular surgery? (Literature Search 11)

Guideline 29. *We strongly recommend ACT monitoring of heparin anticoagulation and neutralization in the cardiac surgery arena.*

Strength/consensus of recommendation: A

Level of evidence: I and II (at least 1 randomized controlled trial, small randomized controlled trials, nonrandomized controlled trials)

Guideline 30. *There is insufficient evidence to recommend specific target times for use in ACT-managed heparin dosing during cardiovascular surgery.*

Strength/consensus of recommendation: I (conflicting evidence across clinical trials)

By far the largest number of outcome-related publications for point-of-care coagulation testing is represented by studies performed in cardiac surgery or percutaneous coronary intervention applications with the ACT. First described by Hattersley in 1966 *(32)*, the use of the ACT to predict heparin requirements and the cardiopulmonary bypass surgery target recommendation was described by Bull and colleagues in 1975 *(33, 34)*. In general, these publications fall into one of 2 categories, those evaluating the use of the ACT to optimize heparin and protamine dosing and those studies that specifically examine patient outcome.

In the cardiovascular surgery studies, accurate dosing was defined as predicting the dose required to obtain an ACT above a predefined clotting time (range, 400–600 seconds) *(35–39)*. Using the Hemochron ACT test, these investigators clearly showed the differing heparin requirements between patients, as well as between populations *(36–38)*, most notably pediatric vs adult patients *(35)*. Two studies evaluated the correlation of the ACT to heparin level determined either through laboratory assays *(37)* or using the Hepcon (now Medtronic HMS, Medtronic, Inc., Minneapolis, MN, USA) system *(40)* to measure heparin level. Both studies support the use of the ACT showing good correlation to heparin level for ACTs $<$ 600 seconds *(37)* and a strong correlation between postoperative bleeding and increased ACTs after heparin reversal *(40)*.

Cardiac surgery outcomes are defined as postoperative blood loss as measured by chest-tube drainage during 12 or 24 h, blood product usage, and total heparin or protamine given. In all studies reviewed, if statistical analyses were used, there was a statistically significant decrease in each of these characteristics when ACT-managed heparin dosing was compared with empirical dosing. The earliest studies *(41–43)* indicated reductions of near 50% in blood loss in the initial postoperative 12-h period for patients monitored by ACT to optimize anticoagulation vs those patients dosed empirically with heparin at 2–4 mg/kg and additional heparin administered on a time-postbolus basis.

Later studies, using combinations of the Hemochron, HemoTec (now Medtronic ACTII), or HMS systems confirmed these findings *(44–46)*, adding observations on reduced blood-product usage *(47, 48)*. Interestingly, one study *(49)* noted no reduction in postoperative blood loss but significant reductions in intraoperative blood loss, as well as heparin and protamine doses given for ACT-monitored patients compared with the empirically dosed group ($P < 0.001$). Changes in dosing with ACT varied by trial, with reports of increased *(46)* and decreased *(41, 44, 49)* heparin in the ACT group. All studies agreed that ACT monitoring reduced the total protamine dose *(38, 44–46, 49)* given; in one case, this reduction correlated closely with reduced 24-h blood loss ($P = 0.02$) *(45)*. The target times used for the ACT-monitored groups varied widely, with each author recommending differing minimal ACTs for safe extracorporeal circulation. These recommendations range from 350 seconds *(45)* to targeting values in excess of 500 seconds *(47)* to achieve optimal patient outcomes.

Questions surrounding optimal target times are further confounded by evaluations comparing heparin-coated tubing or heparin-bonded tubing vs standard tubing use in the extracorporeal circuit. These studies suggest comparable or improved outcomes, with target times as low as 180 seconds with fully heparin-bonded circuits compared with either routine or heparin-coated circuits, with ACT targets of $>$450 seconds *(50–52)*.

Is there evidence of improved clinical outcome with ACT testing? Is there evidence for optimal target times to be used with ACT monitoring? In interventional cardiology?

Guideline 31. *We strongly recommend ACT monitoring of heparin anticoagulation and neutralization during interventional cardiology procedures.*

Strength/consensus of recommendation: A

Level of evidence: II (small randomized controlled trials, nonrandomized controlled trials, and case-controlled analytic studies from more than 1 center or research group)

Guideline 32. *We recommend the use of target times specific to ACT system used that differ if specific platelet inhibitors are used concurrently with heparin. Without intravenous platelet inhibitors, the evidence suggests that targets of >250 seconds with the Medtronic ACTII or >300 seconds with the Hemochron FTCA510 tube assay are appropriate.*

Strength/consensus of recommendation: B

Level of evidence: II (small randomized controlled trials, nonrandomized controlled trials, case-controlled analytic studies from more than 1 center or research group)

Guideline 33. *With the intravenous platelet inhibitors abciximab or eptifibatide, a target of 200–300 seconds is recommended; with tirofiban, a somewhat tighter range of 250–300 seconds is recommended.*

Strength/consensus of recommendation: B

Level of evidence: I (at least 1 randomized controlled trial)

Published references in the cardiac catheterization laboratory consist primarily of studies of patients undergoing percutaneous transluminal coronary angioplasty (PTCA) rather than other interventional procedures. Only 1 publication was identified that specifically examined patient outcomes comparing anticoagulation management with ACT to empirical, unmonitored heparin dosing *(53)*. In this retrospective study, records were examined for 1200 sequential PTCA procedures. The group managed by ACT showed increased risk of abrupt or late vessel closure according to preprocedural demographic analyses yet showed a statistically significant reduced incidence of closure than the historic controls ($P < 0.05$). In studies of this population comparing the clinical utility of ACT monitoring vs fibrinopeptide A formation, ACTs exceeding 200 seconds were shown to be indicative of significant reduction of thrombin formation *(54)*. The ACT was also shown to be superior to the laboratory aPTT for monitoring anticoagulation in this population, as judged by heparin dose response *(55)* and cost *(56)* when clinical outcomes were similar for the ACT and aPTT groups.

Other studies reviewed wanted to establish optimal target times for patients undergoing PTCA to minimize both bleeding and ischemic complications. Ogilby and colleagues *(57)* reported no bleeding or ischemic complications in 108 patients treated with target Hemochron ACTs of >300 seconds, whereas Kaluski and coworkers *(58)* advocated lower levels of heparinization targeting ACTs (unspecified system) of 160–240 seconds. In this group of 341 patients, there were 6 occlusive events and 1 myocardial infarction within 14 days of procedure, but no bleeding complications.

Retrospective analyses of more than 1200 patients were used to identify patients who experienced abrupt vessel closure and case match them with at least twice their number of patients without ischemic complications *(59, 60)*. Ferguson and coworkers *(59)* were able to identify a target value of 250 seconds on the HemoTec system as significantly reducing ischemic complications ($P < 0.001$). These investigators further determined that a change in ACT on this system of <150 seconds in response to a 10,000-unit heparin bolus was also an indication of increased thrombotic events. Although Narins and colleagues *(60)* were unable to identify an ideal target time for the Hemochron system, their data also showed a significant increase in ischemic events in patients with lower ACTs ($P = 0.004$). This study showed no relationship of increased ACTs with increased bleeding complications. In contrast, Hillegass and colleagues *(61)* found a significant correlation ($P < 0.001$) between increased ACT times and bleeding in their prospective evaluation of 429 patients. Reviews of the existing literature by Ferguson *(62)* and Klein and Agarwal *(63)* in 1995 and 1996, respectively, both recommended that target times be ACT system specific and that optimal targets for PTCA are >250–275 seconds for HemoTec and >300–350 seconds for Hemochron ACTs. These values are lower than those arrived at by Chew and coworkers *(64)* in 2001 after their meta-analysis of data from 6 interventional trials, 5 including platelet inhibitors and 1 comparing heparin and bivalirudin anticoagulation. In these studies, 95% of the ACT results were obtained with Hemochron or Hemochron Jr. ACTs; the remainder, with the HemoTec. Chew's group *(64)* concluded that the lowest composite ischemic event rate in patients receiving only heparin was seen in the ACT range of 350–375 seconds, with significant bleeding observed if the ACT exceeded 400 seconds.

Target time recommendations for patients receiving heparin with concurrent intravenous antiplatelet therapy are best obtained from the clinical trials of these antiplatelet agents *(65–67)*.

Both the EPILOG *(65)* and ESPIRIT *(66)* studies showed an optimal outcome (minimizing both ischemic and bleeding events) when ACTs were maintained between 200 and 300 seconds in the presence of abciximab or eptifibatide, respectively. The EPILOG study used Hemochron ACTs, whereas the type of ACT system in use was not reported for the ESPIRIT. In the TACTICS trial *(67)*, there was a clear relationship between ACT values <250 seconds and ischemic complications ($P = 0.043$) and a trend toward increased bleeding for clotting times in excess of 300 seconds ($P = 0.08$).

Is there evidence of improved clinical outcome using ACT testing? Is there evidence for optimal target times to be used with ACT monitoring? In extracorporeal membrane oxygenation (ECMO)?

Guideline 34. *We strongly recommend ACT monitoring to control heparin anticoagulation during ECMO.*

Strength/consensus of recommendation: A

Level of evidence: III (opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees)

Guideline 35. *We recommend that ACT target times for ECMO be determined according to the ACT system in use.*

Strength/consensus of recommendation: B

Level of evidence: III (opinions of respected authorities according to clinical experience, descriptive studies, or reports of expert committees)

Since 1990, the results of 3 large surveys of ECMO practices have been published *(68–70)*. ACT monitoring was used by all survey respondents in each year, although the mix of systems changed from 1990 to 1996 (the 2002 survey did not list specific ACT instrumentation). Target ranges reported in 1990 for "typical" patients ranged from 180–240 to 220–260, with lower ranges for "bleeding" patients *(68)*. The average target range reported in 2002 was 180–220 *(70)*. Colby and colleagues *(71)* emphasized the need to set target ranges according to the ACT system in use. Without changing target ranges, changing the ACT system from the Hemochron 400 to the Hemochron Jr. ACT-LR led to reduced circuit life and increased circuit clotting ($P = 0.035$). Changing the target range from 200–220 to 220–240 for the Hemochron Jr. system led to improved circuit longevity and reduced circuit clots ($P = 0.049$). There were no differences in bleeding complications across the 3 treatment groups.

Is there evidence of improved clinical outcome using ACT testing? Is there evidence for optimal target times to be used with ACT monitoring? In other applications (e.g., vascular surgery, intravenous heparin therapy, dialysis, neuroradiology, etc)?

Guideline 36. *There is insufficient evidence to recommend for or against ACT monitoring in applications other than cardiovascular surgery, interventional cardiology, or extracorporeal oxygenation.*

Strength/consensus of recommendation: I

Although several publications refer to the use of the ACT for a wide variety of other clinical applications, few focus on the ACT itself or its effect on patient outcome. Mabry and colleagues *(72, 73)* have described the clinical utility of the ACT (manual or Hemochron) in monitoring patients in peripheral vascular surgery, recommending targets of 180–200 seconds. Ouseph and coworkers *(74)* showed the efficacy of defined Hemochron ACT-based algorithms for increasing dialyzer reuse in patients requiring chronic hemodialysis. Simko and coworkers *(75)* found the ACT to be as useful as the aPTT for monitoring intravenous heparin therapy, whereas Smythe and colleagues *(76)* found the aPTT to be a more accurate monitor. Many studies state that ACTs are used, for example, in neuroradiology, femoral sheath removal after cardiac catheterization procedures, and electrophysiology, but these studies simply reference a target time without indication as to the clinical benefit of these procedures.

Overall, point-of-care coagulation testing is appropriate in a wide range of clinical applications. Implementation of point-of-care aPTT and PT testing in the inpatient setting may require evaluation and adjustment of institution-established therapeutic targets, clinical decision points, and general workflow in the area(s) affected by this testing. Whether or not implementation of point-of-care aPTT and PT testing in this environment can truly improve patient outcome is not yet clear and requires additional investigation, though there is a clear impact on turnaround time and the availability of laboratory results.

Point-of-care PT/INR testing is required in the PST and PSM paradigms for oral anticoagulation therapy management. Although it is still unclear whether the outcome improvements observed compared to routine care are due to the use of point of care or to the increased frequency of testing, the benefits of these management modalities are clear. There is an obvious association of the frequency of INR testing and maintenance of therapeutic range.

The use of ACT testing in cardiac surgery and cardiac catheterization laboratories shows the strongest impact on improving patient outcome. Despite this clear evidence, the target times used in these clinical arenas stem from historical clinician comfort rather than clear evidence, yet another area requiring future trials. Furthermore, the ACT is used in a large number of other clinical applications, with some indication, but insufficient conclusive evidence, to determine optimal patient treatment. It is critical that trials be designed and conducted to determine the optimal use of this assay and optimal target times for use of the ACT in all clinical arenas.

REFERENCES

1. Enterprise Analysis Corporation. US Hospital Point-of-Care Study. Stamford, CT: Enterprise Analysis Corporation, 2001.
2. Zimmerman CR. The role of point-of-care anticoagulation monitoring in arterial and venous thromboembolic disorders. J Thromb Thrombolysis 2000;9:187–98.

3. Becker RC, Cyr J, Corrao JM, Ball SP. Bedside coagulation monitoring in heparin treated patients with active thromboembolic disease: a coronary care unit experience. Am Heart J 1994;128:719–23.
4. Boldt J, Walz G, Triem J, Suttner S, Kumle B. Point-of-care (POC) measurement of coagulation after cardiac surgery. Intensive Care Med 1998;24:1187–93.
5. Fitch JC, Mirto GP, Geary KL, Byrne DW, Hines RL. Point-of-care and standard laboratory coagulation testing during cardiovascular surgery: balancing reliability and timeliness. J Clin Monit Comput 1999;15:197–204.
6. Werner M, Gallagher JV, Ballo MS, Karcher DS. Effect of analytic uncertainty of conventional and point-of-care assays of activated partial thromboplastin time on clinical decisions in heparin therapy. Am J Clin Pathol 1994;102:237–41.
7. Nuttall GA, Oliver WC, Beynen FM, Santrach P, Strickland RA, Murray MJ. Determination of normal versus abnormal activated partial thromboplastin time and prothrombin time after cardiopulmonary bypass. J Cardiothor Vasc Anesth 1995;9:355–61.
8. Solomon HM, Mullins RE, Lyden P, Thompson P, Hudoff S. The diagnostic accuracy of bedside and laboratory coagulation: procedures used to monitor the anticoagulation status of patients treated with heparin. Am J Clin Pathol 1998;109:371–8.
9. Schroeder AP, Knudsen LL, Husted SE, Knudsen L, Ingerslev J. Bedside coagulometry during intravenous heparin therapy after coronary angioplasty. J Thromb Thrombolysis 2001;12:157–63.
10. Smythe MA, Koerber JM, Westley SJ, Nowak SN, Begle RL, Balasubramaniam M, et al. Use of the activated partial thromboplastin time for heparin monitoring. Am J Clin Pathol 2001;115:148–55.
11. Liepman CI, Koerber JM, Mattson JC, Westley SJ, Smythe MA. Comparing methods of establishing the aPTT therapeutic range of heparin. Ann Pharmacother 2003;37:794–8.
12. Despotis GJ, Santoro SA, Spitznagel E, Kater KM, Cox JL, Barnes P, et al. Prospective evaluation and clinical utility of on-site monitoring of coagulation in patients undergoing cardiac operation. J Thorac Cardiovasc Surg 1994;107:271–9.
13. Nuttall GA, Oliver WC, Santrach PJ, Bryant S, Dearani JA, Schaff HV, et al. Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after cardiopulmonary bypass. Anesthesiology 2001;94:773–81.
14. Capraro L, Kuitunen A, Salmenpera M, Kekomäki R. On-site coagulation monitoring does not affect hemostatic outcome after cardiac surgery. Acta Anesthesiol Scand 2001;45:200–6.
15. Zabel KM, Granger CB, Becker RC, Bovill EG, Hirsh J, Aylward PE, et al. Use of bedside activated partial thromboplastin time monitor to adjust heparin dosing after thrombolysis for acute myocardial infarction: results of GUSTO-I: Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries. Am Heart J 1998;136:868–76.
16. Becker RC, Ball SP, Eisenberg P, Borzak S, Held AC, Spencer F, et al. A randomized, multicenter trial of weight-adjusted intravenous heparin dose titration and point-of-care coagulation monitoring in hospitalized patients with active thromboembolic disease. Am Heart J 1999;137:59–71.
17. Nichols JH, Kickler TS, Dyer KL, Humbertson SK, Cooper PC, Maughan WL, et al. Clinical outcomes of point-of-care testing in the interventional radiology and invasive cardiology setting. Clin Chem 2000;46:543–50.
18. Newby LK, Harrington RA, Bhapkar MV, Van de Werf F, Hochman JS, Granger CB, et al, PARAGON A Investigators. An automated strategy for bedside aPTT determination and unfractionated heparin infusion adjustment in acute coronary syndromes: insights from PARAGON A. J Thromb Thrombolysis 2002; 14:33–42.
19. Hirsch J, Wendt T, Kuhly P, Schaffartzik W. Point-of-care testing apparatus: measurement of coagulation. Anaesthesia 2001;56:760–3.
20. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, et al, PREVENT Investigators. Long-term, low-dose warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003;348:1425–1434.
21. SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293:690–8.
22. Marzinotto V, Monagle P, Chan A, Adams M, Massicotte P, Leaker M, et al. Capillary whole blood monitoring of oral anticoagulants in children in outpatient clinics and the home setting. Pediatr Cardiol 2000;21:347–352.
23. Pierce MT, Crain L, Smith J, Mehta V. Point-of-care versus laboratory measurement of the international normalized ratio. Am J Health Syst Pharm 2000;57:2271–4.
24. Shiach CR, Campbell B, Poller L, Keown M, Chauhan N. Reliability of point-of-care prothrombin time testing in a community clinic: a randomized crossover comparison with hospital laboratory testing. Br J Haematol 2002;119:370–5.
25. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 Suppl):204S–33.
26. Choudry R, Scheitel SM, Stroebel RJ, Santrach PJ, Dupras DM, Tangalos EG. Patient satisfaction with point-of-care international normalized ratio testing and counseling in a community internal medicine practice. Managed Care Interface 2004;17:44–6.
27. Jacobson AK. The North American experience with patient self-testing of the INR. Semin Vasc Med 2003;3:295–302.
28. Sunderji R, Fung A, Gin K, Shalansky K, Carter C. Patient self-management of oral anticoagulation: a review. Can J Cardiol 2003;19:931–5.
29. Horstkotte D, Piper C. Improvement of oral anticoagulation therapy by INR self-management. J Heart Valve Dis 2004;13: 335–8.
30. Yang DT, Robetorye RS, Rodgers GM. Home prothrombin time monitoring: a literature analysis. Am J Hematol 2004;77:177–86.
31. Horstkotte D, Piper C, Wiemer M. Optimal frequency of patient monitoring and intensity of oral anticoagulation therapy in valvular heart disease. J Thromb Thrombolysis 1998;5(Suppl 1):19–24.
32. Hattersley PG. Activated coagulation time of whole blood. JAMA 1966;196:436–40.
33. Bull BS, Korpman RA, Huse WM, Briggs BD. Heparin therapy during extracorporeal circulation, I: problems inherent in existing heparin protocols. J Thorac Cardiovasc Surg 1975;69:674–84.
34. Bull BS, Huse WM, Brauer FS, Korpman RA. Heparin therapy during extracorporeal circulation, II: the use of dose-response curve to individualize heparin and protamine dosage. J Thorac Cardiovasc Surg 1975;69:685–9.
35. Doty DB, Knott HW, Hoyt JL, Koepke JA. Heparin dose for accurate anticoagulation in cardiac surgery. J Cardiovasc Surg 1979; 20:597–604.
36. Effeney DJ, Goldstone J, Chin D, Krupski WC, Ellis RJ. Intraoperative anticoagulation in cardiovascular surgery. Surgery 1981; 90:1068–74.
37. Stenbjerg S, Berg E, Albrechtsen OK. Heparin levels and activated clotting time (ACT) during open heart surgery. Scand J Haematol 1981;26:281–4.

38. Esposito RA, Culliford AT, Colvin SB, Thomas SJ, Lackner H, Spencer FC. The role of the activated clotting time in heparin administration and neutralization for cardiopulmonary bypass. J Thorac Cardiovasc Surg 1983;85:174–85.
39. Gravlee GP, Rogers AT, Dudas LM, Taylor R, Roy RC, Case LD, et al. Heparin management protocol for cardiopulmonary bypass influences postoperative heparin rebound but not bleeding. Anesthesiology 1992;76:393–401.
40. Martindale SJ, Shayevitz JR, D'Errico C. The activated coagulation time: suitability for monitoring heparin effect and neutralization during pediatric cardiac surgery. J Cardiothorac Vasc Anesth 1996;10:458–63.
41. Verska JJ. Control of heparinization by activated clotting time during bypass with improved postoperative hemostasis. Ann Thorac Surg 1977;24:170–3.
42. Babka R, Colby C, El-Etr A, Pifarre R. Monitoring of intraoperative heparinization and blood loss following cardiopulmonary bypass surgery. J Thorac Cardiovasc Surg 1977;73:780–2.
43. Berg E, Stenbjerg S, Albrechtsen OK. Monitoring heparin and protamine therapy during cardiopulmonary bypass by activated clotting time. J Extracorp Technol 1979;11:229–35.
44. Niinikoski J, Laato M, Laaksonen V, Jalonen J, Inberg MV. Use of activated clotting time to monitor anticoagulation during cardiac surgery. Scand J Thorac Cardiovasc Surg 1984;18:57–61.
45. Gravlee GP, Haddon WS, Rothberger HK, Mills SA, Rogers AT, Bean VE, et al. Heparin dosing and monitoring for cardiopulmonary bypass: a comparison of techniques with measurement of subclinical plasma coagulation. J Thorac Cardiovasc Surg 1990;99:518–27.
46. Dearing JP, Bartles DM, Stroud MR, Sade RM. Activated clotting time versus protocol anticoagulation management. J Extracorp Technol 1983;15:17–9.
47. Akl BF, Vargas GM, Neal J, Robillard J, Kelly P. Clinical experience with the activated clotting time for the control of heparin and protamine therapy during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1980;79:97–102.
48. Preiss DU, Schmidt-Bleibtreu H, Berguson P, Metz G. Blood transfusion requirements in coronary artery surgery with and without the activated clotting time (ACT) technique. Klin Wochenschr 1985;63:252–6.
49. Papaconstantinou C, Radegran K. Use of the activated coagulation time in cardiac surgery: effects on heparin-protamine dosages and bleeding. Scand J Thorac Cardiovasc Surg 1981;15:213–5.
50. Aldea GS, O'Gara P, Shapira OM, Treanor P, Osman A, Patalis E, et al. Effect of anticoagulation protocol on outcome in patients undergoing CABG with heparin-bonded cardiopulmonary bypass circuits. Ann Thorac Surg 1998;65:425–33.
51. Aldea GS, Zhang X, Memmolo CA, Shapira OM, Treanor PR, Kupferschmid JP, et al. Enhanced blood conservation in primary coronary artery bypass surgery using heparin-bonded circuits with lower anticoagulation. J Card Surg 1996;11:85–95.
52. Mullen JC, Bentley MJ, Gelfand ET, Koshal A, Modry DL, Guenther CR, et al. Coronary artery bypass surgery with heparin-coated perfusion circuits and low-dose heparinization. Can J Surg 2002;45:166–72.
53. Voyce SJ, Heller LI, Weiner BH, Laifer LI, Greenwald LL, Carey KT, et al. Clinical experience with routine activated coagulation time monitoring during elective PTCA. J Thromb Thrombolysis 1995;1:201–6.
54. Grady RM, Eisenberg PR, Bridges ND. Rational approach to use of heparin during cardiac catheterization in children. J Am Coll Cardiol 1995;25:725–9.
55. Nath FC, Muller DW, Rosenschein U, Ellis SG, Topol EJ. Heparin monitoring during coronary intervention: activated clotting time versus activated partial thromboplastin time. Can J Cardiol 1993;9:797–801.
56. Thomason T, Riegel B, Jessen D, Smith SC Jr, Gocka I, Rich M. Clinical safety and cost of heparin titration using bedside activated clotting time. Am J Crit Care 1993;2:81–7.
57. Ogilby JD, Kopelman HA, Klein LW, Agarwal JB. Adequate heparinization during PTCA: assessment using activated clotting times. Cathet Cardiovasc Diagn 1989;18:2006–9.
58. Kaluski E, Krakover R, Cotter G, Hendler A, Zyssman I, Milovanov O, et al. Minimal heparinization in coronary angioplasty: how much heparin is really warranted? Am J Cardiol 2000;85:953–6.
59. Ferguson JJ, Dougherty KG, Gaos CM, Bush HS, Marsh KC, Leachman DR. Relation between procedural activated coagulation time and outcome after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1994;23:1061–5.
60. Narins CR, Hillegass WB Jr, Nelson CL, Tcheng JE, Harrington RA, Phillips HR, et al. Relationship between activated clotting time during angioplasty and abrupt closure. Circulation 1996;93:667–71.
61. Hillegass WB, Brott BC, Chapman GD, Phillips HR, Stack RS, Tcheng JE, et al. Relationship between activated clotting time during percutaneous intervention and subsequent bleeding complications. Am Heart J 2002;144:501–7.
62. Ferguson JJ. Conventional antithrombotic approaches. Am Heart J 1995;130:651–7.
63. Klein LW, Agarwal JB. When we "act" on ACT levels: activated clotting time measurements to guide heparin administration during and after interventional procedures. Cathet Cardiovasc Diagn 1996;37:154–7.
64. Chew DP, Bhatt DL, Lincoff AM, Moliterno DJ, Brener SJ, Wolski KE, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. Circulation 2001;103:961–6.
65. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997;336:1689–96.
66. Tolleson TR, O'Shea JC, Bittl JA, Hillegas WB, Williams KA, Levine G, et al. Relationship between heparin anticoagulation and clinical outcomes in coronary stent intervention: observations from the ESPRIT trial. J Am Coll Cardiol 2003;41:386–93.
67. Pinto DS, Lorenz DP, Murphy SA, Marble SJ, DiBattiste PM, Demopoulos LA, et al, TIMI Study Group. Association of an activated clotting time < or = 250 seconds with adverse event rates after percutaneous coronary intervention using tirofiban and heparin (a TACTICS-TIMI 18 substudy). Am J Cardiol 2003;91:976–8.
68. Allison PL, Kurusz M, Graves DF, Zwischenberger JB. Devices and monitoring during neonatal ECMO: survey results. Perfusion 1990;5:193–201.
69. Graves DF, Chernin JM, Kurusz M, Zwischenberger JB. Anticoagulation practices during neonatal extracorporeal membrane oxygenation: survey results. Perfusion 1996;11:461–6.
70. Lawson DS, Walczak R, Lawson AF, Shearer IR, Ing R, Schulman S, et al. North American neonatal extracorporeal membrane oxygenation (ECMO) devices: 2002 survey results. J Extra Corpor Technol 2004;36:16–21.
71. Colby CE, Sheehan A, Benitz W, van Meurs K, Halamek LP, Moss L. Maintaining adequate anticoagulation on extracorporeal membrane oxygenation therapy: Hemochron Junior low range versus Hemochron 400. J Extracorp Technol 2003;35:35–8.

72. Mabry CD, Thompson BW, Read RC. Activated clotting time (ACT) monitoring of intraoperative heparinization in peripheral vascular surgery. Am J Surg 1979;138:894–900.
73. Mabry CD, Thompson BW, Read RC, Campbell GS. Activated clotting time monitoring of intraoperative heparinization: our experience and comparison of two techniques. Surgery 1981;90:889–95.
74. Ouseph R, Brier ME, Ward RA. Improved dialyzer reuse after use of a population pharmacodynamic model to determine heparin doses. Am J Kidney Dis 2000;35:89–94.
75. Simko RJ, Tsung FF, Stanek EJ. Activated clotting time versus activated partial thromboplastin time for therapeutic monitoring of heparin. Ann Pharmacother 1995;29:1015–21.
76. Smythe MA, Koerber JM, Nowak SN, Mattson JC, Begle RL, Westley SJ, et al. Correlation between activated clotting time and activated partial thromboplastin times. Ann Pharmacother 2002;36:7–11.

PUBLIC COMMENTS

No public comments were received on the guidelines.

Chapter **5**

Critical Care

Paul D'Orazio, Niels Fogh-Andersen, Anthony Okorodudu, Greg Shipp, Terry Shirey, and John Toffaletti

INTRODUCTION

The definition used for "critical care setting" in this chapter is any clinical setting in which patients are treated who have major organ dysfunction, severe trauma, major surgical wounds, general anesthesia, severe sepsis, or other high-acuity disorders that require life-sustaining care. These settings include intensive care units (ICUs) (e.g., ICU, CCU, NICU, SICU, PICU, CICU), surgical suites (OR), emergency departments (EDs), ambulance/helicopter transport systems, burn units, and chest pain/trauma/stroke units.

One of the most important characteristics of critical care settings is the potential for rapid (i.e., seconds to minutes) and clinically significant changes in a patient's status that may require prompt intervention. Blood pressure, heart rate and rhythm, temperature, respiration rate, and some biochemical markers can be thought of as "vital signs" that reflect these rapid changes and give evidence that a patient's physiology is unstable. In many of these situations, clinicians must be prepared to diagnose and treat these critical patients quickly to avoid subsequent damage to vital organs and systems. These environments present a potential opportunity for rapid, reliable, precise, and accurate diagnostic testing of critical biomarkers as a necessary part of the care of these patients, resulting in improvement in patient outcomes through real-time treatment of the physiological deterioration.

The required rapid diagnostic test result may be obtained from one of 2 general settings: the central laboratory setting or point-of-care testing (POCT) setting (e.g., a "STAT" laboratory, a satellite laboratory, a near-patient instrument, a bedside testing instrument). If the accuracy, imprecision, quality control, reliability, and cost-effectiveness are generally equivalent for the test settings, the "speed to treatment" or therapeutic turnaround time (TTAT) and how the TTAT relates to the time before irreversible cellular damage of vital organs become the driving forces for the clinical decision of what rapid-test setting should be used to optimally serve a given patient or clinical environment.

As shown in the upcoming pages, there is an abundance of peer-reviewed papers that show that rapid TTAT is crucial in critical care settings. Most studies have shown that POCT, when compared directly to central laboratory testing, will result in a significant decrease in TTAT *(1–3)*. Therefore, if decreased TTAT for a given critical care test leads to an outcome benefit in a given setting and if the clinical testing processes are optimized in that setting, the evidence points toward the use of POCT for that test/setting, leading to a similar improved outcome. Often, POCT is placed into clinical settings without modifications in the processes that were in place before the change. However, process changes are often required in clinical settings after POCT introduction and before improved outcomes can be observed. Otherwise well-designed clinical studies *(4, 5)* that fail to optimize processes (e.g., inpatient admission, response to a 90-min central laboratory result vs a 5-min POCT result) or variables (e.g., testing for noncritical analytes, measuring metric endpoints [e.g., LOS] instead of clinical endpoints [e.g., morbidity, mortality]; see sections below) with introduction of POCT may lead to equivocal results. Future clinical studies comparing POCT to central laboratory testing must take process optimization into account.

Although it has been recognized by many experienced clinicians and laboratorians that POCT has improved patient outcomes during the past 15 years, most of the evidence for improvement in patient outcomes, with the use of POCT in critical care settings, has been anecdotal or intuitive as opposed to being elucidated through well-designed clinical studies. Therefore, more well-designed comparative patient outcome studies and evidence (i.e., each POCT setting vs central laboratory testing) are necessary to more clearly define POCT's definitive role in improving health outcomes in critical care settings.

The following recommendations address the above issues with some of the most commonly measured analytes in the critical care setting: arterial blood gases (PO_2, PCO_2, pH), glucose, lactate, magnesium, cooximetry (O_2 saturation, carboxyhemoglobin [HbCO], methemoglobin [MetHb]), sodium, potassium, chloride, and ionized calcium.

Literature searches were conducted through online databases (e.g., PubMed, MEDLINE) and private libraries maintained by members of the focus group. Peer-reviewed articles from private libraries were used in the systemic review only if the citations and abstracts could be found in the online databases. The search strategy started with the general

terms (e.g., point-of-care testing, bedside testing) and concluded in specific settings, disease states, and outcomes (e.g., emergency department, blunt trauma, mortality). Method comparison studies that only compared a POCT system to a central laboratory system for analytical performance were excluded from the review.

The 2 clinical questions that we sought to address for each analyte and for a given clinical setting, disease state, and outcome measure were:

1. Is there evidence in the peer-reviewed literature that more rapid TTAT of a (*analyte*) result leads to (*outcome*) improvement in the (*setting*) for patients with (*disease*)?
2. Does POCT of (*analyte*) for patients with (*disease*) in the (*setting*) improve (*outcome*) when compared to core laboratory testing?

ARTERIAL BLOOD GASES

Arterial blood gases typically have uses in a variety of settings (including ICUs, ED, cardiac surgery, and extracorporeal membrane oxygenation [ECMO]), each with its own requirements for speed in obtaining results.

Intensive Care Unit

Guideline 37. *There is fair evidence that more rapid TTAT of ABG results in several types of ICU patients leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of ABG results be considered as a way to improve outcomes in at least some types of ICU patients.* (Literature Search 12)

Strength/consensus of recommendation: B

Level of evidence: I

A major concern for ICUs is the maintenance of tissue oxygenation, ventilation, and normal acid-base status. Because life-threatening changes in these characteristics can occur suddenly, rapid results are often needed for effective monitoring and treatment in the ICU *(6)*. The following paragraphs summarize studies that showed either a positive impact or little impact of rapid TTAT in the ICU setting.

In a report on 2 critically ill patients who required frequent arterial blood gas monitoring for assessing pulmonary function and adjusting ventilator settings, some clinical and cost advantages were seen during several days in these ICU patients *(7)*.

During high-frequency oscillatory ventilation (HFOV) in preterm infants with severe lung disease, very rapid results were necessary to detect and evaluate the rapid changes in PO_2 and PCO_2 that occurred with changes in oscillatory amplitude *(8)*.

In patients with sepsis, early goal-directed therapy (EGDT) that was begun before admission to the ICU (i.e., often in the ED) resulted in a significant reduction in mortality (31%) compared with standard treatment protocol (47%). The therapeutic regimen included direct response to frequent monitoring of central venous oxygen saturation, pH, and lactate levels. Among the parameters that were significantly improved after EGDT (7–72 h after the start of therapy) were central venous oxygen saturation (70% vs 65%; $p < 0.001$), pH (7.40 vs 7.36; $p < 0.001$), and lactate (3.0 mmol/L vs 3.9 mmol/L; $p < 0.02$) *(9)*.

In 12 cases of neonatal seizures, clinically significant acidosis was found in 30% of neonates, and the majority of seizures were not associated with intrapartum hypoxia or ischemia *(10)*. In another study, an umbilical artery pH < 7.0 was the most important blood gas characteristic in predicting early onset of neonatal seizure *(11)*. Therapeutic TAT between a central blood gas laboratory, a satellite blood gas laboratory, and POCT devices was compared in a study *(12)*. The article contained the following observations about TTAT and outcomes: (1) more frequent, rapid, blood gas testing did not often cause a change in treatment; (2) most blood gas results were used to confirm that treatment was going well (i.e., patient well ventilated); and (3) glucose and electrolyte testing produced a change in treatment far more often than did blood gas testing.

Guideline 38. *There is fair evidence that POCT of ABG results in the ICU leads to improved clinical outcomes when POCT is found to lead to reduced TTAT compared to that in the central laboratory. Overall, we recommend that POCT of ABG results be considered as a way to improve outcomes in ICU patients. More prospective randomized controlled studies need to be performed.* (Literature Search 13)

Strength/consensus of recommendation: B

Level of evidence: II

Blood gas testing has been mentioned as the most-often-needed POC test in the ICU *(13, 14)*. The observed advantages of POCT were decreased TTAT, fewer errors, and reduced blood loss. There was much less evidence for earlier diagnosis, decreased LOS in ICUs, decreased costs, or decreased mortality. In a neonatal/pediatric ICU, only a marginal improvement in TAT was achieved, and costs were comparable only if labor was not included in POC test costs *(15)*.

Certain modes of POC testing may or may not be optimal for ICU use. An early report from 1990 described the essential nature of blood gas tests in ICU care at a single medical center, with potential benefits and shortcomings of POC blood gas instruments (and pulse oximeters) mentioned *(6)*. Benefits included real-time treatment with reduced TTAT, reduction in unneeded therapies, more rapid administration of needed therapies, decrease in hospital/ICU stay, decrease in medical costs, reduction in laboratory errors (i.e., labeling, transport), and acceptance by

clinicians and patients. Shortcomings included less reliability (in general) compared with laboratory testing; pulse oximetry unable to monitor PO_2, PCO_2, or pH, so it could not be used alone; no direct evidence for improved clinical outcomes; quality-control issues with nonlaboratory users; and need for more clinical studies.

In some hospitals, the central laboratory can perform blood gas measurements as quickly as POCT methods. This was documented in a study at a large academic medical center *(16)*. The quality in both settings was found to be satisfactory. Using a pneumatic tube system, the central laboratory's TTAT was equivalent to that of a satellite laboratory in a neonatal ICU. The total cost per reportable result was substantially higher for the satellite. Therefore, the cost-benefit analysis revealed that the central laboratory was an appropriate path for the ABG testing.

Staff satisfaction was evaluated *(12)*, comparing a central blood gas laboratory, a satellite blood gas laboratory, and other POCT devices. Therapeutic TAT was about the same for satellite and POC testing, with both much faster than the central laboratory. The satellite laboratory scored the highest overall for staff satisfaction, with other types of POC blood gas testing being second.

In newborns on ventilators, use of an in-line device required less blood (1.2 vs 6.7 mL) and led to faster ventilator changes (2 vs 26 min), although no data suggested this led to improved outcomes *(17)*.

In a study of blood gases measured by 3 techniques—intraarterial probes, transcutaneous devices, and standard in vitro blood gas analyzers—although correlations were reasonable, the report noted that many intraarterial probes failed during use and were much more expensive *(18)*. An early report stands the test of time in its assessment and predictions of the limitations of noninvasive devices, implantable blood gas sensors, and in-line sensors *(19)*. Although numerous technical problems have been found, most are related to formation of clots around the invasive sensor.

An interdepartmental team approach is often necessary to achieve the full potential benefits of POC testing. In one report, POCT was regarded as a supplement, not a replacement, for conventional laboratory services. Clinicians expressed a preference for rapid transport systems rather than bedside testing as the solution *(14)*.

Guideline 39. *There is some evidence that POCT of ABG results in the ICU may lead to reduced costs when compared to the central laboratory testing, but the balance of benefit to no benefit is too close to justify in a given hospital. We have no recommendation for POCT of ABG results being considered as a way to reduce costs in the ICU. More prospective randomized controlled studies need to be performed.* (Literature Search 14)

Strength/consensus of recommendation: I

Level of evidence: II

With decision analysis methods, 3 models of postoperative POC blood gas testing for CABG patients were developed and evaluated for economic value. These were (1) a STAT laboratory in a large tertiary-care medical center with 15-min TAT; (2) STAT testing in a central laboratory of a large community hospital with a 30-min TAT; and (3) STAT testing in a central laboratory of a medium-large community hospital with a 45-min TAT *(20)*. The cost savings related to faster TAT were primarily due to fewer adverse events or earlier detection of these adverse events. Some adverse clinical events benefited greatly by faster TAT (ventricular arrhythmias and cardiac arrests), whereas others were relatively independent of TAT (postoperative bleeding and iatrogenic anemia). This study used clinical experts to define probabilities of adverse events leading to a mathematical analysis instead of a prospective clinical study.

Although blood gas testing was a small part of the testing evaluated, one report describes the process, the economics, the attitudes, and the clinical and economic benefits of implementing POC testing in a large medical center that previously had a variety of STAT-type laboratories *(21)*. Although considerable cost savings ($392,000 per year) were reported, the majority of these were in labor savings ($495,000 per year), which more than made up for the otherwise increased cost ($145,000 per year) of POCT. POCT is especially cost-effective when it allows closure of a pre-POCT laboratory that is extremely inefficient, as one described here that averaged less than 1 test/day per FTE (5.0 FTEs worked in this laboratory).

Emergency Department

Guideline 40. *There is fair evidence that more rapid TTAT of ABG results, in some ED patients, leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of ABG results be considered as a way to improve outcomes in at least some types of ED patients.* (Literature Search 15)

Strength/consensus of recommendation: B

Level of evidence: II

In a study of 116 nonintubated adult blunt-trauma patients, ~20% had conditions possibly related to occult shock. Blood gas results helped reveal patients who were hyperventilating ($PCO_2 < 30$ mm Hg) and who had unrecognized metabolic acidosis, patients with worse-than-expected metabolic acidosis, and patients with low PO_2 who responded to positive-pressure ventilation *(22)*. Because blood gas results could help to triage such patients from those who are more stable, they concluded that ABG analysis should be performed on all blunt-trauma patients who meet even minimal-severity criteria.

Guideline 41. *There is fair evidence that POCT of ABG results leads to improved clinical outcomes in some types of ED patients when POCT is found to lead to reduced TTAT compared with that of the central laboratory. Overall, we recommend that POCT of ABG results be considered as a way to improve outcomes in ED patients. More prospective randomized controlled studies need to be performed.* (Literature Search 16)

Strength/consensus of recommendation: B

Level of evidence: II

A review of 99 articles published between 1985 and 2001 on overall POC testing in the ED reported that (1) POC technology appears to be reliable in an ED setting; (2) cost and connectivity are difficult but important issues for greater acceptance of POCT in the ED; (3) ultimately, improved patient care must be evaluated to offset the costs of POC testing *(23)*. The impact of POC testing on outcomes in the ED, ICU, OR, and primary care can be measured in a variety of ways. These include mortality, morbidity, earlier or more effective intervention, lower cost while maintaining quality, safety, patient or physician satisfaction, and return to normal lifestyle *(24)*.

For patients admitted to the ED, POC blood gas testing allowed a decision to be made an average of 21 min earlier compared to central laboratory testing *(5)*. Overall, for all POC tests, a more rapid result led to a change in management in 6.9% of ED patients. Another report similarly noted that, although electrolytes and BUN did not influence initial management of major trauma, Hb, glucose, blood gases, and lactate occasionally helped reduce morbidity or save resources *(25)*. Another report noted that rapid delivery of blood gas results was required for respiratory distress, severe trauma, and head injury *(24)*.

Portable POC devices are often used for patients transported to the ED by helicopter and ambulances. In one report, POC testing allowed the crew to assess the patient, identify problems, and administer treatment earlier *(26)*.

Cardiac Surgery: Adult and Neonatal

Guideline 42: *There is fair evidence that more rapid TTAT of ABG results in cardiac surgery patients leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of ABG results be considered as a way to improve outcomes in cardiac surgery patients.* (Literature Search 17)

Strength/consensus of recommendation: B

Level of evidence: II

During cardiac surgery, blood gas and hemoglobin measurements are often used to calculate O_2 consumption and CO_2 production, with blood lactate measured to evaluate the presence of ischemia *(27)*. Even when O_2 consumption is low during normothermic cardiopulmonary bypass (CPB), the normal blood lactate suggests there is no tissue ischemia present. In another study, the arterial PO_2 decreased markedly during deep hypothermic circulatory arrest (DHCA), and the measurement of arterial PO_2 during DHCA provided a surrogate method for determining maximum safe time under DHCA for adults *(28)*.

In pediatric cardiac surgery, indwelling monitors are often not practical. Therefore, rapid blood gas and other test results often provide the only means to monitor the patient. Rapid blood gas results were noted to allow better control of cerebral blood flow and oxygen delivery in infants during cardiac surgery *(29)*. Another report makes a strong case for rapid blood gas results during operations in neonates with congenital heart defects, during which ventilator adjustments are critical for optimal patient care *(30)*. A recent study of 155 patients presented data that suggest that an abnormal lactate pattern may be useful in determining the timing of cardiopulmonary support initiation in hemodynamically stable patients with high or rising lactate values, before cardiac arrest or end-organ damage *(31)*.

Guideline 43. *There is fair evidence that POCT of ABG results leads to improved clinical outcomes in cardiac surgery patients when POCT is found to lead to reduced TTAT compared to that of the central laboratory. Overall, we recommend that POCT of ABG results be considered as a way to improve outcomes in cardiac surgery patients. More prospective randomized controlled studies need to be performed.* (Literature Search 18)

Strength/consensus of recommendation: B

Level of evidence: II

A recent prospective study (with a historical control group) that included 2366 post–congenital heart surgery patients (710 patients in the POCT group; 1656 patients in the central laboratory control group) evaluated oxygen debt (ischemia) in these critically ill patients as monitored by whole-blood lactate. The study results showed a 50% reduction ($P = 0.02$) in mortality overall between the POCT cohort compared with the central laboratory cohort. Improvement was greatest in the neonates and highest-risk patients *(32)*.

In another clinical evaluation, POC testing during open-heart surgery of ABGs reduced the TAT from 25 min (central laboratory) to 3 min and enhanced the care of patients *(33)*.

GLUCOSE

Guideline 44. *There is good evidence that more rapid TTAT of glucose results in critical care patient settings leads to improved clinical outcomes. Overall, we strongly recommend that more rapid TTAT of glucose results be considered as a way to improve outcomes in critical care patients.* (Literature Search 19)

Strength/consensus of recommendation: A

Level of evidence: I

Four observations have been documented in the literature as important rationales for time-critical testing of glucose: (1) glucose levels may not be known at times when rapid therapeutic options (i.e., glucose or insulin infusions) can influence clinical outcomes *(34–38)*; (2) glucose levels may change rapidly and dramatically in critically ill patients *(35*, *39)*; (3) there are time-dependent risks associated with hypoglycemia, ranging from symptoms of neuroglycopenia (e.g., headache, confusion, blurred vision, dizziness, and epigastric discomfort) to seizures, loss of consciousness, irreversible damage, and even death *(40–48)*; and (4) there are also time-dependent risks associated with hyperglycemia, including irreversible/ischemic brain damage, nosocomial infections, polyneuropathy, and mortality *(35, 44–46, 48–63)*. Taken together, the composite clinical outcome information reveals a persuasive argument for the need for accurate and precise time-critical glucose results in many critical care settings.

In a landmark article *(61)*, Van den Berghe et al demonstrated that intensive insulin therapy maintaining blood glucose at or <110 mg/dL reduces morbidity and mortality among critically ill patients in the surgical ICU, regardless of whether they had a history of diabetes mellitus.

Guideline 45. *There is good evidence that POCT of glucose results leads to improved clinical outcomes in critical care patient settings when POCT is found to lead to reduced TTAT compared to that of the central laboratory. Overall, we strongly recommend that POCT of glucose results be considered as a way to improve outcomes in critical care patients.* (Literature Search 20)

Strength/consensus of recommendation: A

Level of evidence: I

Furnary et al *(64)* demonstrated that continuous insulin infusion eliminates the incremental increase in in-hospital mortality after coronary artery bypass grafting (CABG) associated with diabetes mellitus. They concluded that continuous insulin infusion should become the standard of care for glycometabolic control in patients with diabetes who are undergoing a CABG procedure. Assuming the imprecision and accuracy of the POCT glucose assay is adequate, Furnary et al *(64)* stated that POCT is a necessity for administering the Portland Protocol because there are points in the protocol at which the insulin administration is adjusted every 30 min.

LACTATE

Lactate measurements typically have uses in a variety of critical settings, each with its own requirements for speed in obtaining results.

Guideline 46. *There is good evidence that more rapid TTAT of lactate results in critical care patient settings leads to improved clinical outcomes. Overall, we strongly recommend that more rapid TTAT of lactate results be considered as a way to improve outcomes in ED, OR, and ICU patients.* (Literature Search 21)

Strength/consensus of recommendation: A

Level of evidence: I

To interpret lactate requires 2 key pieces of information: (1) an understanding of the clinical circumstance leading to the increase in lactate (e.g., late septic shock, exercise, liver compromise), and (2) the length of time that lactate has been increased (which requires serial lactate analyses to give an estimate of cumulative oxygen debt). Depending on the clinical setting, recognizing an increase in lactate as soon as possible, coupled with immediate resuscitation, is usually associated with improved outcomes *(65–97)*.

Any location handling critically ill patients (e.g., ED, OR, ICU) whose lactate levels may be increased can better serve their patients by having rapid TTAT of lactate results, including:

- In the ED, patients presenting with acute abdomen *(65–68)*, acute myocardial infarction *(69*, *70)*, asthma *(71)*, cardiac arrest *(72)*, cyanide poisoning *(73–75)*, intracranial pressure *(76)*, pulmonary embolism *(77)*, occult illness *(78–81)*, shock *(82)*, need for transfusion *(83)*, and trauma *(84–86)* may benefit.
- In the OR, patients with congenital heart surgery *(87)*, intracranial pressure *(76)*, liver transplant *(88)*, shock *(82)*, thoracoabdominal aortic aneurysm *(89)*, and transfusion *(83*, *86)* may benefit.
- In the ICU, patients include those with acute myocardial infarction *(70)*, anemia of prematurity *(83)*, circulatory shock *(82*, *90)*, cyanide poisoning *(73–75)*, ECMO *(91*, *92)*, heart surgery *(93–95)*, intracranial pressure *(76)*, liver transplant *(88)*, high-risk surgery (abdominal, vascular) *(96)*, pulmonary embolism *(77)*, transfusion *(83*, *86)*, and burns *(97)* may benefit.

Rivers et al *(9)* showed that goal-directed therapy provided at the earliest stages of severe sepsis and septic shock

(diagnosed and frequently monitored by lactate and other blood gas analytes [e.g., central venous oxygen saturation, pH]), before admission to the ICU, reduced the incidence of multiorgan dysfunction, mortality, and the use of healthcare resources. They concluded that the improved outcomes arise from the early identification of patients at high risk for cardiovascular collapse and from early therapeutic intervention to restore a balance between oxygen delivery and demand.

Guideline 47. *There is good evidence that POCT of lactate results leads to improved clinical outcomes in critical care patient settings when POCT is found to lead to reduced TTAT compared to that of the central laboratory. Overall, we recommend that POCT of lactate results be considered as a way to improve outcomes in critical care patients. More prospective randomized controlled studies need to be performed.* (Literature Search 22)

Strength/consensus of recommendation: B

Level of evidence: II

In a recent prospective study with a historical control group, a goal-directed therapy algorithm (based on frequent serial lactate values obtained from a POCT device) was used in an attempt to test the hypothesis that rapid diagnostic testing combined with goal-directed therapy could reduce the mortality of patients after congenital heart surgery *(32)*. The results showed a 50% reduction ($P = 0.02$) in mortality overall between the POCT cohort compared to the central laboratory cohort. The most significant reductions in mortality were seen in neonates (73%; $P = 0.02$) and patients undergoing higher-risk operations (67%; $P = 0.006$).

MAGNESIUM

Guideline 48. *There is fair evidence that more rapid TTAT of magnesium results in critical care patient settings leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of magnesium results be considered as a way to improve outcomes in critical care patient settings.* (Literature Search 23)

Strength/consensus of recommendation: B

Level of evidence: II

Magnesium has clinical value in cardiovascular and oxidative stress/inflammatory settings *(98–103)*. It is a cofactor in more than 325 enzymatic reactions, including virtually all of the reactions involved in energy exchange. Its involvement with nucleoside triphosphate pumps makes it very important to electrolyte balance. This, in turn, makes it important to conduction and contraction and, therefore, to cardiac rhythm, cardiac output, and blood pressure. It is also a cofactor for enzymes involved in eliminating oxygen free radicals and controlling nuclear factor kappa B activation (cytokine and adhesion molecule production). In general, magnesium is a regulating factor in hemodynamics, vascular tone, reperfusion injury, platelet aggregation, and the inflammatory response *(98–103)*.

Any location handling critically ill patients (e.g., ED, OR, ICU) with cardiovascular symptoms, or where reperfusion injury or an inflammatory response exists, may benefit from rapid TTAT of magnesium results to guide magnesium therapy. This includes patients experiencing electrolyte imbalances, being treated with inotropes (digoxin) and antiarrhythmic drugs, experiencing hypoxia, or receiving i.v. magnesium therapy:

- In the ED, patients presenting with ischemic heart disease (including AMI) *(104–117)*, arrhythmia *(106–109, 113, 117–120)*, asthma *(121)*, cardiac arrest *(122)*, cerebral vascular tension/vasospasm *(107, 123)*, coagulation problems *(124)*, coronary vasospasm *(107, 125)*, digitalis toxicity *(107–109, 113, 117, 126)*, electrolyte imbalances from diuretics *(108, 109)*, adverse drug reactions (nitrates and ACE inhibitors) *(127)*, headache *(128)*, head trauma *(129–136)*, heart failure *(108, 117–120)*, hypotension *(137)*, infarct *(138)*, preeclampsia/eclampsia *(107, 139)*, seizures *(137)*, sepsis *(140–142)*, and stroke *(107)* may benefit.
- In the OR, patients presenting with arrhythmia *(106, 107, 117, 118, 138)*, experiencing clotting problems *(124)*, coronary vasospasm *(107, 125)*, cerebral vasospasm *(107)*, head trauma/surgery *(130, 131, 133–136)*, heart surgery *(122, 143–146)*, liver transplant *(147)*, and stroke *(107)* may benefit.
- In the ICU, patients presenting with ischemic heart disease (including AMI) *(105–116)*, arrhythmia *(106–109, 113, 117–120, 138, 148)*, cardiac arrest *(122)*, cardiogenic shock *(149)*, cerebral vascular tension/vasospasm *(107, 123)*, clotting *(124)*, coronary vasospasm *(107, 125)*, cramps *(150, 151)*, digitalis toxicity *(107–109, 113, 117, 126)*, diuretic therapy *(108, 109)*, drug therapy (nitrates and ACE inhibitors) *(127)*, head trauma/surgery *(129–136)*, heart failure *(108, 117–120)*, heart surgery *(143–146, 148, 152)*, hypotension *(137)*, infarct *(138)*, liver transplant *(147)*, neonates from mothers receiving Mg therapy *(153, 154)*, pain *(155)*, seizures *(137, 148)*, sepsis *(140–142)*, shock *(156)*, and stroke *(107)* may benefit.

Guideline 49. *There is insufficient evidence that POCT of magnesium results leads to improved clinical outcomes in critical care patient settings. Overall, we recommend that prospective randomized controlled studies be performed.* (Literature Search 24)

Strength/consensus of recommendation: I

Level of evidence: III

Taken together, the composite TTAT information above *(98–156)* demonstrates that accurate and precise time-critical Mg results, supplied by POCT, may lead to better outcomes in critical care settings. However, no POCT outcome studies of magnesium in critical care patient populations were found.

COOXIMETRY

"Cooximetry" means measurement of hemoglobin pigments by dedicated multiwavelength spectrophotometry. The instrument for that may be standalone or part of a blood gas analyzer. It usually measures and reports total hemoglobin, oxygen saturation (=HbO_2/(HbO_2 + deoxyHb)) or oxyhemoglobin fraction (=HbO_2/tHb), HbCO, and MetHb.

Oxygen Saturation

Guideline 50. *There is fair evidence that more rapid TTAT of oxygen saturation results in critical care patient settings leads to improved clinical outcomes. Overall, we recommend that rapid TTAT of oxygen saturation results be considered as a way to improve outcomes in critical care patient settings.* (Literature Search 25)

Strength/consensus of recommendation: B

Level of evidence: II

Oxygen saturation by cooximetry can be used to check the PO_2 of blood gas analyzers because oxygen saturation and PO_2 are tightly linked (through the oxygen hemoglobin equilibrium curve). A discrepancy between predicted and measured PO_2 may indicate an error.

Oxygen saturation by cooximetry can also be used to check the pulse oximeter, which is widely used for monitoring a patient's arterial oxygen saturation. Pulse oximetry is a noninvasive POCT technology that continuously measures the oxygen saturation of pulsating blood (by 2-wavelengths absorptiometry). A cooximeter, on the other hand, requires an arterial sample.

Pulse oximetry has been shown to reveal hypoxemic episodes accurately *(157)*. In a number of clinical settings (e.g., asthma, obstetrics, neonatal ICU), pulse oximetry has been shown to improve outcomes *(158–160)*.

Guideline 51. *POCT of oxygen saturation by cooximetry is not required in critical care settings. Overall, we recommend pulse oximetry as the preferred method.* (Literature Search 26)

Strength/consensus of recommendation: C

Level of evidence: II

The applications of oxygen saturation by cooximetry do not require POCT. Pulse oximetry is preferred for POCT of oxygen saturation, rather than by cooximetry.

Carboxyhemoglobin

Guideline 52. *There is good evidence that POCT of HbCO results leads to improved clinical outcomes in critical care patient settings when POCT is found to lead to reduced TTAT compared to that of the central laboratory. Overall, we recommend that POCT of HbCO results be considered as a way to improve outcomes in critical care patients. More prospective randomized controlled studies need to be performed.* (Literature Search 27)

Strength/consensus of recommendation: B

Level of evidence: II

The diagnosis of carbon monoxide (CO) poisoning requires that the physician suspect the condition and order a determination of HbCO. Two studies demonstrate the benefit of screening of patients presenting with flulike symptoms *(161)* or headache *(162)* for CO poisoning.

The studies were performed at 2 different EDs and involved all patients presenting with flu-like symptoms or headache in inner-city populations during the heating months. The emergency physicians suspected or diagnosed none of the 20 patients with HbCO $>$ 10% using clinical examination alone in spite of a prevalence of 20% of this condition. The advantage of screening for CO poisoning is to avoid a return to a hazardous environment, with potentially fatal consequences that may include the cohabitants.

A correct and timely diagnosis of occult CO poisoning in this setting requires easy access to POCT. A third study *(163)* used HbCO by cooximetry to screen all patients admitted from the ED with diagnoses other than CO poisoning. In this population, only 0.4% had HbCO $>$ 10%, 1 of whom was presenting with seizures.

Methemoglobin

Guideline 53. *There is fair evidence that POCT of MetHb results leads to improved clinical outcomes in critical care patient settings. Overall, we recommend that POCT of MetHb results be considered as a way to improve outcomes in critical care patients and that more prospective randomized controlled studies need to be performed.* (Literature Search 28)

Strength/consensus of recommendation: B

Level of evidence: II

A literature review *(164)* describes 54 cases of benzocaine-induced methemoglobinemia during intubation and endoscopy/bronchoscopy. Administration of the local anesthetic benzocaine may produce life-threatening methemoglobinemia. Early detection of the condition is necessary for timely intervention, and it can best be achieved with POCT.

Two studies describe increased MetHb in patients with sepsis and septic shock. One *(165)* compared MetHb between groups of patients in an ICU, and one *(166)* used MetHb as a marker of endogenous nitric oxide production in children with septic shock in a pediatric ICU and compared the results to a matched healthy control group. In both studies, MetHb was significantly higher in patients with sepsis. However, MetHb did not correlate with clinical markers or severity of illness. Sepsis is potentially lethal and must be diagnosed early.

ELECTROLYTES (NA^+, K^+, CL^-)

Emergency Department

Guideline 54. *There is fair evidence that POCT of potassium results leads to improved clinical outcomes in ED patients when POCT is found to lead to reduced TTAT compared to that of the central laboratory. Overall, we recommend that POCT of potassium results be considered as a way to improve outcomes in ED patients. More prospective randomized controlled studies need to be performed.* (Literature Search 29)

Strength/consensus of recommendation: B

Level of evidence: II

Several studies have shown that TTAT is clearly decreased when POCT is used for measurement of electrolytes in the ED, leading to faster decisions on patient management *(4, 5, 167, 168)*.

In one study using randomized controls, change in treatment where timing was critical took place in 7% of patients when POCT was used *(5)*. However, there is no clear evidence that outcomes such as patient length of stay in the ED or in-hospital or total mortality are improved when POCT is used for initial ED screening *(4, 5)*. In one study *(167)*, patient LOS in the ED was decreased to 3:28 from 4:22, but only for discharged patients because patients destined to be hospitalized required further diagnostic testing not offered at the point of care.

Therapeutic TAT is shortened when POCT for electrolytes is used for screening of trauma patients in the ED *(168)*. However, it is not clear that changes in patient management or outcomes result. One exception is measurement of K^+, where there is some indirect evidence that availability of K^+ results in a time-urgent manner (preoperatively) would improve patient outcomes *(168)*. Rapid availability of Na^+ and Cl^- results appear not to be influential in changing treatment of trauma patients *(25, 168)*. An important benefit of using POCT to screen trauma patients is the ability to conduct the blood analysis with small sample volumes, resulting in reduction in blood loss and reduced risk from transfusion when POCT is used *(168)*.

No change in patient treatment in the ED resulted from measurement of electrolytes (Na^+, K^+) with POCT during air transport to the ED *(169)*.

Intensive Care Unit

Guideline 55. *There is little known evidence that POCT of electrolyte results leads to improved clinical outcomes in the ICU setting. Overall, we have no recommendation for POCT of electrolyte results being considered as a way to improve outcomes in the ICU. Prospective randomized controlled studies need to be performed.* (Literature Search 30)

Strength/consensus of recommendation: I

Level of evidence: III

TTAT (relative to the central laboratory) is improved when POCT (either near-patient testing or satellite laboratory) is used for the measurement of electrolytes in the adult ICU *(25)*. ICU staff also favored a dedicated satellite laboratory. There are few correlations between reduced TAT for electrolyte results in the ICU and improved patient outcomes. One important advantage of using POCT in the ICU is the ability to conduct analyses using small sample volumes, resulting in reduction in blood loss and reduced risk from transfusion when POCT is used *(170)*.

IONIZED CALCIUM

Ionized calcium is a component of the critical care profile in the ED, OR, and ICU *(171)*.

Emergency Department

Guideline 56. *There is fair evidence that POCT of ionized calcium results leads to improved clinical outcomes in circulatory arrest patients when POCT is found to lead to reduced TTAT compared to that of the central laboratory. Overall, we recommend that POCT of ionized calcium results be considered as a way to improve outcomes in circulatory arrest patients. More prospective randomized controlled studies need to be performed.* (Literature Search 31)

Strength/consensus of recommendation: B

Level of evidence: II

The availability of this test in the ED leads to faster TAT (within 5 min) and reduced blood utilization. The significance of rapid ionized calcium measurement was stressed for cardiac arrest patients because only 1%–3% of these patients leave the hospital alive or impaired *(172)*. The patients require prompt evaluation of ionized calcium and other electrolytes for proper interpretation and prompt initiation of therapy.

Operating Room

Guideline 57. *There is little evidence that POCT of ionized calcium results leads to improved clinical outcomes in surgical patients when POCT is found to lead to reduced TTAT compared to that of the central laboratory. Overall, we cannot recommend that POCT of ionized calcium results be considered as a way to improve outcomes in surgical patients. More prospective randomized controlled studies need to be performed*. (Literature Search 32)

Strength/consensus of recommendation: I

Level of evidence: III

The significance of rapid ionized calcium measurement was stressed for patients undergoing cardiopulmonary bypass and liver transplant surgeries *(171)*. The patients require prompt evaluation of ionized calcium and other electrolytes for proper interpretation and prompt initiation of therapy.

Intensive Care Unit

Guideline 58. *There is fair evidence that more rapid TTAT of ionized calcium results in the ICU leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of ionized calcium results be considered as a way to improve outcomes in ICU patients.* (Literature Search 33)

Strength/consensus of recommendation: B

Level of evidence: II

The availability of this test in the ICU leads to faster TAT and reduced blood utilization. The significance of rapid ionized calcium measurement was stressed for shock burns and electrolyte imbalance patients and those patients receiving blood transfusion. The patients require prompt evaluation of ionized calcium and other electrolytes for proper interpretation and prompt initiation of therapy *(171)*.

An article by Singh et al *(173)* showed the significance and frequency of abnormalities of calcium in the PICU and the fact that mortality rate was higher in hypocalcemic patients. These hypocalcemic patients had longer hospital stays. In addition, Zivin et al *(174)* showed that hypocalcemia was associated with higher mortality and correlates with severity of illness.

Guideline 59. *There is fair evidence that POCT of ionized calcium results leads to improved clinical outcomes in ICU patients when POCT is found to lead to reduced TTAT compared to that of the central laboratory. Overall, we recommend that POCT of ionized calcium results be considered as a way to improve outcomes in ICU patients. More prospective randomized controlled studies need to be performed.* (Literature Search 34)

Strength/consensus of recommendation: B

Level of evidence: II

In a comprehensive review of criteria for POCT instrument evaluation, test menus, analysis times, and performance criteria, Kost *(175)* indicated that, in the critical care setting, ionized calcium measurement is obligatory because of the well-documented impact of ionized calcium on vital functions such as conduction and contraction of muscle cells. Specific examples cited included impact of ionized calcium for critically ill individuals with sepsis, hypocalcemia crisis, hypotension, heart failure, hyperkalemic dysrhythmia, and electromechanical dissociation *(176, 177)*. This review included references to the excellent correlation between the degree of hypocalcemia with mortality rate and the use of 0.70 mmol/L as a low-limit threshold for ionized calcium *(178)*. It alludes to the fact that POCT of ionized calcium is critical for the continued proper management of critically ill patients and patients undergoing transplantation, cardiac, or other surgical procedure.

REFERENCES

1. Lee-Lewandrowski E, Corboy D, Lewandrowski K, Sinclair J, McDermot S, Benzer TI. Implementation of a point-of-care satellite laboratory in the emergency department of an academic medical center: impact on test turnaround time and patient emergency department length of stay. Arch Pathol Lab Med 2003;127: 456–60.
2. Collinson PO. The need for a point of care testing: an evidence-based appraisal. Scand J Clin Lab Invest Suppl 1999;230:67–73.
3. Christenson R. Biochemical markers and the era of troponin. Md Med 2001;(Suppl):98–103.
4. Parvin CA, Lo SF, Deuser SM, Weaver LG, Lewis LM, Scott MG. Impact of point-of-care testing on patients' length of stay in a large emergency department. Clin Chem 1996;42:711–7.
5. Kendall J, Reeves B, Clancy M. Point of care testing: randomised controlled trial of clinical outcome. BMJ 1998;316:1052–7.
6. Zaloga GP. Evaluation of bedside testing options for the critical care unit. Chest 1990;97:185S–90S.
7. Menzel M, Henze D, Soukup J, Engelbrecht K, Senderreck M, Clausen T, et al. Experiences with continuous intra-arterial blood gas monitoring. Minerva Anestesiol 2001;67:325–31.
8. Morgan C, Dear PR, Newell SJ. Effects of changes in oscillatory amplitude on $PaCO_2$ and PaO_2 during high frequency oscillatory ventilation. Arch Dis Child Fetal Neonatal Ed 2000;82:F237–42.
9. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early Goal-Directed Therapy Collaborative Group. Early

goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77.
10. Graham EM, Holcroft CJ, Blakemore KJ. Evidence of intrapartum hypoxia-ischemia is not present in the majority of cases of neonatal seizures. J Matern Fetal Neonatal Med 2002;12:123–6.
11. Williams KP, Singh LA. The correlation of seizures in newborn infants with significant acidosis at birth with umbilical artery cord gas values. Obstet Gynecol 2002;100:557–60.
12. Kilgore ML, Steindel SJ, Smith JA. Evaluating stat testing options in an academic health center: therapeutic turnaround time and staff satisfaction. Clin Chem 1998;44:1597–1603.
13. Drenk N. Point of care testing in critical care medicine: the clinician's view. Clin Chim Acta 2001;307:3–7.
14. Gray TA, Freedman DB, Burnett D, Szczepura A, Price CP. Evidence based practice: clinicians' use and attitudes to near patient testing in hospitals. J Clin Pathol 1996;49:903–8.
15. Murthy JN, Hicks JM, Soldin SJ. Evaluation of i-STAT portable clinical analyzer in a neonatal and pediatric intensive care unit. Clin Biochem 1997;30:385–9.
16. Winkelman JW, Wybenga DR. Quantification of medical and operational factors determining central versus satellite laboratory testing of blood gases. Am J Clin Pathol 1994;102:7–10.
17. Raake JL, Taeed R, Manning P, Pearl J, Schwartz SM, Nelson DP. Evaluation of a fiberoptic blood gas monitor in neonates with congenital heart disease. Respir Care 2000;45:1105–12.
18. Lang CJ, Heckmann JG, Erbguth F, Druschky A, Haslbeck M, Reinhardt F, et al. Transcutaneous and intra-arterial blood gas monitoring: a comparison during apnoea testing for the determination of brain death. Eur J Emerg Med 2002;9:51–6.
19. Misiano DR, Meyerhoff ME, Collison ME. Current and future directions in the technology relating to bedside testing of critically ill patients. Chest 1990;97:204S–14.
20. Halpern MT, Palmer CS, Simpson KN, Chesley FD, Luce BR, Suyderhoud JP, et al. The economic and clinical efficiency of point-of-care testing for critically ill patients: a decision-analysis model. Am J Med Qual 1998;13:3–12.
21. Bailey TM, Topham TM, Wantz S, Grant M, Cox C, Jones D, et al. Laboratory process improvement through point-of-care testing. Jt Comm J Qual Improv 1997;23:362–80.
22. Barquist E, Pizzutiello M, Burke M, Bessey P. Arterial blood gas analysis in the initial evaluation of the nonintubated adult blunt trauma patient. J Trauma 2002;52:601–2.
23. Fermann GJ, Suyama J. Point of care testing in the emergency department. J Emerg Med 2002;22:393–404.
24. Price CP. Point of care testing: impact on medical outcomes. Clin Lab Med 2001;21:285–303.
25. Asimos AW, Gibbs MA, Marx JA, Jacobs DG, Erwin RJ, Norton HJ, et al. Value of point-of-care blood testing in emergent trauma management. J Trauma 2000;48:1101–8.
26. Burritt MF, Santrach PJ, Hankins DG, Herr D, Newton NC. Evaluation of the i-STAT portable clinical analyzer for use in a helicopter. Scand J Clin Lab Invest 1996;56(Suppl 224): 121–8.
27. Engoren M, Evans M. Oxygen consumption, carbon dioxide production and lactic acid during normothermic cardiopulmonary bypass. Perfusion 2000;15:441–6.
28. Kim TS, Kang BS, Kim HS, Kim KM. Changes in arterial blood PO_2, PCO_2, and pH during deep hypothermic circulatory arrest in adults. J Korean Med Sci 1997;12:199–203.
29. Laussen PC. Optimal blood gas management during deep hypothermic paediatric cardiac surgery: α stat is easy, but pH stat may be preferable. Paediatr Anaesth 2002;12:199–204.
30. Moya MP, Clark RH, Nicks J, Tanaka DT. The effects of bedside blood gas monitoring on blood loss and ventilator management. Biol Neonate 2001;80:257–61.
31. Hannan RL, Ybarra MA, White JA, Ojito JW, Rossi AF, Burke RP. Patterns of lactate values after congenital heart surgery and timing of cardiopulmonary support. Ann Thorac Surg 2005;80:1468–73; discussion 1473–4.
32. Rossi AF, Khan DM, Hannan R, Bolivar J, Zaidenweber M, Burke R. Goal-directed medical therapy and point-of-care testing improve outcomes after congenital heart surgery. Intensive Care Med 2005;31:98–104.
33. Davis Z, Pappas P, Foody W. Meeting the special needs of the open-heart surgery patient. MLO special issue: Point of care testing. MLO Med Lab Obs 1991,23:12–5.
34. Hughes C. Glucose infusion may magnify hyperglycemia in hypothermic children during CPB. Anesth News September 1988; 35–7.
35. Kaufman FR. Efforts to control blood glucose levels during surgery found beneficial for diabetic patients [abstract]. Anesth News April 1990;4.
36. Lee E, Grabenkort R, Gambrell S, Bailey J. Hyperglycemia in patients undergoing elective cardiopulmonary bypass procedures [abstract]. Crit Care Med 1999;27:A98.
37. Mills NL, Beaudet RL, Isom OW, Spencer FC. Hyperglycemia during cardiopulmonary bypass. Ann Surg 1973;177:203–5.
38. Welborn LG, McGill WA, Hannallah RS, Nisselson CL, Ruttimann UE, Hicks JM. Perioperative blood glucose concentrations in pediatric outpatients. Anesthesiology 1986;65:543–7.
39. Ellison DA, Forman DT. Transient hyperglycemia during abdominal aortic surgery. Clin Chem 1990;36:815–7.
40. Aoufi A, Neidecker J, Vedrinne C, Bompard D, Cherfa A, Laroux MC, et al. Glucose versus lactated Ringer's solution during pediatric cardiac surgery. J Cardiothorac Vasc Anesth 1997;11:411–4.
41. Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. Pediatrics 2000;105:1141–5.
42. Feld RD. Hypoglycemia. Clin Chem News December 1988;14–5.
43. Gambino SR, Faulkner WR. Diabetes mellitus: frequent monitoring, intensive treatment. Lab Rep 1994;16:33–7.
44. Sieber FE, Traystman RJ. Special issues: glucose and the brain. Crit Care Med 1992;20:104–14.
45. Siemkowicz E, Hansen AJ. Clinical restitution following cerebral ischemia in hypo-, normo- and hyperglycemic rats. Acta Neurol Scand 1978;58:1–8.
46. Zaritsky A. Recent advances in pediatric cardiopulmonary resuscitation and advanced life support. New Horiz 1998;6:201–11.
47. Berry FA. Glucose prescribed routinely poses important risks. Anesthesiol News April 1988;1–5.
48. Sachs DB. Carbohydrates. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd ed. Philadelphia, PA: W.B. Saunders Company, 1999:773–4.
49. Clements F. Strategies to reduce tachycardia urged to prevent ischemia. Anesthesiology News Oct 1988;1–4.
50. Cherian L, Hannay HJ, Vagner G, Goodman JC, Contant CF, Robertson CS. Hyperglycemia increases neurological damage and behavioral deficits from post-traumatic secondary ischemic insults. J Neurotrauma 1998;15:307–21.
51. Estrada CA, Young JA, Nifong LW, Chitwood RW Jr. Outcomes and perioperative hyperglycemia in patients with or without diabetes mellitus undergoing coronary artery bypass grafting. Ann Thorac Surg 2003;75:1392–9.

52. Fava S, Aquilina O, Azzopardi J, Agius Muscat H, Fenech FF. The prognostic value of blood glucose in diabetic patients with acute myocardial infarction. Diabet Med 1996;13:80–3.
53. Gonzalez ER. Pharmacological interventions for cardiopulmonary resuscitation [abstract]. 23rd Society of Critical Care Medicine Educational and Scientific Symposium, 1994.
54. Gore DC, Chinkes DL, Hart DW, Wolf SE, Herndon DN, Sanford AP. Hyperglycemia exacerbates muscle protein catabolism in burn-injured patients. Crit Care Med 2002;30:2438–42.
55. Hill AG, Groom RC. Glucose monitoring during cardiopulmonary bypass. Proc Am Acad Cardiovasc Perfusion 1984;5:51–5.
56. Inamura K, Smith M-L, Olsson Y, Siesjoe BK. Pathogenesis of substantia nigra lesions following hyperglycemic ischemia: changes in energy metabolites, cerebral blood flow, and morphology of pars reticulata in a rat model of ischemia. J Cereb Blood Flow Metab 1988;8:375–84.
57. Kawai N, Keep RF, Betz AL. Hyperglycemia and the vascular effects of cerebral ischemia. Acta Neurochir Suppl (Wien) 1997;70:27–9.
58. Sieber FE. The neurologic implications of diabetic hyperglycemia during surgical procedures at increased risk for brain ischemia. J Clin Anesth 1997;9:334–40.
59. Siesjo BK. Mechanisms of ischemic brain damage. Crit Care Med 1988;16:954–63.
60. Zapp MA, Kofke WA, Davis DW, Derr JA. Dose-dependent neurochemical effects of volatile anesthetics in brain ischemia [abstract]. World Congress Anesthesiologists (9th) May 1988; Abstract 2:AO644.
61. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–67.
62. Baxter J, Babineau TJ, Apovian CM, Elsen RJ, Driscoll DF, Forse RA, et al. Perioperative glucose control predicts increased nosocomial infection in diabetics [abstract]. Crit Care Med 1990;18:S207.
63. Black CT, Hennessey PJ, Andrassy RJ. Short-term hyperglycemia depresses immunity through nonenzymatic glycosylation of circulating immunoglobulin. J Trauma 1990;30:830–3.
64. Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003;125:1007–21.
65. Fernandes CMB. Mesenteric ischemia [review]. Emergency Physician Monthly June 2001;1:21.
66. Lange H, Jackel R. Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. Eur J Surg 1994;160: 381–4.
67. Meyer T, Klein P, Schweiger H, Lang W. How can the prognosis of acute mesenteric artery ischemia be improved? results of a retrospective analysis. Zentralbl Chir 1998;123:230–4.
68. Delaurier GA, Ivey RK, Hohnson RH. Peritoneal fluid lactic acid and diagnostic dilemmas in acute abdominal disease. Am J Surg 1994;167:302–5.
69. Schmiechen NJ, Han C, Milzman DP. ED use of rapid lactate to evaluate patients with acute chest pain. Ann Emerg Med 1997;30:571–7.
70. Henning RJ, Weil MH, Weiner F. Blood lactate as a prognostic indicator of survival in patients with acute myocardial infarction. Circ Shock 1982;9:307–15.
71. Appel D, Rubenstein R, Schrager K, Williams MH. Lactic acidosis in severe asthma. Am J Med 1983;75:580–4.
72. Carden DL, Martin GB, Nowak RM, Foreback CC, Tomlanovich MC. Lactic acid as a predictor of downtime during cardiopulmonary arrest in dogs. Am J Emerg Med 1985;3:120–4.
73. Baud FJ, Borron SW, Megarbane B, Trout H, Lapostolle F, Vicaut E, et al. Value of lactic acidosis in the assessment of the severity of acute cyanide poisoning. Crit Care Med 2002;30:2044–50.
74. Toffaletti J. Lactate [review]. Clin Chem News December 1988;9.
75. Zerbe NF, Wagner BKJ. Use of vitamin B12 in the treatment and prevention of nitroprusside-induced cyanide toxicity. Crit Care Med 1993;21:465–7.
76. Scalea TM, Maltz S, Yelon J, Trooskin SZ, Duncan AO, Sclafani SJA. Resuscitation of multiple trauma and head injury: role of crystalloid fluids and inotropes. Crit Care Med 1994; 22:1610–5.
77. Kurkciyan I, Meron G, Sterz F, Janata K, Domanovits H, Holzer M, et al. Pulmonary embolism as a cause of cardiac arrest: presentation and outcome. Arch Intern Med 2000;160:1529–35.
78. Aduen J, Bernstein WK, Khastgir T, Miller J, Kerzner R, Bhatiani A, et al. The use and clinical importance of a substrate-specific electrode for rapid determination of blood lactate concentrations. JAMA 1994;272:1678–85.
79. Bernstein WK, Milzman D, Aduen J, Linden J, Kergner R, Batiani A, et al. Validation of the sensitivity and specificity of hyperlactatemia in the prediction of mortality and hospital admission [abstract]. 24th Society of Critical Care Medicine and Educational and Scientific Symposium, 1995.
80. Milzman DP, Rothenhaus TC. Resuscitation of the geriatric patient. Emerg Med Clin North Am 1996;14:233–44.
81. Milzman DP, Manning D, Presman D, Lill D, Howell J, Shirey T. Rapid lactate can impact outcome prediction for geriatric patients in the emergency department [abstract]. Crit Care Med 1995; 23(Suppl):A32.
82. Mizock BA, Falk JL. Lactic acidosis in critical illness. Crit Care Med 1992;20:80–95.
83. Izraeli S, Ben-Sira L, Hareli D, Naor N, Balin A, Davidson S. Lactic acid as a predictor for erythrocyte transfusion in healthy preterm infants with anemia of prematurity. J Pediatr 1993;122:629–31.
84. Livingston DH, Lavery RF, Tortella BJ, Sambol J, Slomovitz B. Lactate identifies major trauma better than standard triage [abstract]. Acad Emerg Med 1996;3:532.
85. Milzman D, Boulanger B, Wiles C, Hinson D. Admission lactate predicts injury severity and outcome in trauma patients [abstract]. Crit Care Med 1992;20:S94.
86. Moomey CB, Melton SM, Croce MA, Fabian TC, Proctor KG. Prognostic value of blood lactate, base deficit, and oxygen-derived variables in an LD50 model of penetrating trauma. Crit Care Med 1999;26:154–61.
87. Munoz R, Laussen PC, Palacio G, Zienko L, Piercy G, Wessel D. Changes in whole blood lactate levels during cardiopulmonary bypass surgery for congenital cardiac disease: an early indicator of morbidity and mortality. J Thorac Cardiovasc Surg 2000; 119:155–62.
88. Begliomini B, De Wolf JA, Freeman J, Kang Y. Intraoperative lactate levels can predict graft function after liver transplantation [abstract]. Anesthesiology 1989;71/3A:A180.
89. Drenger B, Parker SD, Frank SM, Beattie C. Changes in cerebrospinal fluid pressure and lactate concentrations during thoracoabdominal aortic aneurysm surgery. Anesthesiology 1997; 86:41–7.
90. Jeng JC, Lee K, Jablonski K, Jordan MH. Serum lactate and base deficit suggest inadequate resuscitation of patients with burn injuries: application of a point-of-care laboratory instrument. J Burn Care Rehabil 1997;18:402–5.
91. Toffaletti J, Hansell D. Interpretation of blood lactate measurements in paediatric open-heart surgery and in extracorporeal membrane oxygenation. Scand J Clin Lab Invest 1995;55:301–7.

92. Grayck EN, Meliones JN, Kern FH, Hansell DR, Ungerleider RM, Greeley WJ. Elevated serum lactate correlates with intracranial hemorrhage in neonates treated with extracorporeal life support. Pediatrics 1995;96:914–7.
93. Cheifetz I, Kern FH, Schulman SR, Greeley WJ, Ungerleider RM, Meliones JN. Serum lactates correlate with mortality after operations for complex congenital heart disease. Ann Thorac Surg 1997;64:735–8.
94. Shemie S. Serum lactate predicts post-operative complications after pediatric cardiac surgery [abstract]. Pediatrics 1996;98S: 550.
95. Davies AR, Bellomo R, Raman JS, Gutteridge GA, Buxton BF. High lactate predicts the failure of intraaortic balloon pumping after cardiac surgery. Ann Thorac Surg 2001;71:1415–20.
96. Toffaletti J. Elevations in blood lactate: overview of use in critical care. Scand J Clin Lab Invest 1996;56(Suppl 224):107–10.
97. Jeng JC, Lee K, Jablonski K, Jordan MH. Serum lactate and base deficit suggest inadequate resuscitation of patients with burn injuries: application of a point-of-care laboratory instrument. J Burn Care Rehabil 1997;18:402–5.
98. Altura BM, Altura BT. Magnesium as an extracellular signal in cardiovascular pathobiology. Journal of the Japanese Society for Magnesium Research 1996;15:17–32.
99. Altura BM, Altura BT. Magnesium and cardiovascular biology: an important link between cardiovascular risk factors and atherogenesis. Cell Mol Biol Res 1995;41:347–59.
100. Rayssiguier Y, Malpuech C, Nowacki W, Rock E, Gueux E, Mazur A. Inflammatory response in magnesium deficiency. In: Smetana R, ed. Advances in Magnesium Research. London, UK: John Libbey, 1997:415–21.
101. Weglicki WB, Kramer JH, Mak I-T, Dickens BF, Komarov AM. Pro-oxidant and pro-inflammatory neuropeptides in magnesium deficiency. In: Rayssiguier Y, Mazur A, Durlach J, eds. Advances in Magnesium Research: Nutrition and Health. London, UK: John Libbey & Co Ltd, 2001:285–9.
102. Weglicki WB, Mak IT, Dickens BF, Stafford RE, Komarov AM, Gibson B, et al. Neuropeptides, free radical stress and antioxidants in models of Mg-deficient cardiomyopathy. In: Theophanides T, ed. Magnesium: Current Status and New Developments: Theoretical, Biological and Medical Aspects. Amsterdam, The Netherlands: Kluwer Academic, 1997:169–178.
103. Weglicki WB, Phillips TM, Freedman AM, Cassidy MM, Dickens BF. Magnesium-deficiency elevates circulating levels of inflammatory cytokines and endothelin. Mol Cell Biochem 1992;110:169–73.
104. Antman EM. Magnesium in acute myocardial infarction: clinical benefits of intravenous magnesium therapy [abstract]. Magnes Res 1995;(Suppl 1):8–9.
105. Balkin J. The use of magnesium in critical coronary care patients: management of cardiac arrhythmias. In: Smetana R, ed. Advances in Magnesium Research: Magnesium in Cardiology: Fifth European Magnesium Congress, Viennnesa, 1995. London, UK: Libbey & Co, 1997:21–7.
106. Balkin J. Magnesium in critical coronary care patients: management of cardiac arrhythmias [abstract]. Magnes Res 1995;(Suppl 1):10.
107. Gomez MN. Magnesium and cardiovascular disease. Anesthesiology 1998;89:222–40.
108. Iseri LT, Ginkel ML, Allen BJ, Brodsky MA. Magnesium-potassium interactions in cardiac arrhythmia. Magnes Trace Elem 1991;10:193–204.
109. Keren A, Tzivoni D. Magnesium therapy in ventricular arrhythmias [review]. Pacing Clin Electrophysiol 1990;13:937–45.
110. Mohan G, Jain VK. Serum magnesium: a prognostic tool of acute myocardial infarction. Indian J Physiol Pharmacol 1994; 38:294–6.
111. Shechter M, Hod H, Chouraqui P, Kaplinsky E, Rabinowitz B. Acute myocardial infarction without thrombolytic therapy: beneficial effects of magnesium sulfate. Herz 1997;22 (Suppl 1):73–6.
112. Shibata M, Ueshima K, Tachibana H, Abiko A, Harada M, Fukami K, et al. The effect of magnesium sulfate pretreatment and the significance of interleukin-6 levels in patients with acute myocardial infarction. Journal of the Japanese Society for Magnesium Research 1999;18:59–65.
113. Sjogren A, Edvinsson L, Fallgren B. Magnesium deficiency in coronary artery disease and cardiac arrhythmias. J Int Med 1989; 226:213–22.
114. Smetana R. Cardiovascular medicine: the importance of Mg in coronary artery disease and AMI. In: Smetana R, ed. Advances in Magnesium Research: 1, Magnesium in Cardiology. Fifth European Magnesium Congress, Vienna 1995, London, UK: Libbey & Co, 1997.
115. Thogersen AM, Johnson O, Wester PO. Effects of magnesium infusion on thrombolytic and non-thrombolytic treated patients with acute myocardial infarction. Int J Cardiol 1993;39:13–22.
116. Woods KL, Fletcher S, Smith LFP. Intravenous magnesium in suspected acute myocardial infarction [abstract]. BMJ 1992; 304:119.
117. Douban S, Brodsky MA, Whang DD, Whang R. Significance of magnesium in congestive heart failure. Am Heart J 1996;132: 664–71.
118. Dyckner T, Wester PO. Ventricular extrasystoles and intracellular electrolytes before and after potassium and magnesium infusions in patients on diuretic treatment. Am Heart J 1979;97:12–18.
119. Lasserre B. Magnesium and heart failure: an update: where do we stand? where do we go? In: Smetana R, ed. Advances in Magnesium Research: Magnesium in Cardiology. London, UK: Libbey & Co, 1997:12–20.
120. Sueta CA, Patterson JH, Adams KF. Antiarrhythmic action of pharmacological administration of magnesium in heart failure: a critical review of new data [abstract]. Journal of the Japanese Society for Magnesium Research 1996;15:89.
121. Silverman RA, Osborn H, Runge J, Gallagher EJ, Chiang W, Feldman J, et al; Acute Asthma Magnesium Study Group. IV magnesium sulfate in the treatment of acute severe asthma. Chest 2002;122:489–97.
122. Lonchyna VA, Lipsius SL. Myocardial preservation: the role of Mg [abstract]. Ann Thorac Surg 1989;48:148.
123. Evers S, Happe S, Bauer B, Suhr B. The influence of intravenous magnesium application on cerebral blood flow [abstract]. Magnes Res 1995;(Suppl 1):27.
124. Seelig MS. Increased need for magnesium with the use of combined oestrogen and calcium for osteoporosis treatment. Magnes Res 1990;3:197–215.
125. Chadda KD, Schultz NA. Magnesium deficiency and coronary vasospasm: role in sudden cardiac death. Magnesium 1982; 1:84–94.
126. Young IS, Goh EML, McKillop UH, Stanford CF, Nicholls DP, Trimble ER. Magnesium status and digoxin toxicity. Br J Clin Pharmacol 1991;32:717–21.
127. Grigore AM, Mathew JP. Con: magnesium should not be administered to all coronary artery bypass graft surgery patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2000;14:344–6.

128. Mauskop A, Altura BM. Magnesium for migraine: rationale for use and therapeutic potential. CNS Drugs 1998;9:185–90.
129. Altura BT, Altura BM, Memon Z, Benjamin J, Cracco RQ. Ionized magnesium (Img2+) and ionized calcium Ca2+) measurements in human subjects early after head trauma (HT): relationship to degree of injury [abstract]. IVth European Congress on Magnesium in Giessen (abstracts) 1992:11.
130. Bareyre FM, Saatman KE, Raghupathi R, McIntosh TK. Post-injury treatment with magnesium chloride attenuates cortical damage after traumatic brain injury in rats. J Neurotrauma 2000; 17:1029–39.
131. Heath DL, Vink R. Neuroprotective effects of MgSO4 and MgCL2 in closed head injury: a comparative phosphorus NMR study. J Neurotrauma 1998;15:183–9.
132. Hoffman DJ, Marro PJ, McGowan JE, Mishra OP, Delivoria-Papadopoulos M. Protective effect of MgSO4 infusion on NMDA receptor binding characteristics during cerebral cortical hypoxia in the newborn piglet. Brain Res 1994;644:144–9.
133. McIntosh TK. Novel pharmacologic therapies in the treatment of experimental traumatic brain injury: a review. J Neurotrauma 1993;10:215–61.
134. Memon ZI, Altura BT, Benjamin JL, Cracco RQ, Altura BM. Predictive value of serum ionized but not total magnesium levels in head injuries. Scand J Clin Lab Invest 1995;55:671–7.
135. Vink R, O'Conner CA, Nimmo AJ, Heath DL. Magnesium attenuates persistent functional deficits following diffuse traumatic brain injury in rats. Neurosci Lett 2003;336:41–4.
136. Vink R, McIntosh TK, Demediuk P, Weiner MW, Faden AI. Decline in intracellular free Mg is associated with irreversible tissue injury after brain trauma. J Biol Chem 1988;263:757–61.
137. Salem M, Stacey J, Chernow B. Ionized magnesium values in critically ill patients: a novel ion selective electrode for determining free extracellular magnesium concentrations [abstract]. Crit Care Med 1993;21(Suppl):S256.
138. Boyd WC, Thomas SJ. Pro: magnesium should be administered to all coronary artery bypass graft surgery patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2000; 14:339–43.
139. Van Hook JW. Hypermagnesemia. Crit Care Clin 1991;7:215–23.
140. Malpuech-Brugere C, Nowacki W, Rock E, Gueux E, Mazur A, Rayssiguier Y. Enhanced tumor necrosis factor-α production following endotoxin challenge in rats is an early event during magnesium deficiency. Biochim Biophys Acta 1999;1453:35–40.
141. Malpuech-Brugere C, Nowacki W, Daveau M, Gueux E, Linard C, Rock E, et al. Inflammatory response following acute magnesium deficiency in the rat. Biochim Biophys Acta 2000;1501: 91–8.
142. Salem M, Kasinski N, Munoz R, Chernow B. Progressive magnesium deficiency increases mortality from endotoxin challenge: the protective effects of acute magnesium replacement therapy. Crit Care Med 1995;23:108–18.
143. Aglio LS, Stanford GG, Maddi R, Boyd JL, Nussbaum S, Chernow B. Hypomagnesemia is common following cardiac surgery. J Cardiothorac Vasc Anesth 1991;5:201–8.
144. England MR, Gordon G, Salem M, Chernow B. Magnesium administration and dysrhythmias after cardiac surgery. JAMA 1992;268:2395–402.
145. Munoz R, Laussen PC, Palacio G, Zienko L, Piercy G, Wessel D. Whole blood ionized magnesium: age-related differences in normal values and clinical implications of ionized hypomagnesemia in patients undergoing surgery for congenital cardiac disease. J Thorac Cardiovasc Surg 2000;119:891–8.
146. Ohashi Y, Uchida O, Kuro M. The effect of magnesium rich cardioplegic solution upon blood ionized magnesium level during open heart surgery [abstract]. Am Soc Anesthesiol 1996.
147. Bennett MW, Webster NR, Sadek SA. Alterations in plasma magnesium concentrations during liver transplantation. Transplantation 1993;56:859–61.
148. Brusco L. Magnesium homeostasis in the operating room and intensive care unit. In: Eisenkraft JB, ed. Progress in Anesthesiology VIII. Philadelphia, PA: W.B. Saunders, 1994:47–56.
149. Storm W, Zimmerman JJ. Magnesium deficiency and cardiogenic shock after cardiopulmonary bypass. Ann Thorac Surg 1997;64:572–7.
150. Canzanello VJ, Burkart JM. Hemodialysis-associated muscle cramps. Semin Dial 1992;5:299–304.
151. Niederstadt C, Brinckmann C, Sack K, Rob PM. Magnesium to treat muscle cramps during dialysis. Deutsch-Oesterreichisch-Schweizerisches Magnesium Symposium; Berlin: September 1996.
152. Fanning WJ, Thomas CS, Roach A, Tomichek R, Alford WC, Stoney WS. Prophylaxis of atrial fibrillation with magnesium sulfate after coronary artery bypass grafting. Ann Thorac Surg 1991;52:529–33.
153. Rasch DK, Huber BA, Richardson CJ, L'Hommedieu CS, Nelson TE, Reddi R. Neurobehavioral effects of neonatal hypermagnesemia. J Pediatr 1982;100:272–6.
154. Morisaki H, Yamamoto S, Morita Y, Kotake Y, Ochiai R, Takeda J. Hypermagnesemia-induced cardiopulmonary arrest before induction of anesthesia for emergency cesarean section. J Clin Anesth 2000;12:224–6.
155. Dubray C, Rayssiguier Y. Magnesium, inflammation and pain. In: Theophanides T, ed. Magnesium: Current Status and New Developments: Theoretical, Biological and Medical Aspects. Amsterdam, The Netherlands: Kluwer Academic, 1997:303–11.
156. Vobruba V, Cerna O. Magnesium in the treatment of critically ill neonates: cardiology case reports [abstract]. Magnes Res 1995; 8(Suppl 1):74.
157. Pedersen T. Does perioperative pulse oximetry improve outcome? seeking the best available evidence to answer the clinical question. Best Pract Res Clin Anaesthesiol 2005;19:111–23.
158. Mehta SV, Parkin PC, Stephens D, Keogh KA, Schuh S. Oxygen saturation as a predictor of prolonged, frequent bronchodilator therapy in children with acute asthma. J Pediatr 2004;145:641–5.
159. Kuhnert M, Schmidt S. Intrapartum management of nonreassuring fetal heart rate patterns: a randomized controlled trial of fetal pulse oximetry. Am J Obstet Gynecol 2004;191:1989–95.
160. Salyer JW. Neonatal and pediatric pulse oximetry. Respir Care 2003;48:386–96.
161. Dolan MC, Haltom TL, Barrows GH, Short CS, Ferriell KM. Carboxyhemoglobin levels in patients with flu-like symptoms. Ann Emerg Med 1987;16:782–6.
162. Heckerling PS. Occult carbon monoxide poisoning: a cause of winter headache. Am J Emerg Med 1987;5:201–4.
163. Heckerling PS, Leikin JB, Maturen A, Terzian CG, Segarra DP. Screening hospital admissions from the emergency department for occult carbon monoxide poisoning. Am J Emerg Med 1990;8:301–4.
164. Rodriguez LF, Smolik LM, Zbehlik AJ. Benzocaine-induced methemoglobinemia: report of a severe reaction and review of the literature. Ann Pharmacother 1994;28:643–9.
165. Ohashi K, Yukioka H, Hayashi M, Asada A. Elevated methemoglobin in patients with sepsis. Acta Anaesthesiol Scand 1998;42:713–6.
166. Krafte-Jacobs B, Brilli R, Szabo C, Denenberg A, Moore L, Salzman AL. Circulating methemoglobin and nitrite/nitrate

concentrations as indicators of nitric oxide overproduction in critically ill children with septic shock. Crit Care Med 1997;25: 1588–93.
167. Murray RP, Leroux M, Sabga E, Palatnick W, Ludwig L. Effect of point of care testing on length of stay in an adult emergency department. J Emerg Med 1999;17:811–4.
168. Frankel HL, Rozycki GS, Ochsner MG, McCabe JE, Harviel JD, Jeng JC, et al. Minimizing admission laboratory testing in trauma patients: use of a microanalyzer. J Trauma 1994;37:728–36.
169. Herr DM, Newton NC, Santrach PJ. Airborne and rescue point-of-care testing. Am J Clin Pathol 1995;104:S54–8.
170. Guiliano KK. Blood analysis at the point of care: issues in application for use in critically ill patients. AACN Clin Issues 2002; 13:204–20.
171. Shirey TL. Critical care profiling for informed treatment of severely ill patients. Am J Clin Pathol 1995;104(4 Suppl 1): S79–87.
172. Krause GS, White BC, Aust SD, Nayini NR, Kumar K. Brain cell death following ischemia and reperfusion: a proposed biochemical sequence. Crit Care Med 1988;16:714–26.
173. Singh SC, Singh J, Prasad R. Hypocalcemia in a paediatric intensive care unit. J Trop Pediatr 2003;49:298–302.
174. Zivin JR, Gooley T, Zager RA, Ryan MJ. Hypocalcemia: a pervasive metabolic abnormality in the critically ill. Am J Kidney Dis 2001;37:689–98.
175. Kost GJ. New whole blood analyzers and their impact on cardiac and critical care. Crit Rev Clin Lab Sci 1993;30:153–202.
176. Broner CW, Stidham GL, Westenkirchner DF, Tolley EA. Hypermagnesemia and hypocalcemia as predictors of high mortality in critically ill pediatric patients. Crit Care Med 1990; 18:921–8.
177. Zaloga GP. Hypocalcemia in critically ill patients. Crit Care Med 1992;20:251–62.
178. Zaloga GP. Hypocalcemic crisis. Crit Care Clin 1991; 7:191–200.

PUBLIC COMMENTS

No public comments were received on the guidelines.

Chapter **6**

Diagnosis and Management of Diabetes Mellitus

Aasne Karine Aarsand, David Alter, Stephen J. Frost, Bob Kaplanis, Atle Klovning, Christopher P. Price, David B. Sacks, Sverre Sandberg, Andrew St John, Ramasamyiyer Swaminathan, and William E. Winter

INTRODUCTION

Diabetes mellitus is one of the most common diseases in the world and constitutes one of the largest chronic disease burdens throughout the world. It is a disease that is defined by the biochemical abnormalities associated with changes in glucose metabolism, but is also characterized by a more complex pathophysiology. The morbidity and mortality associated with diabetes mellitus result from the complications of the disease, which include both micro- and macrovascular complications most commonly resulting in blindness, renal failure, and cardiovascular disease (CVD). In 1992, the cost of diabetes in the United States was estimated to be $98 billion, while in the United Kingdom it consumes ~10% of the healthcare budget. In vitro biochemical testing plays a central role in the diagnosis and management of diabetes mellitus, and the reader is referred to the National Academy of Clinical Biochemistry (NACB) "Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus" *(1)*.

The diagnosis of diabetes mellitus is based on an accurate assessment of the fasting blood glucose concentration, followed by a glucose tolerance test in the case of an equivocal result *(1)*. Point-of-care testing (POCT) has no role to play in the diagnosis of diabetes, although it may be used as a screening test preceding the use of a laboratory test. The role of a range of biochemical tests in the management of diabetes was systematically reviewed by Sacks et al. *(1)* and reported in the NACB guidelines referred to earlier. The management of diabetes today is largely guided by the work from the Diabetes Control and Complications Trial (DCCT) for type 1 diabetes *(2)* and the United Kingdom Prospective Diabetes Study (UKPDS) for type 2 diabetes *(3)*, which investigated the use of intensive treatment to maintain normoglycemia on the rate of progression of the complications of the disease.

Intuitively, the delivery of the biochemical testing through the modality of POCT has the potential to improve the quality of patient care and generate beneficial health outcomes. Indeed, within the DCCT and UKPDS studies the majority of the blood glucose testing was undertaken by self-monitoring of blood glucose (SMBG), one style of POCT, albeit in the UKPDS the treatment decisions were made on the basis of the hemoglobin A1c (HbA1c) result. There have been reports of a number of tests being performed by POCT, and the literature will be reviewed to determine whether robust guidelines can be developed to support POCT in the management of diabetes. The review will focus on SMBG, POCT of HbA1c in assessing glycemic control, fructosamine in assessing glycemic control, blood ketones for the assessment of diabetic crises, and urine albumin excretion (often referred to as *microalbuminuria*) for the detection of renal dysfunction.

It should be stressed at the outset that "absence of evidence of effect does not constitute evidence of absence of effect" *(4)*. The following sections describe the recommendations made in relation to the main tests performed at the point of care (POC) in relation to the diagnosis and management of diabetes mellitus.

BLOOD GLUCOSE

The following questions were searched in PubMed (682 different hits) and the Cochrane library (66 different hits) in December 2003. (Literature Searches 35–40) A total of 695 abstracts were found, of which 53 were duplicates. The abstracts were read by 2 reviewers to determine whether the articles should be retrieved or not. Disagreement was solved by consensus or by the assessment of a third person. A total of 88 articles were retrieved. All the articles retrieved were compared to those found by Coster et al. *(5)*, a systematic review dealing exclusively with SMBG. Papers on SMBG (guidelines 60–63 and 66–67) not included in this review were dealt with by using the same methodology and added to those already assessed in Coster et al. *(5)*. For hospital and POC glucose testing (guidelines 64 and 65), all articles were selected. The role for urine glucose self-testing is dealt with within the framework of guidelines 60–63 and 66–67.

The 88 retrieved articles were read by 2 people who selected and classified the relevant articles according to the forms in Coster et al. *(5)*. Of the additional articles to those in Coster et al. *(5)*, 3 were found that dealt with type 1 diabetes mellitus, 8 were found (7 after 2000) dealing with type 2 diabetes

mellitus, and we found no additional articles dealing with gestational diabetes. Concerning the secondary-care setting (hospital and POC in the clinical departments), we found 3 articles. We did not find any previous reviews addressing hospital and POC in the secondary care setting.

Our recommendations are compared with those given by Coster et al. *(5)*, the World Health Organization *(6)*, the American Diabetes Association (ADA) *(7)*, the NACB *(1)*, and the National Institute for Clinical Excellence (NICE) *(8)*.

Type 1 Diabetes Mellitus

Does blood glucose self-testing (i.e., primary care setting) lead to an improved patient (clinical) outcome in diabetes mellitus? (Literature Searches 35 and 36)

Guideline 60. *There is insufficient evidence to recommend for or against routinely using SMBG. There is fair evidence that SMBG can improve health outcome. The balance between benefits and costs must be evaluated in each single environment. The consensus agreement to use SMBG in DM type 1 among experts is very strong (e.g., the ADA (7)), and it is difficult to advise against SMBG. However greater objective evidence is still required to decide whether SMBG is really needed and which patients will benefit from it. If SMBG is going to be used, high-quality instruments should be chosen and patients must be educated in their practical use, as well as being instructed in how to use the results to monitor their insulin therapy. The evidence to support our view is from systematic reviews, randomized controlled trials (RCTs), as well as controlled trials without randomization, and cohort/case control studies. The evidence is, however, conflicting, and our recommendation is therefore of type I, i.e., there is insufficient evidence to recommend for or against routinely using SMBG.*

Strength/consensus of recommendation: I

Level of evidence: I and II

We found 9 RCTs *(9–17)*, of which 1 was not in Coster et al. *(5)*. The review of Coster et al. *(5)* found 8 RCTs. Two of these showed improved diabetes control, whereas 6 did not. In addition, we found 1 RCT study *(13)* that dealt with 11 children aged 10–17 years who were followed up for 3 months. The intervention group consisted of children performing continual subcutaneous glucose monitoring in addition to SMBG, whereas the control group was children performing ordinary SMBG. There was a slight effect in detecting asymptomatic nocturnal hypoglycemia, as well as lowering the HbA1c of 0.6% without increasing the risk of severe hypoglycemia in the intervention group. The number of persons studied, however, was very small.

Sixteen studies *(18–33)* were excluded by Coster et al. *(5)* because they were not RCTs. Two more *(34, 35)* were identified by our search. The study by Allen et al. *(34)* was a cross-sectional cohort study in 415 persons up to 28 years of age that were followed up for 4–6.5 years. The authors' main conclusions were that intensive insulin management and blood glucose monitoring independently predicted frequent but not severe hypoglycemia. In the study by Kaufman et al. *(35)*, 47 children were followed up for 3 months with a continual glucose monitoring system. A significant decrease of 0.2% HbA1c was found compared to conventional monitoring.

When comparing our results with the recommendations given by others *(1, 6–8)*, we find that the WHO *(6)* gives the following recommendation concerning SMBG: "The insulin-treated patient is commonly requested to build up a 'glycemic profile' by self-measurement of blood glucose at specific times of the day (and night). A '7-point profile' is useful, with samples taken before and 90 min after breakfast, before and 90 min after lunch, before and 90 min after an evening meal, and just before going to bed. Occasionally patients may arrange to wake at 0300 h to collect and measure a nocturnal sample. The complete profile rarely needs to be collected within a single 24-h period, and it may be compiled from samples collected at different times over several days. Measurement of glucose in urine: Insulin-treated patients who do not have access to facilities for self-measurement of blood glucose should test urine samples passed after rising, before main meals, and before going to bed." However, this recommendation is not based on any stated evidence or references. The ADA *(7)* recommends that (1) SMBG be an integral component of diabetes therapy, (2) that SMBG be included in the management plan, and (3) the patient be instructed in SMBG and the technique routinely evaluated to use data to adjust therapy. The first recommendation is claimed to be based on "supportive evidence from well conducted cohort studies," whereas the 2 others are consensus statements. However their evidence seems to be based on consensus statements from 1987 and 1994 *(36, 37)*. Sacks et al. *(1)* state that SMBG is recommended for all insulin-treated patients with diabetes. For type 1 patients, SMBG is recommended 3 or more times a day. This is a "B" recommendation using the same system as ADA (which is equivalent to level of evidence II), i.e., it is based on "supportive evidence from well conducted cohort studies." In the references cited, however, the evidence for this is not obvious. Intuitively, it is felt that close monitoring of blood glucose is needed in adjusting insulin dosage, and SMBG is the most practical way to carry this out. However Coster et al. *(5)* pointed out the lack of evidence to support this view, and we have not found data to strengthen the case for SMBG. Coster et al. *(5)* suggested further studies to examine whether certain groups of patients particularly benefit from SMBG. It is true that the DCTT study *(2)* showed that intensive treatment of diabetics, including SMBG, is beneficial. However, SMBG was also used to some extent in the control group, and it is difficult to objectively separate from this study the contribution of SMBG compared to other factors, such as education and more patient contact.

Type 2 Diabetes Mellitus

Guideline 61. Type 2, insulin treated. *The evidence to support our view is from systematic reviews, RCTs and controlled trials without randomization, and cohort/case control studies. The evidence is, however, conflicting and our recommendation is therefore of type I, i.e., there is insufficient evidence to recommend for or against routinely using SMBG.* (Literature Searches 35 and 36)

Strength/consensus of recommendation: I

Level of evidence: I and II

Guideline 62. Type 2, not insulin treated. *We conclude that the evidence is insufficient to recommend for or against routinely using SMBG. The evidence to support our view is from systematic reviews, RCTs and controlled trials without randomization, and cohort/case control studies. The evidence is conflicting, with a lot of poor studies, although there is some evidence that SMBG is not effective in improving glycemic control or avoiding hypoglycemic attacks. Recommendation is therefore of type I, i.e., we conclude that the evidence is insufficient to recommend for or against routinely using SMBG. If SMBG is going to be used, high-quality instruments should be chosen and patients must be educated in their practical use, as well as being instructed in how to use the results to monitor their insulin therapy.* (Literature Searches 35 and 36)

Strength/consensus of recommendation: I

Level of evidence: I and II

Nine RCTs concerning SMBG type 2 DM were found, 8 *(38–45)* of which were included in Coster et al. *(5)*. The ninth, by Schwedes et al. *(46)*, followed up 250 patients, with an intervention of 6 months. Blood glucose was measured 6 times (before and 1 h after main meals) on 2 days per week. Patients were seen every 6 weeks by nurses who gave advice and assessed correct use of SMBG. A total of 10% of the patients were excluded because of noncompliance. In the per-protocol analysis, the use of SMBG devices significantly reduced HbA1c levels by 1.0 ± 1.08% compared with 0.54 ± 1.41% for the control group ($P = 0.0086$). Body weight, total cholesterol, and microalbumin improved when a Glucometer was used, but there was no statistically significant difference between the 2 groups concerning these characteristics. The study design has, however, been criticized *(47)*. None of the RCTs included in the Coster et al. *(5)* review could show a similar effect. In a meta-analysis of 4 studies *(39, 40, 43, 45)* performed by Coster et al. *(5)*, a nonsignificant decrease of 0.25% HbA1c was found. In a similar meta-analysis of 3 studies *(34, 40, 42)* comparing blood monitoring with urine monitoring, no difference in HbA1c was found. However, most of these studies were performed before 1995; they did not address instrument quality. There was limited information on whether patients were educated in the use of the instruments and whether they had information about what to do with the results. One large RCT concerning the use of SMBG in type II diabetes is in progress in the UK and will be finished in late 2006/early 2007 (Andrew Farmer).

Ten non-RCT studies were found *(48–57)* by Coster et al. *(5)*. In addition to these, we found another 6 *(58–63)*. Out of the 10 cross-sectional studies, 6 showed no effect, 3 showed effects only in insulin-treated patients, and 1 showed an effect on all type II patients. Of the 2 case-control studies, one showed a possible effect, whereas the other showed none. Of the 4 prospective cohort studies, 2 showed an effect, whereas the other 2 did not. Our conclusions are similar to that given in other reviews *(5, 64, 65)*. In a systematic review by Norris et al. *(66)*, it was concluded that "positive effects of self-management training on knowledge, frequency and accuracy of SMBG, self-reported dietary habits, and glycemic control were demonstrated in studies with short follow-up (<6 months). Educational interventions that involved patient collaboration may be more effective than didactic interventions in improving glycemic control, weight, and lipid profiles. No studies demonstrated the effectiveness of self-management training on CVD-related events or mortality; no economic analyses included indirect costs." It is underlined that the importance of SMBG on other factors than HbA1c and long-term complications may be underestimated. In another criteria-based review article by Holmes and Griffiths *(67)*, it is concluded that "the efficacy of blood and urine glucose monitoring testing, for people with type 2 diabetes, in improving glycemic control as measured by HbA1c levels is still questionable. A rigorous RCT is needed to establish these answers although there is no evidence of harm. Clinical protocols that make recommendations for glucose monitoring strategies for people with type 2 diabetes should acknowledge that the evidence is weak. There is no basis to recommend 1 method above another."

The recommendations given in a guideline developed by the Royal College of General Practitioners, Diabetes UK, the College of Physicians, and the Royal College of Nursing for the National Institute of Clinical Excellence *(8)* are all grade C, equivalent to level of evidence III (evidence from expert committee reports or opinions and/or clinical experience of respected authorities). The recommendations given are that (1) self-monitoring should not be considered as a standalone intervention, (2) self-monitoring should be taught if the need/purpose is clear and agreed on with the patient, and (3) self-monitoring can be used in conjunction with appropriate therapy as part of integrated self-care. The WHO *(6)* gives the following recommendation, however, without any stated evidence: "Non-insulin-dependent patients do not need to monitor their urine so frequently [as type I diabetic patients]." No recommendations concerning SMBG are given. Sacks et al. *(1)* state that "SMBG may help achieve better control, particularly when therapy is initiated or changed. However, there are no data to support this concept. The role of SMBG in patients with stable type 2 diabetes controlled by diet alone is not known." See above for the ADA *(7)* recommendations.

Does blood glucose self-testing (i.e., primary care setting) lead to an economic benefit in diabetes mellitus? (Literature Searches 35 and 36)

Guideline 63. *There is insufficient evidence of economical aspects to recommend for or against routinely using SMBG.*

Strength/consensus of recommendation: I (there is little evidence)

Level of evidence: III

One study dealing with cost-effectiveness of SMBG in type I DM found that urine monitoring was cost-effective, whereas blood monitoring was not *(15)*. However, these findings are difficult to transfer to other settings.

For type II patients, no articles dealing with the possible economic benefit of SMBG were found.

Does blood glucose POCT in the hospital (i.e., secondary care setting) lead to an improved patient (clinical) outcome in diabetes mellitus compared with central laboratory testing? (Literature Searches 37 and 38)

Guideline 64. *There is insufficient evidence to recommend for or against routinely using POC glucose testing in the hospital.*

Strength/consensus of recommendation: I (there is little evidence)

Level of evidence: III

No articles could be found dealing with clinical outcome or change in HbA1c, and recommendations will therefore depend on practical issues locally. Because most patients have a rather short stay in the hospital, it is obvious that studies addressing the question will be difficult to perform.

Does blood glucose POCT in the hospital (i.e., secondary care setting) lead to an economic benefit compared with central laboratory testing? (Literature Searches 37 and 38)

Guideline 65. *We recommend against routinely using POC glucose testing in the hospital setting on economic grounds.*

Strength/consensus of recommendation: C

Level of evidence: II

Three articles were retrieved *(68–70)*. Lee-Lewandrowski et al. *(68)* found that bedside glucose testing is not inherently more expensive than centralized laboratory measurements, but implementation on inefficient care units with low use can add substantially to the cost. Much of the excess cost of the bedside method can be attributed to the high costs of quality control and quality assurance, training, and documentation. Nosanchuk and Keefner *(69)* compared the operating cost of POC testing for glucose and an electrolyte/glucose/blood urea nitrogen (BUN) chemistry panel with the cost of central laboratory stat testing in a 204-bed community hospital. In the scenarios studied, POC testing costs exceed central laboratory stat costs from 1.1 to 4.6 times. The more the POC testing is used, the greater the excess costs compared to the central laboratory. Cost analysis demonstrates that the investment in acquiring automated transport and data management systems for the authors' hospital was far less expensive than POC testing for an individual stat test and on an annual cost basis. Parvin et al. *(70)* addressed whether a POC instrument shortened the length of stay (LOS) of patients at the hospital. The POC testing device performed Na, K, Cl, glucose, and BUN testing. Stratifying patients by presenting condition (chest pain, trauma, etc.), discharge/admit status, or presence/absence of other central laboratory tests did not reveal a decrease in patient LOS for any patient subgroup during the experimental period, and the median LOS was 209 min.

The evidence behind the recommendation is rather weak and may be challenged in the local environment. Practicality issues may, for example, be a reason for introducing POC glucose testing in the hospital, but one should try to document the effect of this intervention.

Does blood glucose POCT (primary and secondary care) lead to an improved patient (clinical) outcome (mother and/or baby) in the case of the pregnant woman with gestational diabetes when compared with central laboratory testing? (Literature Searches 39 and 40)

Guideline 66. *There is insufficient evidence to recommend for or against routinely using SMBG. The evidence to support our view is both from a systematic review* (5)*, RCTs, as well as controlled trials without randomization, and cohort/case control studies. The evidence is, however, conflicting, and our recommendation is therefore of type I, i.e., there is insufficient evidence to recommend for or against routinely using SMBG. If SMBG is going to be used, high-quality instruments should be chosen and patients must be educated in their practical use, as well as being instructed in how to use the results to monitor their insulin therapy. It seems, however, rational to apply the same policy as for DM type I.*

Strength/consensus of recommendation: I

Level of evidence: II

We found no additional RCTs compared to the 5 RCTs *(71–75)* found by Coster et al. *(5)*. Four of these were performed before 1984 and 1 in 1995 *(71)*. The study from 1995 compared the effect of SMBG before or after meals and found that HbA1c was lower in the after-meal monitoring group. The conclusion that this is due to SMBG, however, has been criticized *(76)*.

We did not find any additional non-RCTs compared to the 6 case series studies *(77–82)* found by Coster et al. *(5)*. These

6 are all from before 1992. From the present literature, it can be summarized *(5)* that (1) patients with gestational diabetes manage as well with SMBG as patients admitted to intensive control at the hospital and (2) hospital use can be decreased in patients performing SMBG. Coster et al. *(5)* are, however, reluctant to give any recommendation concerning the use of SMBG, but it is reasonable to think that the recommendations should be similar to those given for type I diabetes. The guidelines reviewed in this document *(1, 6–8)* do not give any specific recommendations concerning gestational diabetes and SMBG.

Does blood glucose POCT (primary and secondary care) lead to an economic benefit in the case of the pregnant woman with gestational diabetes when compared with central laboratory testing? (Literature Searches 39 and 40)

Guideline 67. *There is insufficient evidence of economical aspects to recommend for or against routinely using SMBG in gestational diabetes mellitus. No studies have evaluated the possible economic benefit of SMBG in gestational diabetes.*

Strength/consensus of recommendation: I

Level of evidence: III

HbA1c TESTING

The relationship between HbA1c and the mean blood glucose concentration over a period of weeks is now well established *(83)*. Furthermore, the role of HbA1c measurement in the management of diabetes is now also well established, largely as a result of the DCCT and UKPDS studies *(2, 3)*. Thus, it is used as a measure of glycemic control *(84)*, as well as an indicator of the risk of developing the complications associated with poor glycemic control *(85, 86)*. The HbA1c level is now also used in many healthcare systems to indicate the overall effectiveness of the diabetes management programs (87*, 88)*. The measurement of HbA1c is now enshrined in several guidelines for the management of diabetes *(89–92)*.

There are a large number of papers on POCT for HA1c, although the majority of them deal with the technical performance of the tests. Most papers describe the performance of the Bayer Diagnostics DCA 2000 system, which uses a monoclonal antibody raised against a specific glycated amino acid sequence of HbA1c, in a light-scattering immunoassay, encapsulated in a plastic cassette. Pope et al. *(93)* evaluated the system and found a coefficient of variation of 1.6% and 2.4% at HbA1c levels of 5.2% and 13.0%, respectively. When used by 4 separate operators, the coefficient of variation was <3.4%. The mean difference between the DCA and the laboratory HPLC method varied between −0.29% and −0.93% (absolute value), depending on the clinic source of the samples used in the comparison. Investigation of the clinical utility of the system in a small number of patients revealed that in half of those studied (9 out of 18), the use of POCT led to a change in treatment. John et al. *(94)* found a within-assay coefficient of variation of 1.9% to 3.1% and a between-batch value of 2.2%, again with a good correlation of results with an HPLC method. Carter et al. *(95)* studied the performance of the system in the primary care environment and found the performance to be "valid and reliable." Guerci et al. *(96)* undertook a multicenter trial and found the system to be "reliable and easy to use." More recently, other assays for HbA1c at the POC have been developed, although at present there are very few publications describing their performance. ECRI (formerly the Emergency Care Research Institute) recently reported on the performance of 5 HbA1c POCT systems. The evaluation focused on "the analyzers' accuracy, precision, and ease of use and provides purchasing guidance for different types of healthcare facilities" *(97)*.

A search was conducted on MEDLINE from 1990 to May 2004, and the results are summarized in Literature Search 41. A total of 14 papers were chosen for full review after the abstracts from the 123 papers identified were read, of which 10 were cited in the recommendations. One additional paper was found by hand searching the references from the main papers cited.

Does the provision of the HbA1c result at the POC lead to an improved patient (clinical) outcome when compared with central laboratory testing? (Literature Search 41)

Guideline 68. *We conclude that there is good evidence to support the use of POCT for HbA1c in both the primary and secondary care setting. The benefit comes from the diabetes specialist having the result at the time of the patient consultation. This recommendation assumes that the POCT is implemented under proper conditions, e.g., trained and certificated operators, quality control and quality assurance, and with an analytical system comparable with that used in the central laboratory. The evidence base would benefit from studies conducted over a longer period of time.*

Strength/consensus of recommendation: A

Level of evidence: I and II (2 RCTs and 2 controlled trials)

There are 4 independent trials reported, together with a multifaceted health technology assessment, on POCT for HbA1c. Cagliero et al. *(98)* reported on an RCT involving 201 type 1 and type 2 diabetic patients attending a secondary-care diabetes center, in which patients were randomized to a consultation in which the clinician received immediate feedback on the HbA1c result as against the routine service when the result came back from the laboratory at a later date. A total of 37 patients were lost to follow-up. The HbA1c results fell in the POCT group at 6- and 12-month follow-up (-0.57 ± 1.44 and $-0.40 \pm 1.65\%$, respectively; $P < 0.01$) but did not fall in the control group (-0.011 ± 0.70 and $-0.019 \pm 1.16\%$, respectively;

not significant). Thaler et al. *(99)*, in a controlled trial, studied 1138 diabetic individuals attending an urban diabetes center and found that more appropriate management was achieved in those patients treated with HbA1c results generated by POCT (<0.0001), with fewer changes in treatment when the HbA1c was $<7.0\%$ and more when $>7.0\%$. Over the 2- to 7-month follow-up period, the HbA1c levels rose more in the conventional group compared with the POCT group. Miller et al. *(100)* performed a similar study in an urban primary-care setting with 597 patients with diabetes. They found that treatment intensification was greater in those receiving POCT, and with increased HbA1c levels. Furthermore, the HbA1c levels fell over the course of the study in the POCT group (8.4% to 8.1%, $P = 0.04$, compared with 8.1% to 8.0%, $P = 0.31$). Grieve et al. *(101)* investigated the feasibility of introducing POCT for HbA1c, together with other biochemical tests, studying 599 individual patient clinic visits. They found that there were more management changes made in the group of patients treated with POCT HbA1c compared with the conventional approach, where the results were available at some later date (23 vs 18%), with the larger proportion made in those patients with increased HbA1c levels. They also studied patient and clinician satisfaction with questionnaires and found increased satisfaction levels in those clinic visits using POCT. In a retrospective study of 2 cohorts of patients attending clinics, one using POCT for HbA1c and the other receiving results back at a later date, the mean HbA1c was significantly higher in the cohort receiving the results at a later date (8.66 ± 0.056 vs 7.79 ± 0.058; $P < 0.001$). Ferenczi et al. *(102)*, in a retrospective review of medical records of new referrals, found that those patients receiving care with immediate HbA1c results showed a greater decrease in HbA1c compared to those where the result was communicated 2 days later ($1.03 \pm 0.33\%$ vs $0.33 \pm 0.83\%$). Holman et al. *(103)* used an alternative approach, sending out bottles for patients to return, containing a blood specimen. A total of 74% of the bottles sent out over 1 year were usable upon return, and this was associated with a reduction of the mean HbA1c result of 0.8% compared with the previous year ($P < 0.001$). It is also possible to bring the patient up to the clinic for phlebotomy the week before, although this may be less convenient for the patient.

There have been many studies on the role of education in diabetes management, the majority of which have dealt with education regarding blood glucose measurement, as well as studies covering aspects of lifestyle. Karter et al. *(62)* reported on the use of an intensive diabetes management program and the relation between blood glucose testing and HbA1c. Raji et al. *(104)* reported a randomized trial comparing passive and intensive education and found that intensive education led to a substantial improvement in HbA1c. Levetan et al. *(105)* studied the impact of computer-generated personalized goals in 150 patients, using a randomized study design, and found that these led to a reduction in the HbA1c. These illustrative studies show the importance of a holistic approach to disease management and the use of HbA1c as an indicator of treatment effectiveness and program compliance for the clinician and the patient. Intuitively, one expects HbA1c to play a role in this process.

Does the provision of the HbA1c result at the POC lead to an economic benefit when compared with central laboratory testing? (Literature Search 41)

Guideline 69. *We conclude that there is some evidence to show that POCT testing for HbA1c will lead to an economic benefit. However, the data are limited, and more detailed studies are required that should focus on the wider benefit of POCT, i.e., beyond the immediate costs of providing the test and the change in clinic attendance. The evidence would benefit from studies conducted (and impacts judged) over a longer period of time.*

Strength/consensus of recommendation: I

Level of evidence: II (randomized controlled trial and controlled trial, but small numbers)

Economic assessments of the use of diagnostic tests are rare, and invariably the economic data are poor. In the field of laboratory medicine, the main emphasis has been on the cost per test, and there has been little attention given to the wider benefits of testing. The situation is no different in the case of POCT for HbA1c. Cagliero et al. *(98)* in their study looked at the use of a wide range of healthcare resources, including outpatient visits and contact time with staff, and found that POCT did not lead to any significant change in the use of resources. Grieve et al. *(101)* found that the costs of POCT for HbA1c were higher than the laboratory provided service; when a laboratory analyzer was taken down to the clinic and run by a technologist, the costs were marginally higher that that of the conventional laboratory service. However, from an analysis of the retrospective cohort study, they found that there was a reduction in clinic visits using the POCT modality (from 2.28 visits per year per patient to a figure of 1.81), which helped to ameliorate the increased cost of testing. The prospective trial of POCT was only undertaken for a 3-month period, and a longer study is needed to provide more robust economic data.

Economic modeling from the DCCT and UKPDS studies shows an economic benefit from intensive glycemic control, with a long-term benefit, albeit at increased short-term cost *(106, 107)*. An economic analysis of diabetes care in the Kaiser Permanente healthcare system has shown that improved glycemic control does lead to an improved economic outcome when judged in terms of the long-term benefit *(108)*, primarily due to the reduction in hospital costs associated with emergency admissions, increased periods of hospital stay, and more clinic visits. It is only by modeling the use of POCT into this environment that the true economic assessment of POCT can be made.

Does patient self-testing for HbA1c lead to an improved patient (clinical) outcome when compared with central laboratory testing? (Literature Search 41)

Guideline 70. *We cannot make a recommendation here, because no studies have been reported.*

Strength/consensus of recommendation: I

Level of evidence: III (no studies addressing the question)

What is the optimal frequency of HbA1c testing? Does more frequent testing lead to better outcomes? (Literature Search 41)

Guideline 71. *There are no studies that have investigated the optimal frequency of POCT for HbA1c, and therefore we can only recommend that the guidelines generated from studies using a laboratory service for the measurement of HbA1c be adopted in the POCT setting. There are no studies that have formally investigated the frequency of measurement of HbA1c in any setting. We therefore recommend that HbA1c testing be performed between 2 and 4 times per year, in line with the patient's individual requirements. It is recommended that more frequent testing be required in those patients with extremely increased HbA1c levels and less frequently in those with levels approaching the reference range.*

Strength/consensus of recommendation: I

Level of evidence: III (opinion of respected authorities based on clinical experience)

A systematic review on the frequency of blood glucose monitoring found that there were no studies that investigated the frequency of HbA1c measurement and its impact on health outcomes but indicated that testing every 3 months in a type 1 diabetic patient would be reasonable *(5)*.

FRUCTOSAMINE

A search of Highwire and Pubmed was conducted; the details of the search and findings are summarized in Literature Search 42.

Does the provision of the fructosamine result at the POC lead to an improved patient (clinical) outcome when compared with central laboratory testing? (Literature Search 42)

Guideline 72. *Inadequate data are available to determine whether provision of fructosamine at the POC will improve glycemic control***.**

Strength/consensus of recommendation: I

Does the provision of the fructosamine result at the POC lead to an economic benefit when compared with central laboratory testing? (Literature Search 42)

Guideline 73. *No studies have evaluated the possible economic benefit of fructosamine POCT.*

Strength/consensus of recommendation: I

Does patient self-testing for fructosamine lead to an improved patient (clinical) outcome when compared with central laboratory testing? (Literature Search 42)

Guideline 74. *Published evidence does not support the hypothesis that patient self-testing for fructosamine (compared to central laboratory testing) leads to improved patient outcome. There are few published studies and the data are contradictory.*

Strength/consensus of recommendation: I

Level of evidence: III

There are 4 published studies that have evaluated POCT fructosamine measurement in the management of patients with diabetes. The number of patients in most studies was relatively small (≤60 in all but 1 study). One study *(109)* had no control group, and the clinical value of fructosamine cannot be evaluated. A second study (with 25 patients) showed that weekly fructosamine measurement improved glycemic control *(110)*. In contrast, 2 larger studies (comparing 60 and 140 patients) observed that addition of fructosamine to standard glucose self-monitoring did not improve glycemic control *(111, 112)*. In fact, the last study *(112)* noted a statistically significant benefit in the control group (glucose alone) compared with the study group (glucose plus weekly fructosamine), revealing that adding measurement of fructosamine actually worsened glycemic control.

What is the optimal frequency of fructosamine testing? Does more frequent testing lead to better outcomes? (Literature Search 42)

Guideline 75. *No studies have addressed the optimal frequency of fructosamine POCT.*

Strength/consensus of recommendation: I

Patients performed weekly home fructosamine monitoring in most published studies. It should also be noted that the LXN Corporation InCharge device—used in most of the self-monitoring studies—has been removed from the market and is not commercially available at the time of writing.

BLOOD KETONES

Does the provision of the blood ketone result at the POC lead to an improved patient (clinical) outcome when compared with central laboratory testing? (Literature Search 43)

Guideline 76. *In light of the absence of studies addressing this question, we make no recommendation for or against routinely providing POCT for blood ketones.*

Strength/consensus of recommendation: I

Level of evidence: II and III

In systematic review of the literature regarding the evidence for or against the clinical appropriateness (e.g., impact on patient outcomes and cost) of POCT for serum ketone measurements, the review of this question extended beyond the question of POCT to encompass the larger question of the utility of ketone measurement in diabetes. Because the need to measure glucose, regardless of methodology (laboratory or near patient testing), in diagnosis and management of diabetes is self-evident, at the outset, it was not clear that this concept extended to ketone measurement. As a result, the literature review was designed to address the broader topic of ketone measurement utility in diabetic disease management, as well as the appropriateness of POCT for serum ketones.

A MEDLINE search strategy was conducted using either Medical Subject Heading (MeSH) or Freetext (FTXT) terms. The strategy is summarized in Literature Search 43, together with the "hits" obtained.

Due to the vagaries *(113)* associated with ketonuria testing, the study was limited to serum ketone analysis. Citations that primarily focused on ketonuria monitoring, alcoholic ketoacidosis, or reports of new/enhanced measurement methods were not included as part of the final review. Titles and or abstracts were all reviewed with the following questions in mind: Is there an indication that this citation discusses the use of serum ketones in some aspect of patient management, or does the citation reflect, in whatever fashion, a clinical use for serum ketone measurement? Ketones measured in the serum are acetone (ACE), acetoacetate (AcAc), or β-hydroxybutyrate (BOHB); however, most of the literature discusses BOHB. No distinction was made between specific ketone measured, method used, or vendor represented. Two hundred citations were culled from this review. Of these 200, 19 citations were identified as most relevant, with 1 of the citations being a brief report in parallel with a more replete later published study; therefore, there were a total of 18 reviewed citations.

In addition, a MEDLINE search for review articles from the past 10 years that discussed diabetic ketoacidosis (DKA), as well as consensus articles on the management of diabetes, was performed to assess the current standard of care prescribed to diabetes; 13 citations were collected. In the 18 identified references, 11 studies *(114–124)* were specific for the use of serum POCT monitoring of BOHB levels, and 7 studies *(125–131)* discussed the clinical utility of serum ketone measurement based on a reference method.

Of the first group of citations, 8 *(114–116, 118, 120, 122–124)* were primarily studies that evaluated analytic characteristic of POC BOHB meter. All studies showed good accuracy (compared with reference laboratory result), precision, and linearity of results. Three citations *(119, 121, 124)* compared near patient testing of serum BOHB levels, with urine ketone body (UKB) measurement. All 3 concluded that serum BOHB was a better marker of ketosis than UKB. The studies reported in *(119)* and *(121)* were designed to evaluate BOHB compared to UKB in monitoring of recovery from DKA. Another study *(117)* compared the efficacy of insulin treatment regimens with cessation of ketosis, as measured by near patient testing of BOHB. This study was classified as an RCT.

Five citations *(115, 117, 119–121)* looked at some aspect of diabetes with the use of ketones as a marker of disease diagnosis, management, prognosis, or treatment. All of the studies were small cohort to anecdotal case reports (comparative studies). Three citations *(120, 122, 130)* compared serum BOHB (POCT and/or reference method) with other biochemical characteristics of DKA to determine the necessity, or lack thereof, for serum BOHB testing. A fourth study *(123)* compared biochemical characteristics to serum BOHB with a different intended purpose (to determine whether BOHB testing could replace serial measurements of standard biochemical testing). The former 3 similarly concluded that serum BOHB testing did not add any significant clinical information to the acute management of DKA, except to sort out hyperglycemic excursions from DKA and to monitor a potential biochemical endpoint (cessation of ketosis). The latter fourth had a similar conclusion, inferred from their discussion and conclusion.

Of the second group of citations (general clinical utility of serum ketone testing), *(126)* appeared to be a case-control study (but classified by the National Library of Medicine as descriptive). Studies reported in *(126)* and *(127)* were classified as RCTs. The remainder was either descriptive or comparative. All supported the evidence that ketones were present in individuals with uncontrolled or poorly controlled diabetes. Only 1 citation *(127)* attempted to provide an outcomes-based analysis. In this study, patients admitted with clinical DKA who had both ACE and glucose measurements performed had a serum BOHB measurement performed. All ($n = 44$) were positive for BOHB. It was noted that patients positive for ACE had significantly ($P = 0.005$) longer intensive care stays and significantly higher ($P = 0.05$) glucose levels. The study raises, but does not answer, the question that serum BOHB is a better discriminator of disease severity.

Thirteen citations were identified as review articles, consensus statements, or practice guidelines for diabetes mellitus and/or DKA *(1, 113, 132–142)*. All but 2 of the citations *(132, 136)* recommended the use of either serum or urine ketones in some part of diabetes management. Six recommend ketone monitoring as an outpatient to detect early DKA in stress or hyperglycemic situations *(1, 133–136, 141, 142)*. Of those, 2 focused only on outpatient management *(113, 133)*. In addition, 2 citations specifically state that serum BOHB should be used preferably to urine *(133, 134)*, with 2 additional citations favoring serum but stating the need for further studies *(1, 113)*. Of the 9 citations that discussed inpatient management, 2 *(135, 140)* raised questions regarding the need for ketone measurement in acute diabetic management beyond diagnosis, and a third *(138)* clearly stated that there was no need for ketone-body measurement in postdiagnosis diabetic disease management because other biochemical characteristics were clearly superior in monitoring acidosis. An excellent and detailed discussion on the specifics of ketogenesis in diabetes is given in *(113)*.

No grade I studies were identified for ketone analysis in general or, in specific, for near patient analysis. None of the identified citations provided a strong evidence-based argument for the measurement of ketones in patients with DKA. There was no identified study that examined patient outcomes associated

with performance or nonperformance of serum ketone measurement for either methodology of testing (reference or near patient). The majority of references were classified or classifiable as comparative studies, with only 2 classified as RCTs. Multiple studies gave evidence that supported the argument that serum BOHB levels did not provide any additional information to DKA management than already given by routine biochemical characteristics performed as part of the laboratory workup of DKA. There was agreement among all of the first group of citations that, in physiologic terms, serum BOHB was a better analyte to measure than UKB and that POCT of BOHB provided results as good as laboratory reference methods. All of the first and second group of citations qualitatively agreed that increased serum BOHB levels were characteristic for poorly controlled diabetes or DKA. There was consensus among the citations that serum BOHB was a good discriminator between hyperglycemic excursions and DKA. The recommendation *(1, 114, 123, 126, 128, 129)* was also given in several citations for serum BOHB monitoring in stress situations such as infection or clinically "unwell" to determine whether DKA was imminent.

The standard of care for ketone measurement in diabetic disease management varies by recommended ketone for measurement and varies depending on disease condition. There is general agreement that for crisis situations, serum ketone measurement is recommended for confirmation of DKA. Beyond diagnosis, there is varying opinion regarding the utility of ketone measurement in guiding treatment endpoints that range from no mention to unequivocal statements that there is no utility to ketone testing.

Among all identified articles, there was no disagreement on the existence of ketosis in stressed or poorly controlled diabetic patients. There should be no argument of this point, because it supported by the physiology and biochemistry of diabetes. However, there are no studies that clearly support an absolute need for serum ketone measurement in diabetic disease management. There are relative needs such as DKA confirmation and distinction between hyperglycemic excursions and DKA. At-home serum ketone monitoring is recommended for "stressed" individuals with diabetes to predict incipient DKA before advent of clinical symptoms; however, it does not appear to be practical as part of the daily routine monitoring. POCT inpatient serum ketone monitoring is also recommended to determine the biochemical endpoint of DKA management in light of treatment regimens that are based on degree of ketosis. On the other hand, there are several studies that question the need for serum ketone testing beyond diagnosis because their results are redundant in light of routine biochemical testing (tCO_2 and pH). Serum ketone POCT testing is associated with no harm (except redundant testing) and has qualitative supportive benefits, but no data exist in support of an absolute testing indication. The majority of references are based on descriptive clinical experiences and expert opinion. Although a priori reasoning suggests that POCT serum ketone must play a relevant role in diabetic disease management, there are no good studies that demonstrate an absolute need for serum ketone testing in either reference or POCT modalities.

Does the provision of the blood ketone result at the POC lead to an economic benefit when compared with central laboratory testing? (Literature Search 43)

Guideline 77. *In light of the absence of studies addressing this question, we make no recommendation for or against routinely providing POCT for blood ketones.*

Strength/consensus of recommendation: I

Grade of evidence: II and III

Does patient self-testing for blood ketone lead to an improved patient (clinical) outcome when compared with central laboratory testing?

Guideline 78. *In light of the absence of studies addressing this question, we make no recommendation for or against routinely providing POCT for blood ketones.*

Strength/consensus of recommendation: I

Grade of evidence: II and III

URINE ALBUMIN

Does the provision of the urine albumin result at the POC (i.e., secondary-care setting) in the management of diabetes (e.g., early detection of diabetic nephropathy) lead to an improved patient (clinical) outcome compared with central laboratory testing? (Literature Search 44)

Guideline 79. *There are no studies that have formally addressed the issue of screening for early signs of renal disease in patients with diabetes mellitus through the use of urine testing for protein or albumin at the POC. However, there is clear evidence to demonstrate an increase in urinary excretion of albumin associated with early diabetic nephropathy. Furthermore, there are several guidelines that advocate the regular checking of the urine albumin excretion in patients with diabetes mellitus.*

Strength/consensus of recommendation: I

Level of evidence: III

The complications of diabetes mellitus are classified as follows: macrovascular disease involving the coronary arteries, carotid arteries, and peripheral vasculature (e.g., the aortic, iliac, femoral, popliteal, and renal arteries); microvascular disease, including retinopathy and diabetic nephropathy; and neuropathy, including mononeuropathies, polyneuropathies, and autonomic neuropathies. The renal complications of diabetes mellitus can be classified as follows: (1) diabetic vascular disease (renal artery atherosclerosis and arteriolosclerosis of afferent arterioles);

(2) diabetic nephropathy; (3) increased susceptibility to infection; (4) atonic bladder (autonomic neuropathy); and (5) renal failure from radiocontrast dye where dehydration and dye toxicity can produce acute tubular necrosis. This discussion will focus on diabetic nephropathy.

Diabetic nephropathy involves glomerular damage that contributes to the development of hypertension and renal failure. Diabetic nephropathy affects 30% or more of cases of type 1 diabetes mellitus and 20% of cases of type 2 diabetes mellitus. Diabetes is the most common cause of end-stage renal disease (ESRD) in the United States *(143)* Approximately 30% to 35% of dialysis patients have diabetes, and 40% of all subjects beginning dialysis are diabetic *(143)*. Despite a more severe degree of hyperglycemia and a longer duration of diabetes in type 1 diabetes mellitus patients than in type 2 diabetes mellitus patients, more patients with type 2 diabetes mellitus have ESRD and are receiving dialysis than patients with type 1 diabetes mellitus *(144)* because ~90% of cases of diabetes result from type 2 diabetes mellitus vs only 10% of cases that result from type 1 diabetes mellitus. Renal failure is the second leading cause of death in type 1 diabetes mellitus *(145)*. CVD is the leading cause of death in type 2 diabetes mellitus: ~65% of type 2 diabetes mellitus patients will die of heart disease or stroke *(146)*. However, with improvements in the prevention and treatment of CVD, more type 2 diabetes mellitus patients will live longer *(147)*, and their risk for developing diabetic nephropathy will rise.

The etiologies of diabetic nephropathy include chronic hyperglycemia, hypertension, hyperlipidemia, intrarenal angiotensin II production, and familial predisposition *(148)*. The major factors contributing to the development and progression of diabetic nephropathy are chronic hyperglycemia and hypertension. Chronic hyperglycemia produces glomerular basement membrane (GBM) damage and induces mesangial proliferation of both mesangial cells and the mesangial matrix. Either systemic or intraglomerular hypertension (from hyperfiltration and flow shifts from destroyed glomeruli to healthy glomeruli) damages glomeruli and can produce ischemia. Hyperlipidemia is a modest risk factor for nephropathy *(149)*. It is controversial to what degree a family history of diabetic nephropathy predisposes to diabetic nephropathy in the propositus *(150)*. To date, no nephropathy-susceptibility genes have been identified.

Chronic hyperglycemia leads to nonenzymatic glycosylation (*glycation* is the preferred term for nonenzymatic addition of glucose) of many of the body's proteins *(151)*. Glycosylation of the GBM appears to decrease its negative charge, which impairs the selectively of the GBM to retain proteins, and the GBM becomes "leaky," permitting proteinuria to develop *(152)*. Increased blood volume from hyperglycemia induces glomerular hyperfiltration and produces intraglomerular hypertension. In aggregate, these factors produce glomerular damage. Glomerular damage is manifested in a 3- to 5-fold increased width of the GBM and mesangial proliferation. Thickening of the GBM and mesangial proliferation obliterate capillary loops, leading to obstruction of individual nephrons. This ultimate loss of surface area for filtration of waste produces chronic renal failure.

Glomerular damage and destruction leading to a loss of surface area for filtration leads to waste retention, described as renal insufficiency or renal failure if the glomerular filtration rate (GFR) is sufficiently reduced. The National Kidney Foundation (www.kidney.org) defines reductions in GFR as follows:

Degree of GFR decrease (mL/min/1.73 M^2)

- Mild = 60–89
- Moderate = 30–59
- Severe 15–29
- Kidney failure = <15 (or dialysis)

Systemic volume overload (from fluid retention) and possible hyperreninism from diabetic renovascular disease produce hypertension. Hypertension further damages glomeruli through pressure injury and ischemia. A positive feedback loop with worsening hypertension and progressive renal failure ensues.

The earliest biochemical evidence of glomerular injury is minimal albumin excretion (minimal albuminuria, a.k.a. microalbuminuria). Increased amounts of albumin are excreted because albumin is the most abundant plasma protein. The traditional urine dipstick test is negative for protein at such low levels of protein excretion. Microalbuminuria indicates "incipient" nephropathy *(143)*. There are a number of guidelines that recommend screening for microalbuminuria for the early detection of renal disease in individuals with diabetes *(153)* and in individuals with hypertension *(154)*.

There are 5 proposed stages in the development of diabetic nephropathy in type 1 diabetes mellitus (Table 6-1):

I Early hypertrophy-hyperfunction
II Glomerular lesions without clinical disease
III Incipient diabetic nephropathy
IV Clinical (overt) diabetic nephropathy
V ESRD

Table 6-1 Five Proposed Stages of Diabetic Nephropathy in Type 1 Diabetes Mellitus

Stage	GFR	MA (UAE)	Dipstick proteinuria	BP
I: Hypertrophy-hyperfunction	Increased	Transient	Transient	Normal
II: Glomerular lesions without clinical disease	Normal	Normal	Negative	Normal
III: Incipient diabetic nephropathy	Normal	Increased	Negative	± Increased
IV: Overt diabetic nephropathy	Decreased	—	Positive	Increased
V: ESRD	Very decreased	—	Positive	Increased

ESRD, end-stage renal disease; MA, microalbuminuria; UAE, Urinary albumin excretion; ±, possibly.

Stage I (early hypertrophy-hyperfunction) is present after the diagnosis of type 1 diabetes mellitus and is a consequence of expanded blood volume from hyperglycemia. Hyperfunction relates to hyperfiltration (i.e., an increased GFR). The kidneys are physically enlarged. Proteinuria is transient. GFR is increased by 20%–30%. With insulin treatment of type 1 diabetes mellitus and control of hyperglycemia, GFR normalizes. All type 1 diabetes mellitus patients progress to stage II nephropathy.

In stage II nephropathy (silent nephropathy), histologic glomerular lesions develop without other evidence of clinical disease. Systemic blood pressure is normal and proteinuria is absent. Thickening of the GBM and mesangial cellular and matrix expansion occur. Such histological changes are visible after 3 to 5 years of type 1 diabetes mellitus. Progression to stage III nephropathy occurs in ~40% of type 1 diabetes mellitus patients.

Stage III nephropathy (incipient diabetic nephropathy) is recognized by increased albumin excretion (minimal albumin excretion [a.k.a. microalbuminuria]) despite a negative routine dipstick test result for protein. The low-end analytical sensitivity of the routine urine dipstick for albumin detection, at best, is a urine albumin concentration of 15 mg/dL (usually, the urine dipstick lower limit of detection for protein varies between 15 and 30 mg/dL). At a detection limit of 15 mg/dL and a urine output of 2000 mL/day, the dipstick would detect 300 mg/day of albumin excretion, or ~500 mg of protein excreted. Macroproteinuria is defined as >300 mg of albumin excreted per 24 h. Microalbuminuria is routinely determined by immunoassay, e.g., RIA, ELISA, radioimmunodiffusion, or immunoturbidimetry.

Stage III is reached after 7–15 years of type 1 diabetes mellitus and can last for 5–15 years. Progressive histologic changes occur in stage III nephropathy. There can be mild to moderate hypertension. Without intervention, progression to stage IV nephropathy occurs in ~80% to 100% of type 1 diabetes mellitus patients.

Albumin excretion can be studied and reported as a 24-h collection (mg/24 h; this is considered the gold standard), a timed urine collection (μg/min) or a spot collection (e.g., AM urine), with the albumin to creatinine (Cr) ratio expressed (μg albumin/mg of Cr; or mg albumin/g of Cr). Urine albumin measurements are sometimes referred to as urinary albumin excretion (UAE). The 24-h collection is the most difficult sample to correctly obtain. For this reason, the albumin to Cr ratio is advantageous. Within-day variation of protein and albumin excretion is minimized when the ratio is used *(155)*. The albumin:Cr ratio also displays good correlation with 24-h collections *(156–158)*.

All forms of albumin excretion can be measured in central laboratories. At the POC, Bayer Diagnostics LLC (Medfield, MA, USA) offers the DCA2000+, which can measure, in addition to HbA1c, urinary albumin and Cr to determine microalbumin excretion, with a specially designed cartridge for urine testing. Several studies have demonstrated significant analytical robustness for this system *(159–162)*.

Dipsticks for minimal albumin excretion measurement are also available such as the Micral II (Roche Diagnostics, Indianapolis, IN, USA) *(163)* and ImmunoDip (Diagnostic Chemicals Limited, Prince Edward Island, Canada). Both of these sticks use antibodies to detect albumin. The Bayer Clinitek benchtop analyzer reads Clinitek Microalbumin strips (Bayer Diagnostics) that semiquantitatively determine albumin and Cr using chemical methods (albumin: sulfonephthalein dye binding at pH 1.5; Cr: peroxidase-like activity of copper Cr complexes) *(164–166)*. There are no current references for the Miles Laboratory MicroBumintest, which was available during the late 1980s *(167)*.

Microalbumin dipsticks measure albumin concentration and show fair to good correlations with standard immunoanalytic methods of albuminuria assessment *(143)*. If such microalbumin dipstick results are positive, they are informative and require central laboratory confirmation. The Micral II dipsticks may be sensitive but display modest degrees of specificity that require central laboratory confirmation *(168–170)*. On the other hand, some studies have found good specificity (92%–98%) but lower sensitivity (58%–78%) with the Micral II strips *(171, 172)*. In the single peer-reviewed publication concerning ImmunoDip, the ImmunoDip device exhibited good sensitivity but a specificity of only 80% *(173)*. The Clinitek Microalbumin strips displayed good sensitivity (~95%) and a similar specificity (~80%) *(174)*. Dipsticks that measure albumin and Cr may reduce false positives and false negatives *(174, 175)*. Guidelines from the National Kidney Foundation state that, whereas dipstick detection of proteinuria is adequate, the albumin to Cr ratio is more reliable *(176)*. Improving availability of any testing modality for proteinuria is desirable *(177, 178)*.

Repeated POCT measurements for the detection of minimal albumin excretion may not improve the sensitivity or specificity of microalbuminuria detection *(179)*. Certainly the predictive value of POCT for microalbuminuria is affected by disease prevalence *(180)*. A valid concern is that urine volume variation and sample dilution will produce a false-negative result. In development is the "MicroalbuminuriaNow" test for POCT. This product is conceived as a single-use, disposable device that can be used by patients at home or in clinics (http://www.metrika.com/3medical/products.html).

The theoretical advantage of POCT is that results are immediately available. Unfortunately, there are no data to suggest that the availability of microalbumin results at the time of the patient's visit changes clinical outcome. However, in another critical aspect of diabetes management, when HbA1c results are available at the time of the patient's visit, patients achieve better glycemic control, evidenced by subsequently lower HbA1c values *(97–102)*. POCT for microalbuminuria has been used in research studies *(181–183)* and general practice settings *(184)*, and its performance has been found to be reasonably user friendly.

Table 6-2 provides ranges recommended for the interpretation of albumin excretion *(143)*. When the routine urine dipstick result is positive, clinical (overt) proteinuria is present.

The ADA recommends that patients with type 2 diabetes mellitus be examined for albuminuria at diagnosis and patients

Table 6-2 Albuminuria: Definitions

	Nephropathy stage	24-h Timed collection		Spot Alb/Cr
		(μg/min)	(mg/24 h)	(μg/mg)
Normal	—	<20	<30	<30
MAU[a]	III	20–199	30–299	30–299
Clinical albuminuria[b]	IV	≥200	≥300	≥300

[a] Microalbuminuria (ie., minimal albumin excretion).
[b] Also known as overt (clinical) diabetic nephropathy; dipstick (+).

with type 1 diabetes mellitus be examined after 5 years of disease *(143)*. Patients are then tested yearly. Because of the gradual, often subtle onset of type 2 diabetes mellitus and the frequent delay in the diagnosis of type 2 diabetes mellitus, according to the recognition of symptoms alone, many patients have had long periods of unrecognized diabetes that can contribute to type 2 diabetes mellitus subjects' already having significant albuminuria at disease diagnosis *(185)*.

To reduce the cost of testing for albuminuria, many laboratories will screen all urines submitted for microalbumin testing by initial dipstick screening. If the dipstick result is positive, macroproteinuria, by definition, is present. In this case, with the routine dipstick result being positive for protein, a 24-h urine sample should be collected for measurement of protein excretion and calculation of Cr clearance. A repeatedly positive routine dipstick test for protein indicates stage IV, clinical (overt) nephropathy (see below).

If the routine dipstick test result is negative, albuminuria is sought by any of the 3 accepted approaches outlined above. According to the ADA, if the albumin excretion rate is normal, the test should be repeated in 1 year. If increased minimal albumin excretion is detected, the test should be repeated to confirm the finding in the next 3 to 6 months. If minimal albumin excretion is identified in 2 of 3 tests, microalbuminuria is diagnosed, consistent with incipient nephropathy.

In a report (No. 84) from the Agency for Healthcare Research and Quality (AHRQ), the clinical relevance of increased urinary albumin excretion was linked to increased risk of progression to ESRD, increased cardiovascular morbidity, increased cardiovascular mortality, and increased total mortality *(87)*. Furthermore, this AHRQ publication reported that the risks associated with microalbuminuria are graded: higher levels of urine albumin excretion are associated with greater degrees of declining renal function and faster rates of declining renal function. Higher levels of urine albumin excretion are associated with a greater magnitude of risk for cardiovascular morbidity, cardiovascular mortality, and total mortality.

When microalbuminuria is confirmed, therapy to delay or prevent progression of nephropathy should be instituted. According to the ADA 2004 Clinical Practice Guidelines *(143)*, the key interventions are (1) improve glycemic control, (2) initiate antihypertensive therapy in normotensive and hypertensive patients with either angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, and (3) restrict dietary protein (0.8 g/kg/day).

There is strong evidence that antihypertensive treatment decreases the likelihood of progression from incipient nephropathy to more severe forms of nephropathy *(186–188)*. The drug class of first choice is the angiotensin-converting enzyme inhibitors. In addition, benefit has been shown in type 2 diabetes mellitus patients treated with angiotensin-receptor blockers *(189)*. If these drugs are not tolerated, nondihydropyridine calcium-channel blockers (NDCCB), β-blockers, or diuretics should be therapeutically considered.

Stage IV nephropathy (i.e., clinical [overt] diabetic nephropathy) displays dipstick-detectable albuminuria and albumin excretion increased above minimal levels (Table 6-1). Stage IV nephropathy occurs after an average duration of diabetes of 15 to 17 years, with a range of 10 to 30 years. Decreasing renal function is observed as a declining GFR. Hypertension is routinely present. There is increased risk for coronary heart disease and mortality, with a 100-fold increased risk. Retinopathy is almost always present. Progression to stage V nephropathy is observed in ~75% to 100% of stage IV type 1 diabetes mellitus patients.

With persistent proteinuria (stage IV), the 5-year survival rate is 65%, the 10-year survival rate is 28%, and median survival is 10 years. Death usually results within 20 years from renal or cardiovascular causes. In summary, stage IV diabetic nephropathy is a clinical syndrome of sustained high-level albuminuria (proteinuria), hypertension, and progressive renal insufficiency when action is not taken to halt nephropathy.

Stage IV nephropathy histologically is characterized by progressive glomerulosclerosis. Diabetic glomerulosclerosis is characterized by thickened GBMs and mesangial expansion. Over time, diffuse diabetic glomerulosclerosis evolves into nodular diabetic glomerulosclerosis. Nodular lesions within the glomeruli are referred to as Kimmelstiel-Wilson nodules or lesions. Tubulointerstitial disease is also possible in cases of diabetic nephropathy, noted by the presence of hyperkalemia and a type IV renal tubular acidosis.

The value of annual microalbumin measurements after the diagnosis of incipient nephropathy and the institution of therapy is controversial. Serial GFR measurements should be obtained to assess glomerular function in patients with diabetic nephropathy *(178)*. Transient elevations in albumin excretion can follow short-term hyperglycemia, exercise, urinary tract infection, marked hypertension, and heart failure and with acute febrile illnesses. Microalbuminuria is best sought when these conditions are absent or are under control to avoid false-positive tests for microalbuminuria.

Stage V nephropathy is characterized by the development of ESRD. Azotemia (e.g., the retention of nitrogenous wastes with an increased BUN level) prestages uremia and oliguria. Uremia is the clinical syndrome that results from renal failure that includes increased fatigability, headache, anorexia, nausea

and vomiting, diarrhea, hiccups, restlessness, and depression. The signs of uremia encompass epistaxis (nosebleeds), melena (blood in the stools), dyspnea (shortness of breath), irregular start-stop breathing, halitosis, dehydration, muscle twitching, seizures, and delirium. Biochemical findings in addition to increased BUN and Cr (in an approximate 10:1 ratio) include systemic acidosis (low serum CO_2), hyperkalemia, hyperphosphatemia, hypocalcemia, normocytic normochromic anemia, and urine specific gravity usually $<$1.010 to $<$1.012. Untreated, uremia progresses to coma and death.

ESRD eventually requires dialysis or transplantation. Stage V nephropathy is reached after 20 to 40 years of diabetes and usually develops 5 to 7 years after the onset of stage IV nephropathy. Ultimately, 75% of ESRD cases occur within 10 years of dipstick-test-positive proteinuria.

New methodologies are being developed for the determination of urinary albumin levels *(190)*. Earlier markers of progressive nephropathy are being sought. Elevations in nocturnal blood pressure appear to precede the appearance of microalbuminuria *(191)*. Also, albumin excretion measured by HPLC has demonstrated higher rates of microalbuminuria and earlier onset of microalbuminuria in diabetes than immunologically measured albumin determinations *(192–194)*. Thus, HPLC can detect both nonimmunoreactive and immunoreactive albumin. This is a developing field that bears review.

The field of microalbumin testing and diabetic nephropathy is not without controversy. One recent paper reported a high frequency of renal insufficiency in type 2 diabetes in the absence of albuminuria *(195)*, whereas another paper reported that microalbuminuria frequently does not progress to more severe degrees of renal impairment *(196)*.

Finally, up to at least 2001, "no controlled trials of screening to prevent progression to nephropathy or that compared sequential repeated screening strategies were identified" *(188)*. A search of PubMed (see Literature Search 44) and selected recent review articles did not reveal any controlled trials of screening to prevent progression to nephropathy.

Does the provision of the urine albumin result at the POC (i.e., secondary-care setting) in the management of diabetes (i.e., early detection of diabetic nephropathy) lead to an economic benefit when compared with central laboratory testing? (Literature Search 44)

Guideline 80. *From the 1 available study, POCT for microalbuminuria with central laboratory confirmation of microalbuminuria is more expensive than testing alone, recognizing that this only takes into account the marginal cost of testing.*

Strength/consensus of recommendation: I

Level of evidence: II (evidence from well-designed case-control study)

It is only a possible postulate in the absence of any formal trials that there will be an economic benefit to be obtained from POCT for microalbuminuria, although it is assumed that clinician and patient benefit will result in some economic benefit.

Does patient self-testing for urine albumin (i.e., primary-care setting) lead to an improved patient (clinical) outcome when compared with central laboratory testing? (Literature Search 44)

Guideline 81. *In the absence of data on self-testing for microalbuminuria, there is no basis to recommend for or against this practice.*

Strength/consensus of recommendation: I

There is no evidence of studies investigating the use of self-monitoring of albuminuria, and therefore it is not possible to provide an answer to this question.

What is the optimal frequency of urine albumin testing? Does more frequent testing lead to better outcomes? (Literature Search 44)

Guideline 82. *In the absence of any data on the frequency of POCT for microalbuminuria, it is not possible to make any recommendation on this point, and guidance should be sought from the guidelines documents that have been published on testing for microalbuminuria in diabetic patients.*

Strength/consensus of recommendation: I

Level of evidence: III (opinions of respected authorities according to clinical experience)

It has been suggested that type 1 diabetic patients should be screened on an annual basis starting about 5 years after initial diagnosis. In the case of type 2 diabetes, screening should begin immediately after diagnosis. In the event of an abnormal result being found, then 2 further tests should be undertaken, and if 2 of the results are found to be abnormal, then a 24-h collection should be undertaken to confirm microalbuminuria. These guidelines have been devised with POCT in mind.

FINAL CONCLUSIONS

In drawing together the conclusions from this review of the evidence on POCT in the diagnosis and management of diabetes mellitus, the reader is referred to an observation made at the commencement of this discussion, namely, that "absence of evidence of effect does not constitute evidence of absence of effect" *(4)*. It has been acknowledged on many occasions in the literature that generating data on the outcomes from the use of "diagnostic tests" with robust study design can be extremely challenging, particularly true in the case of a complex condition such as

diabetes mellitus, where, in the management of the condition, the test and the intervention are intimately linked and it is the combined use of test and intervention that yields an improved health outcome. In addition, it is also recognized that it can be difficult to design studies that minimize the risk of bias in the study results, as with the use of an RCT. Thus, as has been suggested in earlier systematic reviews of aspects of diabetes care (e.g., *5*), it may be necessary to look at other types of study design, e.g., observational studies. This effectively looks at a package of care and measures taken to involve patients in managing their own healthcare. In this respect, it is worthy of note that many of the current guidelines on the management of diabetes mellitus indicate the use of "diagnostic tests" as part of an "integrated package of care" and "taking account of patient's needs and expectations." Further research is needed on the use of POCT as part of an integrated package of care in the management of diabetes mellitus.

REFERENCES

1. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436–72.
2. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.
3. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
4. Alderson P. Absence of evidence is not evidence of absence. BMJ 2004;328:477–9.
5. Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R. Monitoring blood glucose control in diabetes mellitus: a systematic review. Health Technol Assess 2000;4:1–93.
6. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications, part I: diagnosis and classification of diabetes mellitus. Geneva: World Health Organization, 1999.
7. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2003;26(Suppl 1): S33–50.
8. McIntosch A, Hutchinson S, Home P, Brown F, Bruce A, Damerell S, et al. Clinical guidelines and evidence review for type 2 diabetes: management of blood glucose. Sheffield: ScHARR, University of Sheffield, 2001:1–235.
9. Carney RM, Schechter K, Homa M, Levandoski L, White N, Santiago J. The effects of blood glucose testing versus urine sugar testing on the metabolic control of insulin-dependent diabetic children. Diabetes Care 1983;6:378–80.
10. Chase HP, Kim LM, Owen SL, MacKenzie TA, Klingensmith GJ, Murtfeldt R, et al. Continuous subcutaneous glucose monitoring in children with type 1 diabetes. Pediatrics 2001; 107:222–6.
11. Daneman D, Siminerio L, Transue D, Betschart J, Drash A, Becker D. The role of self-monitoring of blood glucose in the routine management of children with insulin-dependent diabetes mellitus. Diabetes Care 1985;8:1–4.
12. Gordon D, Semple CG, Paterson KR. Do different frequencies of self-monitoring of blood glucose influence control in type 1 diabetic patients? Diabet Med 1991;8:679–82.
13. Mann NP, Noronha JL, Johnston DI. A prospective study to evaluate the benefits of long-term self-monitoring of blood glucose in diabetic children. Diabetes Care 1984;7:322–6.
14. Miller F, Stratton C, Tripp J. Blood testing compared with urine testing in the long term control of diabetes. Arch Dis Child 1983; 58:294–7.
15. Starostina EG, Antsiferov M, Galstyan GR, Trautner C, Jorgens V, Bott U, et al. Effectiveness and cost-benefit analysis of intensive treatment and teaching programmes for type 1 (insulin-dependent) diabetes mellitus in Moscow: blood glucose versus urine glucose self-monitoring. Diabetologia 1994;37:170–6.
16. Terent A, Hagfall O, Cederholm U. The effect of education and self-monitoring of blood glucose on glycosylated hemoglobin in type I diabetes: a controlled 18-month trial in a representative population. Acta Med Scand 1985;217:47–53.
17. Worth R, Home PD, Johnston DG, Anderson J, Ashworth L, Burrin JM, et al. Intensive attention improves glycaemic control in insulin-dependent diabetes without further advantage from home blood glucose monitoring: results of a controlled trial. BMJ (Clin Res Ed) 1982;285:1233–40.
18. Belmonte MM, Schiffrin A, Dufresne J, Suissa S, Goldman H, Polychronakos C. Impact of SMBG on control of diabetes as measured by HbA1: 3-yr survey of a juvenile IDDM clinic. Diabetes Care 1988;11:484–8.
19. Dorchy H, Roggemans MP. Improvement of the compliance with blood glucose monitoring in young insulin-dependent diabetes mellitus patients by the Sensorlink system. Diabetes Res Clin Pract 1997;36:77–82.
20. Geffner ME, Kaplan SA, Lippe BM, Scott ML. Self-monitoring of blood glucose levels and intensified insulin therapy: acceptability and efficacy in childhood diabetes. JAMA 1983; 249:2913–6.
21. Gill GV, Huddle KR, Krige LP. Improving diabetic control in adverse social conditions: a home blood glucose monitoring study in Soweto, South Africa. Diabetes Res 1986;3:145–8.
22. Hermansson G, Ludvigsson J, Larsson Y. Home blood glucose monitoring in diabetic children and adolescents: a 3-year feasibility study. Acta Paediatr Scand 1986;75:98–105.
23. Kelly CA, Barrett EJ, Nash J. Home monitoring and self-management of diabetes in a rural population. Ir Med J 1981;74:321–4.
24. Lam KS, Ma JT, Chan EY, Yeung RT. Sustained improvement in diabetic control on long-term self-monitoring of blood glucose. Diabetes Res Clin Pract 1986;2:165–71.
25. Lombrail P, Obadia G, Thibult N, Eschwege E, Passa P. [Lack of benefit of blood glucose autosurveillance in insulin-treated diabetics routinely followed up in a department specializing in diabetology]. Presse Med 1986;15:1909–12.
26. Peveler RC, Davies BA, Mayou RA, Fairburn CG, Mann JI. Self-care behaviour and blood glucose control in young adults with type 1 diabetes mellitus. Diabet Med 1993;10:74–80.
27. Sonksen PH, Judd SL, Lowy C. Home monitoring of blood-glucose: method for improving diabetic control. Lancet 1978;1:729–32.
28. Strowig SM, Raskin P. Improved glycemic control in intensively treated type 1 diabetic patients using blood glucose meters with storage capability and computer-assisted analyses. Diabetes Care 1998;21:1694–8.
29. Walford S, Gale EA, Allison SP, Tattersall RB. Self-monitoring of blood-glucose: improvement of diabetic control. Lancet 1978;1:732–5.

30. Wing RR, Lamparski DM, Zaslow S, Betschart J, Siminerio L, Becker D. Frequency and accuracy of self-monitoring of blood glucose in children: relationship to glycemic control. Diabetes Care 1985;8:214–8.
31. Wysocki T, Hough BS, Ward KM, Allen AA, Murgai N. Use of blood glucose data by families of children and adolescents with IDDM. Diabetes Care 1992;15:1041–4.
32. Ziegler O, Guerci B, Crea-Avila T, Candiloros H, Drouin P. [How I take charge and treat type II diabetes resistant to usual treatment]. Journ Annu Diabetol Hotel Dieu 1993:139–54.
33. Ziegler O, Kolopp M, Got I, Genton P, Debry G, Drouin P. Reliability of self-monitoring of blood glucose by CSII-treated patients with type I diabetes. Diabetes Care 1989;12:184–8.
34. Allen C, LeCaire T, Palta M, Daniels K, Meredith M, D'Alessio DJ. Risk factors for frequent and severe hypoglycemia in type 1 diabetes. Diabetes Care 2001;24:1878–81.
35. Kaufman FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P. A pilot study of the continuous glucose monitoring system: clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects. Diabetes Care 2001;24:2030–4.
36. American Diabetes Association. Consensus statement on self-monitoring of blood glucose. Diabetes Care 1987;10:95–9.
37. American Diabetes Association. Self-monitoring of blood glucose. Diabetes Care 1994;17:81–6.
38. Allen BT, DeLong ER, Feussner JR. Impact of glucose self-monitoring on non-insulin-treated patients with type II diabetes mellitus: randomized controlled trial comparing blood and urine testing. Diabetes Care 1990;13:1044–50.
39. Estey AL, Tan MH, Mann K. Follow-up intervention: its effect on compliance behavior to a diabetes regimen. Diabetes Educ 1990; 16:291–5.
40. Fontbonne A, Billault B, Acosta M, Percheron C, Varenne P, Besse A, et al. Is glucose self-monitoring beneficial in non-insulin-treated diabetic patients? results of a randomized comparative trial. Diabet Metab 1989;15:255–60.
41. Gallichan M. Self-monitoring by patients receiving oral hypoglycaemic agents: a survey and comparative trial. Practical Diabetes 1994;20:1482–6.
42. Miles P, Everett J, Murphy J, Kerr D. Comparison of blood or urine testing by patients with newly diagnosed non-insulin dependent diabetes: patient survey after randomised crossover trial. BMJ 1997;315:348–9.
43. Muchmore DB, Springer J, Miller M. Self-monitoring of blood glucose in overweight type 2 diabetic patients. Acta Diabetol 1994;31:215–9.
44. Rutten G, van Eijk J, de Nobel E, Beek M, van der Velden H. Feasibility and effects of a diabetes type II protocol with blood glucose self-monitoring in general practice. Fam Pract 1990; 7:273–8.
45. Wing RR, Epstein LH, Nowalk MP, Scott N, Koeske R, Hagg S. Does self-monitoring of blood glucose levels improve dietary compliance for obese patients with type II diabetes? Am J Med 1986;81:830–6.
46. Schwedes U, Siebolds M, Mertes G. Meal-related structured self-monitoring of blood glucose: effect on diabetes control in non-insulin-treated type 2 diabetic patients. Diabetes Care 2002;25: 1928–32.
47. Persell S. What is the role of self-monitoring of blood glucose in non-insulin-treated diabetes? JCOM 2003;10:7–10.
48. Cohen M, Zimmet P. Self-monitoring of blood glucose levels in non-insulin-dependent diabetes mellitus. Med J Aust 1983;2: 377–80.
49. Gilden JL, Casia C, Hendryx M, Singh SP. Effects of self-monitoring of blood glucose on quality of life in elderly diabetic patients. J Am Geriatr Soc 1990;38:511–5.
50. Klein CE, Oboler SK, Prochazka A, Oboler S, Frank M, Glugla M, et al. Home blood glucose monitoring: effectiveness in a general population of patients who have non-insulin-dependent diabetes mellitus. J Gen Intern Med 1993;8:597–601.
51. Malik RL, Horwitz DL, McNabb WL, Takaki ET, Hawkins HA, Keys AG, et al. Adjustment of caloric intake based on self-monitoring in noninsulin-dependent diabetes mellitus: development and feasibility. J Am Diet Assoc 1989;89:960–1.
52. Martin B, Young R, Kesson C. Home monitoring of blood glucose in elderly non-insulin dependent diabetics. Pract Diabetes 1986;3:37.
53. Newman WP, Laqua D, Engelbrecht D. Impact of glucose self-monitoring on glycohemoglobin values in a veteran population. Arch Intern Med 1990;150:107–10.
54. Oki JC, Flora DL, Isley WL. Frequency and impact of SMBG on glycemic control in patients with NIDDM in an urban teaching hospital clinic. Diabetes Educ 1997;23:419–24.
55. Patrick AW, Gill GV, MacFarlane IA, Cullen A, Power E, Wallymahmed M. Home glucose monitoring in type 2 diabetes: is it a waste of time? Diabet Med 1994;11:62–5.
56. Tajima N, Yamada C, Asukata I, Yamamoto K, Hokari M, Sakai T. Pilots with non-insulin-dependent diabetes mellitus can self-monitor their blood glucose. Aviat Space Environ Med 1989;60:457–9.
57. Wieland LD, Vigil JM, Hoffman RM, Janis LW. Relationship between home glucose testing and hemoglobin Alc in type II diabetes patients. Am J Health Syst Pharm 1997;54:1062–5.
58. Blonde L, Ginsberg BH, Horn S, Hirsch IB, James B, Mulcahy K, et al. Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. Diabetes Care 2002;25:245–6.
59. Evans JM, Newton RW, Ruta DA, MacDonald TM, Stevenson RJ, Morris AD. Frequency of blood glucose monitoring in relation to glycaemic control: observational study with diabetes database. BMJ 1999;319:83–6.
60. Franciosi M, Pellegrini F, De Berardis G, Belfiglio M, Cavaliere D, Di Nardo B, et al. The impact of blood glucose self-monitoring on metabolic control and quality of life in type 2 diabetic patients: an urgent need for better educational strategies. Diabetes Care 2001;24:1870–7.
61. Harris MI. Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. Diabetes Care 2001;24:979–82.
62. Karter AJ, Ackerson LM, Darbinian JA, D'Agostino RB Jr, Ferrara A, Liu J, et al. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes Registry. Am J Med 2001;111:1–9.
63. Meier JL, Swislocki AL, Lopez JR, Noth RH, Bartlebaugh P, Siegel D. Reduction in self-monitoring of blood glucose in persons with type 2 diabetes results in cost savings and no change in glycemic control. Am J Manag Care 2002;8:557–65.
64. Faas A, Schellevis FG, Van Eijk JT. The efficacy of self-monitoring of blood glucose in NIDDM subjects: a criteria-based literature review. Diabetes Care 1997;20:1482–6.
65. Halimi S. [Benefits of blood glucose self-monitoring in the management of insulin-dependent (IDDM) and non-insulin-dependent diabetes (NIDDM): analysis of the literature: mixed results]. Diabetes Metab 1998;24(Suppl 3):35–41.
66. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. Diabetes Care 2001;24:561–87.

67. Holmes V, Griffiths P. Self-monitoring of glucose levels for people with type 2 diabetes. Br J Community Nurs 2002;7:41–6.
68. Lee-Lewandrowski E, Laposata M, Eschenbach K, Camooso C, Nathan DM, Godine JE, et al. Utilization and cost analysis of bedside capillary glucose testing in a large teaching hospital: implications for managing point of care testing. Am J Med 1994;97:222–30.
69. Nosanchuk JS, Keefner R. Cost analysis of point-of-care laboratory testing in a community hospital. Am J Clin Pathol 1995;103:240–3.
70. Parvin CA, Lo SF, Deuser SM, Weaver LG, Lewis LM, Scott MG. Impact of point-of-care testing on patients' length of stay in a large emergency department. Clin Chem 1996;42:711–7.
71. de Veciana M, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. N Engl J Med 1995;333:1237–41.
72. Goldstein A, Elliott J, Lederman S, Worcester B, Russell P, Linzey EM. Economic effects of self-monitoring of blood glucose concentrations by women with insulin-dependent diabetes during pregnancy. J Reprod Med 1982;27:449–50.
73. Hanson U, Persson B, Enochsson E, Lennerhagen P, Lindgren F, Lundstrom V, et al. Self-monitoring of blood glucose by diabetic women during the third trimester of pregnancy. Am J Obstet Gynecol 1984;150:817–21.
74. Stubbs SM, Brudenell JM, Pyke DA, Watkins PJ, Stubbs WA, Alberti KG. Management of the pregnant diabetic: home or hospital, with or without glucose meters? Lancet 1980;1:1122–4.
75. Varner MW. Efficacy of home glucose monitoring in diabetic pregnancy. Am J Med 1983;75:592–6.
76. Miles JM, Coppack SW. Blood glucose monitoring in gestational diabetes mellitus. N Engl J Med 1996;334:598.
77. Espersen T, Klebe JG. Self-monitoring of blood glucose in pregnant diabetics: a comparative study of the blood glucose level and course of pregnancy in pregnant diabetics on an out-patient regime before and after the introduction of methods for home analysis of blood glucose. Acta Obstet Gynecol Scand 1985;64:11–4.
78. Goldberg JD, Franklin B, Lasser D, Jornsay DL, Hausknecht RU, Ginsberg-Fellner F, et al. Gestational diabetes: impact of home glucose monitoring on neonatal birth weight. Am J Obstet Gynecol 1986;154:546–50.
79. Jovanovic L, Druzin M, Peterson CM. Effect of euglycemia on the outcome of pregnancy in insulin-dependent diabetic women as compared with normal control subjects. Am J Med 1981;71:921–7.
80. Jovanovic L, Peterson CM, Saxena BB, Dawood MY, Saudek CD. Feasibility of maintaining normal glucose profiles in insulin-dependent pregnant diabetic women. Am J Med 1980;68:105–12.
81. Peacock M, Chunter J, Walford S. Self-monitoring of blood glucose in diabetic pregnancy. BMJ 1979;ii:1333–6.
82. Wechter DJ, Kaufmann RC, Amankwah KS, Rightmire DA, Eardley SP, Verhulst S, et al. Prevention of neonatal macrosomia in gestational diabetes by the use of intensive dietary therapy and home glucose monitoring. Am J Perinatol 1991;8:131–4.
83. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA1c: analysis of glucose profiles and HbA1c in the Diabetes Control and Complications Trial. Diabetes Care 2002;25:275–8.
84. Miedema K. Laboratory tests in diagnosis and management of diabetes mellitus: practical considerations. Clin Chem Lab Med 2003;41:1259–65.
85. Klein R, Klein BE, Moss SE, Cruickshanks KJ, Brazy PC. The 10-year incidence of renal insufficiency in people with type 1 diabetes. Diabetes Care 1999;22:743–51.
86. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–529.
87. US Department of Health and Human Services, Agency for Health Research and Quality. EPC Evidence Reports Technology Assessment: Number 84. Use of glycated hemoglobin and microalbuminuria in the monitoring of diabetes mellitus. http://www.ahrq.gov/clinic/epc/epcseries.htm (Accessed June 1, 2004).
88. British Medical Association. Quality and outcomes framework guidance: investing in general practice: the new general medical services contract: annex a: quality indicators: summary of points. http://www.bma.org.uk/ap.nsf/Content/NewGMSContract/$file/gpcontractannexa.pdf (Accessed June 1, 2004).
89. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan DM, Peterson CM, American Diabetes Association. Tests of glycemia in diabetes. Diabetes Care 2004;27(Suppl 1):S91–3.
90. UK Department of Health. National service framework for diabetes. http://www.publications.doh.gov.uk (Accessed June 1, 2004).
91. National Institute for Clinical Excellence. Type 1 diabetes: management of type 1 diabetes in adults in primary and secondary care. http://www.nice.org.uk/pdf/Type1diabetes_fullguideline_2ndconsultation.pdf (Accessed June 1, 2004).
92. Canadian Diabetes Association Clinical Practice Guidelines Committee. Clinical practice guidelines 2003 for the prevention and management of diabetes in Canada 2003. http://www.diabetes.ca/cpg2003/chapters.aspx (Accessed June 1, 2004).
93. Pope RM, Apps JM, Page MD, Allen K, Bodansky HJ. A novel device for the rapid in-clinic measurement of haemoglobin A1c. Diabet Med 1993;10:260–3.
94. John WG, Edwards R, Price CP. Laboratory evaluation of the DCA 2000 clinic HbA1c immunoassay analyser. Ann Clin Biochem 1994;31:367–70.
95. Carter JS, Houston CA, Gilliland SS, Perez GE, Owen CL, Pathak DR, et al. Rapid HbA1c testing in a community setting. Diabetes Care 1996;19:764–7.
96. Guerci B, Durain D, Leblanc H, Rouland JC, Passa P, Godeau T, et al. Multicentre evaluation of the DCA 2000 system for measuring glycated haemoglobin: DCA 2000 Study Group. Diabetes Metab 1997;23:195–201.
97. ECRI. ECRI reviews glycohemoglobin analyzers. http://www.ecri.org/Newsroom/Document_Detail.aspx?docid=20031219_97 (Accessed June 7, 2004).
98. Cagliero E, Levina E, Nathan D. Immediate feedback of HbA1c levels improves glycemic control in type 1 and insulin-treated type 2 diabetic patients. Diabetes Care 1999;22:1785–9.
99. Thaler LM, Ziemer DC, Gallina DL, Cook CB, Dunbar VG, Phillips LS, et al. Diabetes in urban African-Americans, XVII: availability of rapid HbA1c measurements enhances clinical decision-making. Diabetes Care 1999;22:1415–21.
100. Miller CD, Barnes CS, Phillips LS, Ziemer DC, Gallina DL, Cook CB, et al. Rapid A1c availability improves clinical decision-making in an urban primary care clinic Diabetes Care 2003;26:1158–63.
101. Grieve R, Beech R, Vincent J, Mazurkiewicz J. Near patient testing in diabetes clinics: appraising the costs and outcomes. Health Technol Assess 1999;3:1–74.
102. Ferenczi A, Reddy K, Lorber DL. Effect of immediate hemoglobin A1c results on treatment decisions in office practice. Endocr Pract 2001;7:85–8.
103. Holman RR, Jelfs R, Causier PM, Moore JC, Turner RC. Glycosylated haemoglobin measurement on blood samples taken

by patients: an additional aid to assessing diabetic control. Diabet Med 1987;4:71–3.
104. Raji A, Gomes H, Beard JO, MacDonald P, Conlin PR. A randomized trial comparing intensive and passive education in patients with diabetes mellitus. Arch Intern Med 2002;162:1301–4.
105. Levetan CS, Dawn KR, Robbins DC, Ratner RE. Impact of computer-generated personalized goals on HbA(1c). Diabetes Care 2002;25:2–8.
106. Diabetes Control and Complications Trial Research Group. Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial. JAMA 1996;276:1409–15.
107. Gray A, Raikou M, McGuire A, Fenn P, Stevens R, Cull C, et al. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trail (UKPDS 41). BMJ 2000;320:1373–8.
108. Wagner EH, Sandhu N, Newton KM, McCulloch DK, Ramsey SD, Grothaus LC. Effect of improved glycemic control on health care costs and utilization. JAMA 2001;285:182–9.
109. Carter AW, Borchardt N, Cooney M, Greene D. Dual-test monitoring of hyperglycemia using daily glucose and weekly fructosamine values. Diabetes Technol Ther 2001;3:399–403.
110. Edelman SV, Bell JM, Serrano RB, Kelemen D. Home testing of fructosamine improves glycemic control in patients with diabetes. Endocr Pract 2001;7:454–8.
111. Lindsey CC, Carter AW, Mangum S, Greene D, Richardson A, Brown S, et al. A prospective, randomized, multicentered controlled trial to compare the annual outcomes of patients with diabetes mellitus monitored with weekly fructosamine testing versus usual care: a 3-month interim analysis. Diabetes Technol Ther 2002;4:637–42.
112. Petitti DB, Contreras R, Dudl J. Randomized trial of fructosamine home monitoring in patients with diabetes. Eff Clin Pract 2001;4:18–23.
113. Laffel L. Sick-day management in type 1 diabetes. Endocrinol Metab Clin North Am 2000;29:707–23.
114. Byrne HA, Tieszen KL, Hollis S, Dornan TL, New JP. Evaluation of an electrochemical sensor for measuring blood ketones. Diabetes Care 2000;23:500–3.
115. Wallace TM, Meston NM, Gardner SG, Matthews DR. The hospital and home use of a 30-second hand-held blood ketone meter: guidelines for clinical practice. Diabet Med 2001;18:640–5.
116. Chiu RW, Ho CS, Tong SF, Ng KF, Lam CW. Evaluation of a new handheld biosensor for point-of-care testing of whole blood β-hydroxybutyrate concentration. Hong Kong Med J 2002;8:172–6.
117. Wiggam MI, O'Kane MJ, Harper R, Atkinson AB, Hadden DR, Trimble ER, et al. Treatment of diabetic ketoacidosis using normalization of blood 3-hydroxybutyrate concentration as the endpoint of emergency management: a randomized controlled study. Diabetes Care 1997;20:1347–52.
118. McBride MO, Smye M, Nesbitt GS, Hadden DR. Bedside blood ketone body monitoring. Diabet Med 1991;8:688–90.
119. Nadgir UM, Silver FL, MacGillivray MH. Unrecognized persistence of β-hydroxybutyrate in diabetic ketoacidosis. Endocr Res 2001;27:41–6.
120. Umpierrez GE, Watts NB, Phillips LS. Clinical utility of β-hydroxybutyrate determined by reflectance meter in the management of diabetic ketoacidosis. Diabetes Care 1995;18:137–8.
121. Vanelli M, Chiari G, Capuano C, Iovane B, Bernardini A, Giacalone T. Direct measurement of 3-β-hydroxy butyrate enhances the management of diabetic ketoacidosis in children and reduces time and costs of treatment. Diabetes Nutr Metab 2003;16:312–6.
122. Porter WH, Yao HH, Karounos DG. Laboratory and clinical evaluation of assays for β-hydroxybutyrate. Am J Clin Pathol 1997;107:353–8. Erratum in: Am J Clin Pathol 1997;108:116.
123. Ham MR, Okada P, White PC. Bedside ketone determination in diabetic children with hyperglycemia and ketosis in the acute care setting. Pediatr Diabetes 2004;5:39–43.
124. Guerci B, Benichou M, Floriot M, Bohme P, Fougnot S, Franck P, et al. Accuracy of an electrochemical sensor for measuring capillary blood ketones by fingerstick samples during metabolic deterioration after continuous subcutaneous insulin infusion interruption in type 1 diabetic patients. Diabetes Care 2003;26:1137–41.
125. Samuelsson U, Ludvigsson J. When should determination of ketonemia be recommended? Diabetes Technol Ther 2002;4: 645–50.
126. Harano Y, Kosugi K, Hyosu T, Suzuki M, Hidaka H, Kashiwagi A, et al. Ketone bodies as markers for type 1 (insulin-dependent) diabetes and their value in the monitoring of diabetic control. Diabetologia 1984;26:343–8.
127. Timmons JA, Myer P, Maturen A, Webster R, Schaller E, Leikin J, et al. Use of β-hydroxybutyric acid levels in the emergency department. Am J Ther 1998;5:159–63.
128. MacGillivray MH, Li PK, Lee JT, Mills BJ, Voorhess ML, Putnam TI, et al. Elevated plasma β-hydroxybutyrate concentrations without ketonuria in healthy insulin-dependent diabetic patients. J Clin Endocrinol Metab 1982;54:665–8.
129. Mercer DW, Losos FJ 3rd, Mason L, Kessler GF Jr. Monitoring therapy with insulin in ketoacidotic patients by quantifying 3-hydroxybutyrate with a commercial kit. Clin Chem 1986;32:224–5.
130. Fulop M, Murthy V, Michilli A, Nalamati J, Qian Q, Saitowitz A. Serum β-hydroxybutyrate measurement in patients with uncontrolled diabetes mellitus. Arch Intern Med 1999;159:381–4.
131. Suzuki M, Kosegawa I, Miura S, Negishi K, Itabashi A, Katayama S, et al. Blood ketone bodies in NIDDM: relationship with diabetic control and endogenous insulin secretion. Diabetes Res 1991;18:11–7.
132. American Association of Clinical Endocrinologists, American College of Endocrinology. Medical guidelines for the management of diabetes mellitus: the AACE system of intensive diabetes self-management: 2002 update. Endocr Pract 2002;8(Suppl 1):40–82.
133. American Diabetes Association. Tests of glycemia in diabetes. Diabetes Care 2004;27(Suppl 1):S91–3.
134. American Diabetes Association. Hyperglycemic crisis in diabetes. Diabetes Care 2004;27(Suppl 1):S94–101.
135. Dunger DB, Sperling MA, Acerini CL, Bohn DJ, Daneman D, Danne TP, et al., European Society for Paediatric Endocrinology, Lawson Wilkins Pediatric Endocrine Society. European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetic ketoacidosis in children and adolescents. Pediatrics 2004;113:e133–40.
136. White NH. Management of diabetic ketoacidosis. Rev Endocr Metab Disord 2003;4:343–53.
137. Casteels K, Mathieu C. Diabetic ketoacidosis. Rev Endocr Metab Disord 2003;4:159–66.
138. Delaney MF, Zisman A, Kettyle WM. Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. Endocrinol Metab Clin North Am 2000;29:683–705.
139. Rosenbloom AL, Hanas R. Diabetic ketoacidosis (DKA): treatment guidelines. Clin Pediatr (Phila) 1996;35:261–6.
140. Kitabchi AE, Wall BM. Diabetic ketoacidosis. Med Clin North Am 1995;79:9–37.

141. Fleckman AM. Diabetic ketoacidosis. Endocrinol Metab Clin North Am 1993;22:181–207.
142. Genuth S. Diabetes mellitus WEBMD ACP medicine. http://www.acpmedicine.com/ (Accessed May 2004).
143. Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, et al., American Diabetes Association. Nephropathy in diabetes. Diabetes Care 2004;27(Suppl 1):S79–83.
144. Pugh JA, Medina RA, Cornell JC, Basu S. NIDDM is the major cause of diabetic end-stage renal disease: more evidence from a tri-ethnic community. Diabetes 1995;44:1375–80.
145. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44(Suppl 2):S14–21.
146. Geiss LS, Herman WH, Smith PJ. Mortality in non-insulin dependent diabetes. In: Diabetes in America. 2nd ed. Washington, DC: NIH Publication No. 95-1468, 1995:233–55.
147. Ritz E, Tarng DC. Renal disease in type 2 diabetes. Nephrol Dial Transplant 2001;16(Suppl 5):11–8.
148. Mohanram A, Toto RD. Outcome studies in diabetic nephropathy. Semin Nephrol 2003;23:255–71.
149. Remuzzi G, Schieppati A, Ruggenenti P. Clinical practice: nephropathy in patients with type 2 diabetes. N Engl J Med 2002;346:1145–51.
150. Mogensen CE. Microalbuminuria and hypertension with focus on type 1 and type 2 diabetes. J Intern Med 2003;254:45–66.
151. Gugliucci A. Glycation as the glucose link to diabetic complications. J Am Osteopath Assoc 2000;100:621–34.
152. Fox JG, Quin JD, Paterson KR, O'Reilly DS, Smith MP, Boulton-Jones JM. Glomerular charge selectivity in type 1 (insulin-dependent) diabetes mellitus. Diabet Med 1995;12:387–91.
153. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1–266.
154. Hemmelgarn BR, Zarnke KB, Campbell NR, Feldman RD, McKay DW, McAlister FA, et al., Canadian Hypertension Education Program, Evidence-Based Recommendations Task Force. The 2004 Canadian Hypertension Education Program recommendations for the management of hypertension, part I: blood pressure measurement, diagnosis and assessment of risk. Can J Cardiol 2004;20:31–40.
155. Newman DJ, Pugia MJ, Lott JA, Wallace JF, Hiar AM. Urinary protein and albumin excretion corrected by creatinine and specific gravity. Clin Chim Acta 2000;294:139–55.
156. Ruggenenti P, Gaspari F, Perna A, Remuzzi G. Cross sectional longitudinal study of spot morning urine protein:creatinine ratio, 24 hour urine protein excretion rate, glomerular filtration rate, and end stage renal failure in chronic renal disease in patients without diabetes. BMJ 1998;316:504–9.
157. Claudi T, Cooper JG. Comparison of urinary albumin excretion rate in overnight urine and albumin creatinine ratio in spot urine in diabetic patients in general practice. Scand J Prim Health Care 2001;19:247–8.
158. Ginsberg JM, Chang BS, Matarese RA, Garella S. Use of single voided urine samples to estimate quantitative proteinuria. N Engl J Med 1983;309:1543–6.
159. Parsons MP, Newman DJ, Newall RG, Price CP. Validation of a point-of-care assay for the urinary albumin:creatinine ratio. Clin Chem 1999;45:414–7.
160. Shephard MD, Barratt LJ, Simpson-Lyttle W. Is the Bayer DCA 2000 acceptable as a screening instrument for the early detection of renal disease? Ann Clin Biochem 1999;36:393–4.
161. Ng WY, Lui KF, Thai AC. Evaluation of a rapid screening test for microalbuminuria with a spot measurement of urine albumin-creatinine ratio. Ann Acad Med Singapore 2000;29:62–5.
162. Collins AC, Vincent J, Newall RG, Mitchell KM, Viberti GC. An aid to the early detection and management of diabetic nephropathy: assessment of a new point of care microalbuminuria system in the diabetic clinic. Diabet Med 2001;18:928–32.
163. Kutter D, Thoma J, Kremer A, Hansen S, Carl R. Screening for oligoalbuminuria by means of Micral-Test II: a new immunological test strip. Eur J Clin Chem Clin Biochem 1995;33:243–5.
164. Pugia MJ, Lott JA, Clark LW, Parker DR, Wallace JF, Willis TW. Comparison of urine dipsticks with quantitative methods for microalbuminuria. Eur J Clin Chem Clin Biochem 1997;35:693–700.
165. Pugia MJ, Lott JA, Luke KE, Shihabi ZK, Wians FH Jr, Phillips L. Comparison of instrument-read dipsticks for albumin and creatinine in urine with visual results and quantitative methods. J Clin Lab Anal 1998;12:280–4.
166. Croal BL, Mutch WJ, Clark BM, Dickie A, Church J, Noble D, et al. The clinical application of a urine albumin:creatinine ratio point-of-care device. Clin Chim Acta 2001;307:15–21.
167. Colwell M, Halsey JF. High incidence of false-positive albuminuria results with the Micro-Bumintest. Clin Chem 1989;35:1252.
168. Gossain VV, Gunaga KP, Carella MJ, Edminster RR, Bowman KA, Rovner DR. Utility of Micral test strips in screening for microalbuminuria. Arch Pathol Lab Med 1996;120:1015–8.
169. Berry J. Microalbuminuria testing in diabetes: is a dipstick as effective as laboratory tests? Br J Community Nurs 2003;8:267–73.
170. Soonthornpun S, Thammakumpee N, Thamprasit A, Rattarasarn C, Leelawattana R, Setasuban W. The utility of conventional dipsticks for urinary protein for screening of microalbuminuria in diabetic patients. J Med Assoc Thai 2000;83:797–803.
171. de Grauw WJ, van de Lisdonk EH, van de Hoogen HJ, van Gerwen WH, van den Bosch WJ, Willems JL, et al. Screening for microalbuminuria in type 2 diabetic patients: the evaluation of a dipstick test in general practice. Diabet Med 1995;12:657–63.
172. Leong SO, Lui KF, Ng WY, Thai AC. The use of semi-quantitative urine test-strip (Micral Test) for microalbuminuria screening in patients with diabetes mellitus. Singapore Med J 1998;39:101–3.
173. Davidson MB, Bazargan M, Bakris G, Peters Harmel A, Campese V, Basta E. ImmunoDip: an improved screening method for microalbuminuria. Am J Nephrol 2004;24:284–8.
174. Parsons M, Newman DJ, Pugia M, Newall RG, Price CP. Performance of a reagent strip device for quantitation of the urine albumin: creatinine ratio in a point of care setting. Clin Nephrol 1999;51:220–7.
175. Pugia MJ, Lott JA, Kajima J, Saambe T, Sasaki M, Kuromoto K, et al. Screening school children for albuminuria, proteinuria and occult blood with dipsticks. Clin Chem Lab Med 1999;37:149–57.
176. Keane WF, Eknoyan G. Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. Am J Kidney Dis 1999;33:1004–10.
177. Harwell TS, Nelson RG, Little RR, McDowall JM, Helgerson SD, Gohdes D. Testing for microalbuminuria in 2002: barriers to implementing current guidelines. Am J Kidney Dis 2003;42:245–8.
178. Hostetter TH. Detecting early chronic kidney disease: are clinical laboratories a problem? Am J Kidney Dis 2003;42:392–4.
179. Webb DJ, Newman DJ, Chaturvedi N, Fuller JH. The use of the Micral-Test strip to identify the presence of microalbuminuria in people with insulin dependent diabetes mellitus (IDDM) participating in the EUCLID study. Diabetes Res Clin Pract 1996; 31:93–102.

180. Jensen JE, Nielsen SH, Foged L, Holmegaard SN, Magid E. The MICRAL test for diabetic microalbuminuria: predictive values as a function of prevalence. Scand J Clin Lab Invest 1996;56:117–22.
181. Mogensen CE, Viberti GC, Peheim E, Kutter D, Hasslacher C, Hofmann W, et al. Multicenter evaluation of the Micral-Test II test strip, an immunologic rapid test for the detection of microalbuminuria. Diabetes Care 1997;20:1642–6.
182. Minetti EE, Cozzi MG, Granata S, Guidi E. Accuracy of the urinary albumin titrator stick "Micral-Test" in kidney-disease patients. Nephrol Dial Transplant 1997;12:78–80.
183. Piehlmeier W, Renner R, Schramm W, Kimmerling T, Garbe S, Proetzsch R, et al. Screening of diabetic patients for microalbuminuria in primary care: the PROSIT-Project: proteinuria screening and intervention. Exp Clin Endocrinol Diabetes 1999;107:244–51.
184. Fernandez Fernandez I, Paez Pinto JM, Hermosin Bono T, Vazquez Garijo P, Ortiz Camunez MA, Tarilonte Delgado MA. Rapid screening test evaluation for microalbuminuria in diabetes mellitus. Acta Diabetol 1998;35:199–202.
185. Lane JT. Microalbuminuria as a marker of cardiovascular and renal risk in type 2 diabetes mellitus: a temporal perspective. Am J Physiol Renal Physiol 2004;286:F442–50.
186. Tobe SW, McFarlane PA, Naimark DM. Microalbuminuria in diabetes mellitus. CMAJ 2002;167:499–503.
187. Mohanram A, Toto RD. Outcome studies in diabetic nephropathy. Semin Nephrol 2003;23:255–71.
188. Scheid DC, McCarthy LH, Lawler FH, Hamm RM, Reilly KE. Screening for microalbuminuria to prevent nephropathy in patients with diabetes: a systematic review of the evidence. J Fam Pract 2001;50:661–8.
189. American Diabetes Association. Nephropathy in diabetes. Diabetes Care 2004;27(Suppl 1):S79–83.
190. Qin QP, Peltola O, Pettersson K. Time-resolved fluorescence resonance energy transfer assay for point-of-care testing of urinary albumin. Clin Chem 2003;49:1105–13.
191. Lurbe E, Redon J, Kesani A, Pascual JM, Tacons J, Alvarez V, et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. N Engl J Med 2002;347:797–805.
192. Comper WD, Osicka TM, Jerums G. High prevalence of immuno-unreactive intact albumin in urine of diabetic patients. Am J Kidney Dis 2003;41:336–42.
193. Comper WD, Osicka TM, Clark M, MacIsaac RJ, Jerums G. Earlier detection of microalbuminuria in diabetic patients using a new urinary albumin assay. Kidney Int 2004;65:1850–1855.
194. Comper WD, Jerums G, Osicka TM. Differences in urinary albumin detected by four immunoassays and high-performance liquid chromatography. Clin Biochem 2004;37:105–11.
195. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289:3273–7.
196. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med 2003;348:2285–93.

PUBLIC COMMENTS

No public comments were received on the guidelines.

Chapter **7**

Drugs and Ethanol

Ian D. Watson, Roger Bertholf, Catherine Hammett-Stabler, Brenda Nicholes, Brian Smith, Steve George, Shirley Welch, Alain Verstraete, and Bruce Goldberger**

INTRODUCTION

Detecting substance abuse using point-of-care testing (POCT) is a multimillion dollar business. Generally, such testing is performed using urine as the sample and targets the more commonly abused substances. The purported flexibility and ease of use make these devices attractive for use in a variety of settings and by an equally varied range of users. These guidelines will focus on the use of POCT for drugs of abuse (DOA) in medical and nonmedical settings. Issues of training, quality control (QC), economics, and accuracy will be addressed, as will limitations. As will be emphasized throughout this chapter, these devices are designed to screen for the presence of designated drugs or groups of drugs. None are intended to serve as confirmation tests. The document will not address the broader issues or questions of urine drug screening; however, those interested may find some of the issues associated with such testing in the medical setting discussed in the National Academy of Clinical Biochemistry Emergency Toxicology Laboratory Medicine Practice Guidelines.

After the initial questions were agreed upon, we found it necessary to perform a broad literature search to identify a sufficient number of papers for review. Pairs of members assessed the papers on the basis of the abstract to identify 100 manuscripts for full review. Additional papers referenced in the reviewed papers were identified and read. All reviewed papers were rated for relevance to particular questions. Members also consulted their personal manuscript collections. The search strategy used is presented in Literature Search 45 (Appendix B).

For many settings, the availability of POCT devices designed to detect abused drugs in urine is an attractive alternative to collection, transport, and subsequent laboratory analysis. POCT devices are available in a range of formats from dipsticks to cup devices, cards, or plastic cassettes. The amount of sample needed for testing ranges from a few drops of urine to ~30 mL. Currently, all devices are immunoassay based and, as such, designed to screen for the presence of defined DOA. Devices are available for the detection of a single drug or drug class, as well as for the detection of groups of drugs, i.e., cannabinoids and cocaine and amphetamines. As with laboratory-based methods, most are designed to detect drug metabolites instead of the parent drug. Following practices stemming from workplace drug testing, a positive result is obtained when the drug(s) or metabolite of interest is present at or above a designated concentration, i.e., the cutoff.

Unlike the automated immunoassay-based laboratory methods, most of the steps for POCT require operator intervention: these include sample application (and, if required, subsequent transfer of the sample to another portion of the device), timing of the reaction, reading/interpreting the visual endpoint, and recording/documenting the result. Turnaround times from initial sample application to a result are 15 min or less. The visual endpoint derived is dependent upon the technological approach and will be discussed shortly. Currently, there is only 1 commercially available system that provides a semiautomated assay and a printable report or record of the result(s). For other devices, the operator is responsible for all manipulations of the sample, reagent application, and timing, as well as interpretation and recording of the results, including quality-control indicators.

Although the devices can be classified as those utilizing agglutination reactions, chromogenic antibodies, or fluorgenic or chromogenic drug-conjugates, it is more common to see the devices separated according to the visual indicator generated when drug is present at or above the designated cutoff. Unlike other qualitative POCT applications, most POCT devices for DOA give a *negative* visual sign when the drug of interest is at or above the defined threshold. In other words, the absence of a line or color means the test result is positive, whereas the development of a line or color indicates the drug is below the threshold. At this time, there is 1 device that indicates the presence of the drug of interest with the appearance of a line.

Sample Preparation and Testing

The simplest to use devices combine the collection and testing device; but for most devices, the operator must perform multiple steps in handling and transferring the sample. Freshly collected urine with no evidence of turbidity and sediment appears optimal

*Alain Verstraete, M.D., Ph.D., Ghent University, Gent, Belgium, and Bruce Goldberger, Ph.D., FACB, University of Florida, Gainesville, FL, USA, served as consultants on this chapter.

for these devices. Samples containing sediment or that are visibly turbid are poorly absorbed into the testing area *(1, 2).* For such samples, precentrifugation may be necessary for proper sample application *(1, 2).* In 1 study, poor absorption was shown to contribute to the occurrence of false-negative results *(1).*

Generally, the literature on POCT for drugs of abuse is dominated by method validations or evaluations *(1, 3–18).* In these evaluations, urine samples were tested using the POCT device(s) and the result(s) compared to those results obtained using an instrument-based immunoassay. For many of the studies, the practice of prescreening samples to ensure the inclusion of a range of drugs and drug levels automatically induces a selection bias. The outcomes on which the comparisons were made included concordance between devices or with the comparator immunoassay methods, sensitivity, specificity, efficiency, and ease of operation. These studies were usually designed to include confirmation of the presence of the drug of interest using gas chromatography/mass spectrometry or high-performance liquid chromatography. However, in the majority of studies, only discordant samples were evaluated in this manner. Very few studies confirmed the absence of drug or did so only randomly. Generally, testing was performed using trained laboratory personnel under laboratory settings, with only a few studies using nonlaboratory analysts in nonlaboratory settings.

No POCT device yielded 100% concordance with the comparator method. Disagreement between methods was highest for samples near the designated thresholds. In some multidevice evaluations, different devices used different thresholds or cutoffs, making comparisons difficult. There was limited discussion or recognition of variability in antibody specificity. Antibody specificity appeared to have the greatest impact when amphetamines, opiates, and benzodiazepines were tested for; i.e., classes containing multiple drugs or compounds of interest. For the amphetamine and opiate classes, confirmation was usually based upon National Institute of Drug Abuse (NIDA) (Substance Abuse and Mental Health Services Administration [SAMHSA] criteria using specified target analytes and concentrations with no evaluation of other amphetamine compounds (ephedra, methylenedioxymethamphetamine [MDMA], etc.) or opioids (hydrocodone, oxycodone, etc.). Disagreement also depended upon the use of synthetic samples as opposed to human-derived samples containing metabolites or related, cross-reacting compounds. We found 5 prospective studies conducted in nonlaboratory settings. Three were conducted in medical settings and included evaluations of patients presenting to a pain clinic, *(10)* an obstetrics service, *(19)* and an emergency department (ED) *(20).* Two were conducted in law enforcement settings evaluating drivers suspected of intoxication and driving under the influence *(5, 21).*

Are there significant differences between POCT devices?

Guideline 83. *Once the potential need for POCT is established, a careful evaluation should be conducted by the staff in the environment in which the devices are to be used and on the relevant population.*

Strength/consensus of recommendation: A

Level of evidence: II

The majority of literature concerning POCT for drugs and ethanol is simple comparisons between POCT and laboratory methods. Differences in analytical performance, ease of use, accuracy, and reproducibility abound *(4–7, 9, 10, 15, 16, 18, 22–30),* with the more recently developed devices generally comparing more favorably with laboratory-based methods.

When a site is considering implementing such testing, it is important that the evaluations be conducted using the staff who will perform the testing and under the conditions in which the testing will be performed *(10);* this advice is often ignored in evaluations so that laboratory staff perform the evaluations, but nursing or others perform the routine testing.

What analytical accuracy issues affect the use of POCT devices?

Guideline 84. *Users of POCT devices should understand any limitations of the devices. This should include the statistical and analytical sensitivity, specificity, and nomenclature of the devices to facilitate their appropriate use.*

Strength/consensus of recommendation: A

Level of evidence: I

Initial screening techniques, even in a controlled laboratory environment, may give rise to both false-positive results and false-negative results *(31).* These findings have been reproduced in the evaluation studies of several POCT devices for urine *(6, 16, 22, 32)* and saliva *(33).*

The efficiency of drug detection by POCT devices has been shown to vary according to the drug being monitored *(32)* or the specific device being used *(6, 16, 22).* It has been concluded that POCT device sensitivity may be the most important characteristic governing their use *(22),* but discrepancies exist between claims and performance of POCT devices *(16),* and their effectiveness in detecting illicit drug use has been questioned *(6).*

What knowledge of cross-reactivity of POCT devices is required for their use?

Guideline 85. *Users of POCT devices need to be aware of any known interferences from drugs or metabolites that could affect results interpretation.*

Strength/consensus of recommendation: A

Level of evidence: I

POCT devices for drugs are based on immunoassay technologies, and it is vital that users understand their strengths, weaknesses, and limitations to facilitate accurate results interpretation *(34).* This is especially true in the case of false-positive results arising from cross-reactivity with foods, over-the-counter preparations, commonly prescribed drugs,

and/or their metabolites that may also be present in the specimen being screened *(35)*. If such limitations are not recognized, then the potential for inaccurate or inappropriate interpretation increases significantly. This is exacerbated when misleading nomenclature is used by manufacturers of POCT devices, causing false-positive reports *(6)*.

What are the chief quality issues associated with POCT?

Guideline 86. *Purchasers of POCT devices should ensure that users are correctly trained in their use, application, and interpretation. This training should include quality issues and recognition of any device limitations.*

Strength/consensus of recommendation: A

Level of evidence: I

The ever-increasing demand for more rapid results availability in certain clinical, employment, and urgent medical situations has resulted in the increased use of POCT devices *(36)*. There are several important quality aspects surrounding the use of POCT technology that need to be taken into account. These include:

1. The accuracy (in terms of analytical sensitivity and specificity) of the POCT technique
2. The cross-reactivity of POCT assays with drugs and metabolites not under investigation
3. The impact of chemical interference or adulteration on POCT devices
4. The issues of quality assurance and QC
5. The appropriate interpretation of POCT technique results
6. The impact of physiological variables
7. Use of acceptable confirmatory methods

What knowledge of sample adulteration is required for the use of POCT devices?

Guideline 87. *Users of POCT devices need to be aware of any known interferences from chemicals and other methods of adulteration/manipulation that could affect results interpretation. Procedures need to be adopted within a protocol framework to ensure specimens are tamper free. In critical situations, the type of POCT chosen should enable the tester to detect manipulation by the donor.*

Strength/consensus of recommendation: A

Level of evidence: II

Staff using POCT devices not only need to be aware of the potential problems raised by cross-reactivity to drugs and metabolites, but also that chemical adulterants can render the test devices inaccurate *(37–41)*. A recent study demonstrated the impact of potential interferents in breath that could give rise to false-positive alcohol results on the evidential infrared-based breath testing device, the Intoxilyzer-5000 (CMI, Inc., Owensboro, KY, USA) *(37)*.

With regard to urine screening, the use of nitrites has been demonstrated to have little or no marked impact on the results generated by POCT devices, but could render the gas chromatograph-mass spectrometer (GC-MS) assay used to confirm the screening results inaccurate, leading to the assumption that the POCT device had produced false-positive screening results. This is especially true for cannabinoids *(39, 40)*. The adulterant "Stealth" is intended to prevent a positive drug-test result; it caused negative results in samples spiked with the carboxylic acid metabolite of cannabis, lysergic acid diethylamide (LSD), and morphine at between 125% and 150% of analytical cutoff *(38)*.

A survey of 50 urine specimens submitted for workplace drug testing under chain-of-custody conditions found that 2 specimens contained pyridinium chlorochromate, "Urine Luck," designed to invalidate urine drug-screening assays *(41)*. Other manipulations include dilution by drinking excess water, sample substitution, and claims of legally obtainable substances that would give positive results e.g., the poppy seed defense for positive opiates. Devices such as TesTcup (Roche Diagnostics, Indianapolis, IN, USA) aid unadulterated collection by including a contact thermometer on the cup to verify that the sample is close to body temperature at the time of collection *(19)*.

Are there significant differences between POCT and central laboratory testing (CLT)?

Guideline 88. *POCT for DOA or ethanol may provide adequate information for clinical intervention. Where a definitive penal or legal action is to be taken, laboratory confirmation is mandatory.*

Strength/consensus of recommendation: A

Level of evidence: I

Are there significant differences between POCT and CLT?

Guideline 89. *POCT screening can be effective, provided quality and data recording issues are addressed. The cost/economic impact needs consideration before introduction. Recording of data is vital, and a legally defensible approach is advised.*

Strength/consensus of recommendation: A

Level of evidence: III

Are there significant differences between POCT and CLT?

Guideline 90. *There is insufficient evidence for or against specimen stability as a justification for testing location.*

Strength/consensus of recommendation: I

Level of evidence: III

In answering this question, it must be recognized that no POCT device is designed to serve a confirmatory role. These devices are designed to be used in a screening role and can only be compared to similar immunoassay-based systems in the central laboratory. When comparisons are based on methods with similar analytical performance in terms of specificity and sensitivity, there is little difference.

The main difference between CLT and POCT is the reduction of time involved between sample collection and testing completion. However, this is not an acceptable justification for POCT if the quality of results is compromised *(10, 24).* Unfortunately, there is evidence that in the nonlaboratory settings, the performance of QC and quality assurance practices falls short of central laboratory standards *(24, 25)*. Data recording from typical POCT devices must usually be performed manually and is poor *(10)* in contrast to CLT, where data are typically captured on a laboratory computer system. Devices are reaching the marketplace that are read by meter and may be interfaceable to an information system.

An additional consideration is cost. POCT devices have a fixed unit cost, which often exceeds those of laboratory-based methods. Thus, the economic/ clinical/penal/liability relevance of POCT should be carefully established and frequently reviewed. There is surprisingly little evidence on the economics of POCT for drugs and ethanol, although cost and economic issues are central to any decision on POCT use.

Although early studies suggested that POCT could supplant laboratory testing, many authors and manufacturers advise performing GC-MS confirmation before taking definitive or punitive actions (e.g., child protection issues) *(27).*

Is there an evidence base to confirm that POCT devices perform adequately at detection limits/cutoffs?

Guideline 91. *The cutoff(s) should be considered in the selection of a device because these will affect the number of samples requiring confirmation. The statistical likelihood of obtaining a negative result for a sample containing drug near the cutoff should be defined by the manufacturer and presented so that the user who is not a laboratorian can understand the implication of false-negative results. Validation studies during selection and implementation should include testing of the defined cutoff.*

Strength/consensus of recommendation: A

Level of evidence: III

Unlike for most other analytical tests, the cutoffs used in DOA testing vary. Some are based upon the analytical performance of the method, but others are determined by governmental or regulatory agencies. Some POCT devices were found to be comparable in terms of the performance near the stated cutoffs *(5),* whereas others did not perform adequately *(4, 16, 20, 24)*. Another issue was the lack of data to support continued performance over several lots of devices.

What is the impact of quality assurance and QC on POCT screening?

Guideline 92. *All users of POCT devices must use QC material and participate in external quality assurance (EQA) schemes.*

Strength/consensus of recommendation: A

Level of evidence: I

The error rates (false-positive and -negative results) associated with all immunoassay techniques, including POCT devices, results in the recommendation of participation in EQA programs *(31),* regardless of the setting and requirements. Because testing for DOA in urine may have medical and legal implications, false-positive results must be identified. Continuous participation in EQA programs enables this process *(42)*. It is only by demonstrating continued accuracy and competence through such programs that the results obtained from the analytical testing system can withstand legal scrutiny *(43).*

There have been several reports from EQA scheme organizers illustrating the level of false-positive and false-negative results obtained from the testing of submitted urine specimens *(44–47).* These audit reports have commented on the improvement in accuracy with time and the fact that some of the false-positive results could have a marked impact on the diagnosis and treatment of individuals.

In addition to EQA participation, there will also be the need for local QC of POCT testing devices to ensure they are fit for purpose and produce accurate results in the hands of the individuals using them. This must occur before applying them to the analysis of urine from patients or employees. However, this may prove difficult when the POCT site is remote from any source of QC material or advice on its interpretation *(36).* This aspect of assay validation typically requires local laboratory involvement and control.

Guideline 93. *The decision to use POCT should be a formal corporate decision after a formal evaluation process of the options to ensure fitness for purpose. Only authorized, trained, competency-assessed staff should be allowed to perform POCT within an agreed governance arrangement.*

Strength/consensus of recommendation: A

Level of evidence: III

Although often not thought of, generating an analytically appropriate test result becomes the responsibility of the POCT device user. This takes the responsibility away from the laboratory and places it firmly on the shoulders of the POCT user. It can therefore be seen that the single most important quality issue surrounding POCT devices is the initial and ongoing training of the individual(s) performing the testing to maintain

competency. Therefore, there is both a corporate and a personal liability arising from the use of POCT. Corporate procedures for governance ensuring initial and continuing application and training and fitness for purpose must be established and be clear.

Are there specific quality issues around interpretation of results obtained from POCT devices?

Guideline 94. *Procedures must be agreed on and in place to ensure only those recognized by the organization as being competent to interpret POCT results do so. The consequences to the patient/client, analyst, and corporation must be recognized.*

Strength/consensus of recommendation: A

Level of evidence: III

Formal studies on this issue are lacking. However, users of devices have to be aware of specificity issues, and they cannot say the degree of positivity or negativity, nor can one determine if someone has reused a drug; this is particularly true for substances with slowly eliminated metabolites. Physiological variation in the concentration of urine or pH may result in a positive result after a negative without reuse. Inappropriate interpretation may carry penalties just as much as an incorrectly performed analysis.

Are there specific quality issues for POCT vs CLT?

Guideline 95. *All analyses, whether POCT or CLT, must be subject to QC and quality assurance. This should encompass a quality system that includes effective training, recordkeeping, and review.*

Strength/consensus of recommendation: A

Level of evidence: II

Although anecdotal evidence of poor POCT practice and result utilization abounds, there is little systematic evidence. Poor training of POCT testers is a common theme *(5, 18),* and though there may be significant differences in skill levels in different countries *(48)*, some users find the analytical part of POCT acceptable but dislike the quality and recordkeeping aspects *(10)*. CLT staff are often highly trained, and therefore a more robust and consistent performance can be anticipated.

There are no systematic evidence-based studies on the quality of POCT for DOA; regrettably, few users of POCT devices participate in external quality assessment schemes, so long-term assessment of performance "in use" is not available.

USE OF POCT FOR DOA IN THE CLINICAL SETTING

What is the effect on outcome of rapid drug screening in EDs?

Guideline 96. *Although immediacy of POC drug testing results is hypothesized to be useful in an ED, this has not been systematically documented in outcome studies. Therefore, no recommendation can be made at this time.*

Strength/consensus of recommendation: C

Level of evidence: I

The value of drug testing in EDs is controversial and has been addressed previously in a National Academy of Clinical Biochemistry Emergency Toxicology Laboratory Medicine Practice Guidelines, available at http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/EmergencyTox/. Although several studies assumed or hypothesized that the availability of a more rapid result would improve patient care by reducing the time for clinical decision and implementation of therapy, no study actually tested the hypothesis using any measurable outcome *(20, 27).* It should be noted in this context that as clinical intervention is the goal, confirmation by GC-MS is not the issue it is in other contexts.

In a pediatric ED, cocaine detection showed higher concentrations in older children (>13 years) and lower concentrations in younger children (<7 years), probably because of passive exposure. Although advocating the use of POCT for better disposition from the ED, and even referral to Child Protective Services, none of these outcomes were tested or observed *(20).* Other similar studies make assumptions about the impact of drug abuse but do not test these hypotheses against outcome *(27).*

Guideline 97. *There is little cumulated outcome literature to support POCT for DOA in outpatient clinic and outreach clinical settings. Although there are situations where utilization of POCT may enable faster decision making regarding patient disposition, as in an addiction clinic, there is little evidence to support this, and therefore introduction and use should be circumspect.*

Strength/consensus of recommendation: I

Level of evidence: III

Guideline 98. *There are no outcome studies that support the use of POCT for DOA in obstetric or pain clinics. Although testing for DOA in these settings is often clinically indicated, there is no evidence of added benefit from performing the test at the point of care.*

Strength/consensus of recommendation: I

Level of evidence: III

Guideline 99. *In clinical settings, the user must be aware of the possibility of sample adulteration/manipulation.*

Strength/consensus of recommendation: I

Level of evidence: III

Is POC Drug Testing Useful in Maternal-Fetal Medicine?

Issues in obstetrics include the impact of abused substances on the physical development of the fetus, teratogenic effects, and the risk to fetal integrity and/or physical risks to the mother. In the latter, identification of drug-using mothers enables referral for treatment and an opportunity to intervene to improve outcome for mother and fetus. Subsequently, a successful live birth may require detoxification of the baby.

Is POC Drug Testing Useful in Pain Management?

In a pain-management clinic, testing is required to both ensure compliance and to identify abuse of nonprescribed drugs. Drugs of interest in these clinical setting include benzodiazepines and opioids such as oxycodone, methadone, hydrocodone, hydromorphone, and morphine. There were no studies identified that addressed the use of POCT in this setting.

Is POC Drug Testing Useful in Detoxification Clinics?

Testing in such clinics has a 2-fold goal: to determine what substances an individual is using (this can be a check on their veracity) to confirm the completeness of abstinence from drug abuse and to confirm compliance with prescribed therapy. Diversion of prescribed medications such as methadone or oxycodone from the individual prescribed the medication to another is a public health problem. Testing to detect diversion is difficult using screening techniques. Confirmatory testing is often necessary to attain the specificity and sensitivity needed.

There is insufficient evidence upon which to base a recommendation for or against the use of POCT devices for detecting DOA in the above outpatient clinical settings. Although much of the literature describing method evaluations makes assumptions about the benefits of using POCT devices, there is no evidence supporting a difference in pregnancy outcome or referral for treatment (in obstetric clinics) or compliance in pain management clinics and addiction medicine/drug treatment programs *(6, 49).*

We identified 1 study comparing POCT for DOA in an inpatient drug treatment detoxification unit *(10).* Concordance for results generated by nursing staff with those determined in laboratory was 82% for cocaine and tetrahydrocannabinol (THC). The nursing staff considered the QC and recordkeeping to be too time consuming and had the opinion that on-site testing in this environment had no advantage in improved patient care.

One study addressed alcohol testing in a short-stay (6–8 h) detoxification unit, comparing tests using blood, breath, urine, and saliva. The investigators reported that some highly intoxicated subjects had difficulty producing a sufficient saliva specimen. Quantitative saliva ethanol concentrations did not correlate well with blood alcohol, especially at high concentrations ($r = 0.75$). Results of alcohol testing did not alter patient management *(50).*

One issue not addressed was that of adulteration, a well-recognized phenomenon in some settings. Because POCT devices are immunoassay based, they are susceptible to many of the same interferences as laboratory-based immunoassays, and false negatives are possible.

What is the evidence from the literature on the need for confirmation from different population groups?

Guideline 100. *Clear guidelines should be developed regarding the need to confirm positive test results using a more sensitive and specific laboratory method, particularly for situations where definitive punitive action will be taken based on the result. In clinical settings where treatment may be based upon unconfirmed results, staff using the data should be educated with respect to the limitations of the testing.*

Strength/consensus of recommendation: A

Level of evidence: I

In clinical practice, the identification of the ingested drug by class may be sufficient to enable appropriate intervention. Using POCT theoretically allows more rapid actions. In some situations, including those in which the patient/client acknowledges use, action or response may be acceptable without confirmation. However, where there is likelihood of a legal/penal action—e.g., referral to child protection agencies, loss of employment, imprisonment—then confirmation is strongly recommended, as is typically identified in the POCT device manufacturers' literature. As discussed previously, these screening devices suffer from the same limitations as the central laboratory immunoassay-based screening methods: antibody specificity is not 100%. It is surprising that some authors do not understand the limitations of POCT devices and the potential legal pitfalls *(51),* though some do *(2, 6, 7, 9, 12, 16, 25, 52).*

URINE VERSUS ALTERNATIVE MATRICES

Does the matrix (blood/serum/plasma, saliva, sweat, urine, meconium) affect acceptability for POCT for drugs, and what is the evidence supporting this recommendation?

Guideline 101. *Urine is the best established matrix for POCT. Cutoff levels, interferences, and interactions have been established and studied more in urine than in testing with other matrices.*

Strength/consensus of recommendation: A

Level of evidence: I

Guideline 102. *If alternate matrices are to be used for POCT, the antibodies and cutoffs must be optimized to detect the parent drug or metabolite most abundant in that matrix. Evidence of accuracy and precision must be documented. Sample sites and collection methods for oral fluid, sweat, and breath must be standardized. Sweat sample contamination issues must be resolved before sweat can be considered an acceptable testing matrix.*

Strength/consensus of recommendation: I

Level of evidence: II

Guideline 103. *Reports using oral fluid for drug screening by POCT demonstrate unsatisfactory results for certain drugs, especially for opiates, THC, and benzodiazepine detection. There is a lack of evidence regarding limitations of oral fluid testing.*

Strength/consensus of recommendation: C

Level of evidence: II

Until recently, screening to detect the use of DOA has been built around the use of urine as the sample for testing. In some settings, adulteration/manipulation of the sample by users to circumvent positive results *(13, 38, 39, 41, 53)* is a major issue. A number of issues, such as invasion of privacy, many methods of manipulation, and cross-reactions, have led to interest in alternative matrices.

Urine

POCT, or near patient testing, for DOA has evolved over the past 30 years, with urine as the best established sample matrix for devices now in use. Urine DAU cassette devices are available with sensitivities and specificities similar to enzyme immunoassays used in central laboratory urine screening. The cutoffs used in POCT devices can be configured to match those used by the central laboratory and to reflect the needs of the testing site. As previously discussed, the antibodies used in the devices target the same drug and/or metabolites detected with urine laboratory screens. The labeling of these devices with respect to what is measured or detected is perhaps even more important because many users may not fully understand that most of these tests are designed to detect classes or groups of drugs. The POCT devices sometimes are inappropriately labeled as detecting a specific drug when actually detecting a class of drugs. This mislabeling may lead to interpretational false positives or negatives when testing personnel do not understand the specificity. For example, a test claiming to detect morphine, e.g., RapiTest MOP (One Step Morphine Test, Morwell Diagnostics, Zurich, Switzerland), may actually detect other opiates, so that a result is read as positive for morphine when codeine is present *(9)*.

There have been reports showing differences in interpretation of POCT results when experienced laboratory personnel read the results vs when the interpretation was performed by nonlaboratory personnel *(8)* Certain devices have been reported as more difficult to read, with an increase in false-positive results shown by confirmatory methods *(24, 54)*. As with laboratory screening results, published results from POCT devices show that screening results should be followed up by confirmation testing if the result could be used for medicolegal processes *(16, 52)*.

Oral Fluid (Saliva)

Saliva, or oral fluid, as an alternate POCT matrix has reported advantages and disadvantages. Oral fluid collection is regarded as easy and noninvasive, and the specimen is less likely to be adulterated. Justification for use of oral fluid because of ease of collection may be disputed by the fact that oral fluid is potentially more infectious than urine. Immunoassays developed for urine are not directed to the optimum parent drug or metabolite in oral fluid, and alternative cutoffs have been advised by SAMHSA, with the proposed cutoffs being considerably lower than in urine, presenting a significant analytical challenge. In addition, for many of the drugs of interest, it is the parent drug that is usually detected, with the compound typically present at higher concentration levels relative to its or its metabolite's (metabolites') concentration in urine. This means that most devices designed for detecting the urinary metabolites will not be useful for oral fluid testing. For roadside testing in law enforcement, an advantage of oral fluid is that drug detection relates more directly to current subject impairment than does drug presence in urine, with its longer detection periods for metabolites.

Collection procedures and devices for collection are not standardized, and drug concentration can differ, depending on collection method *(55)*. Stimulation of saliva flow has been used. Basal pH is around 6.5, whereas stimulated flow has a pH around 8; clearly any drug with a pKa around these values will be substantially affected and may lead to decreased drug concentration *(24)*. Adsorption of the drug of interest to the collection device (to the filters or absorbent material contained in some devices) is also of issue. Oral fluid specimens have shorter but earlier detection times than urine. The sample volume of saliva necessary for laboratory testing and POCT is difficult to obtain *(1, 50)*. In 1 study, interference from foods, drinks, poppy seeds (n = 1), and mouthwash were assessed as not compromising test results based on an unclear number of samples *(56)*. Results were reported to correlate well with urine results from samples collected at the same time as the saliva samples. The detection time after drug use for oral fluid was 3 days for opiates and cocaine and 1 day for THC. Methamphetamine detection time after drug use was not determined.

While some criticize saliva as a medium *(57),* the evidence suggests that saliva is a feasible alternative and an aesthetically more acceptable matrix than urine. However, the shortened time window for detection, the lack of evidence on interferences, oral drug residues, and other issues of manipulation

currently require some circumspection in the general applicability of this matrix to addressing the question of drug usage.

One study comparing POCT oral fluid testing to GC-MS results showed "good" correlation results for opiates and methadone (15% error rate) *(27)*. In a small study (n = 15) using saliva with the DrugWipe (Securetec Detektions-Systeme AG, Germany) device at POCT *(58)*, results obtained by law enforcement officers correlated well with laboratory results for cocaine and amphetamines. The oral fluid POCT was shown to lack sufficient sensitivity to demonstrate heroin abuse. THC detection was unsatisfactory because the antibody is more sensitive to THC-COOH than to THC, which is the major analyte in saliva *(58, 59)*. The immunochromatographic test strip used with the DrugWipe system in these studies is based on the Frontline urine test strip (Roche Diagnostics/Boehringer Mannheim GmbH, Germany). Another study concluded that oral fluid was not adequate for detection of THC and benzodiazepines *(25)*. This study also reported differences in results, based on experience of the analyst. In comparing saliva testing to urinalysis, Yacoubain et al. *(60)* found satisfactory correlation for cocaine, "heroin," and marijuana.

Saliva strips have been used for quick assessment of ethanol ingestion at POCT *(61)*. The authors concluded that the strips were useful for "rule-out" of ethanol use but not for "rule-in." The Q.E.D. TMA-150 test (STC Technologies, Inc., Bethlehem, PA) demonstrated poor correlation between blood ethanol and oral fluid ethanol ($r = 0.75$; n = 36), with increasing differences at higher concentrations *(50)*. Oral fluid specimens have shorter but earlier detection times compared to urine. The sample volume of saliva necessary for laboratory testing and POCT testing is difficult to obtain *(1, 50)*; some drugs inhibit saliva production, resulting in difficult-to-manipulate viscous fluid, making transfer to an on-site device difficult.

Breath

As with oral fluid specimens, obtaining adequate sample with breath alcohol testing is a constant issue *(50),* especially with very intoxicated individuals. With proper sampling, good correlation between blood alcohol and breath ($r = 0.97$; n = 52) was demonstrated.

In a study comparing arterial blood, venous blood, urine, and breath (end-expired air) for ethanol monitoring *(23),* the breath ethanol showed the worst bias and precision compared to arterial blood ethanol measured by GC. The breath analysis was affected by body temperature and breathing patterns at time of sample collection. Wide under- and overestimation of ethanol by breath analysis was demonstrated compared to arterial blood ethanol measured by GC. Others cite the convenience of breath testing in the ED for early results, although adequate recordkeeping was an issue *(62)*. In contrast, Soderstrom et al. *(63)* examined alcohol testing in US trauma centers and reported that only 63.7% of Level I trauma centers routinely perform alcohol analysis. They reported that the primary reasons given for trauma centers not routinely performing alcohol tests were that results are considered "clinically not important" or legal concerns. Alcohol POCT results in drug treatment centers might facilitate immediate confrontation and/or counseling of the patient.

Sweat

There are 2 different approaches to sweat collection. One is a sweat patch worn by the subject for a period of time, resulting in an integrated collection of drugs in sweat over a period of time. In the other, the skin is wiped (DrugWipe) and the collected sweat has been used in roadside testing. Sampling of this matrix is not standardized.

Findings similar to those from oral fluid have been published with laboratory-tested sweat samples *(59, 64),* with the parent drug predominating. The elimination of a drug through the skin is reported to be delayed for many days, and drugs may bind to various skin fractions *(65)*. Drug concentrations in sweat did not correlate with dose or to time of use. Drugs in sweat were found to be present in a wide concentration range, requiring laboratory analytical techniques *(65)*. Collection of sufficient sample is an issue, making POCT impractical. Sweat patches need to be worn for prolonged periods to collect enough sample.

An alternate sweat collection device, DrugWipe, has been used for sweat collection in Europe. Sweat is prone to external contamination of the skin, such as passive exposure to smoke *(66)*. Sweat concentration of several drugs differs according to the collection site *(58)*. Time intervals between drug administration and excretion of the drug in sweat are variable and have not been extensively studied. Good correlation has been shown between sweat samples collected using DrugWipes and blood and urine tested in a central laboratory for MDMA *(67)*.

Other Matrices

Other matrices of interest are hair, nails, and meconium. At present, none of these matrices can be tested using POCT because of the extensive preparation that is required before analysis.

Confirmation of POCT results by laboratory methods is necessary to eliminate many false-positive and false-negative screening results. Ease of use and proper training of testing personnel are obvious recommendations. Manufacturers should design POCT devices to facilitate the required regulatory agency documentation and retrieval of data, including QC data.

POCT devices have been used in postmortem situations. The logic of this application of POCT technology is unclear, but decomposition products can interfere in some assays: e.g., falsely positive detection of amphetamines may occur in the presence of tyramine *(2)*.

NONCLINICAL APPLICATIONS OF POCT FOR DOA AND ETHANOL

Drug testing for nonclinical purposes is very common, but higher price and concerns about legal defensibility of results have limited the applications of point-of-care devices for DOA testing in nonclinical settings. Because none of the POCT devices currently available—with the exception of breath-alcohol analyzers—are sufficiently specific to be considered a confirmatory test, application of point-of-care devices in these settings requires additional confirmatory testing at a laboratory facility. Therefore, the advantage of expediency is often lost

when positive tests must be confirmed. However, there may be some benefit to immediate negative results: In 1 study of the US Postal Service, one third of applicants were lost between the time of the interview and when the drug test results were available. POCT drug testing, which may allow immediate hiring of applicants who tested negative, may reduce that attrition rate.

Point-of-care drug testing may offer another advantage in nonclinical applications. At worksites involving operation of machinery or handling of materials that may pose a threat to workers and public safety if an employee is impaired, screening on site is an efficient way to provide the employer with some assurance that workers are drug free. In this type of setting, the consequences of a false positive are not necessarily severe, as long as a confirmatory test is required. An occasional day or 2 off work until the results of the confirmatory test are available seems to be an acceptable trade for the assurance that negative results provide. Clearly, screening in a central laboratory does not provide the same measure of assurance, because results inevitably are delayed by several hours, if not a day or more, and an impaired employee may present a danger or liability in the interim.

Nonclinical POCT for alcohol is quite common because most states have implied consent laws that compel licensed motorists to submit to breath alcohol analysis. A critical assessment of the literature pertaining to standards of practice for evidentiary breath alcohol analysis is moot because statutory authority directs the use of these devices. Beyond the scope of the implied consent statutes are workplace and other nonclinical settings where alcohol intoxication may be of concern.

In this review, we assess the use of point-of-care devices for DOA and alcohol testing in nonclinical settings. Although there are extensive data in the literature regarding the analytical performance of various point-of-care devices designed to test for DOA, few studies have examined the overall benefit of these devices compared to conventional laboratory testing.

What is the effect of POCT devices on the outcome of drug testing in nonclinical settings?

Guideline 104. *Although drug testing in nonclinical settings may have an overall positive effect of identifying and discouraging drug abuse, there is no evidence that point-of-care drug testing offers any incremental benefit towards those outcomes when compared to conventional testing in a referral laboratory. There may be logistical, and perhaps economic, advantages to point-of-care drug testing, but these benefits are not generalizable.*

Strength/consensus of recommendation: I

Level of evidence: II

The appropriate outcome measure to assess the value of a laboratory test in a nonclinical setting is not always apparent. In clinical settings, there is a rich variety of positive outcomes—success of treatment, length of stay, cost of diagnosis, frequency and severity of adverse events, patient satisfaction, to name just a few—against which the use of new laboratory methods can be evaluated, but the success of nonclinical drug testing rarely pivots on the welfare of the subject. Most would accept without serious debate the notion that prevention of drug abuse, either by identifying abusers and taking appropriate action to remove potential risks that result from their impairment or from the deterrent effect of surveillance programs, is a benefit to society, but this outcome is difficult to quantify. French and Martin *(68)* reviewed the available literature estimating the societal costs of drug abuse and assessed direct expenses associated with drug abuse in several categories, including premature births, aid to families with dependent children (AFDC) and food stamp benefits, acquired immunodeficiency syndrome (AIDS), various crimes, foster care, sexually transmitted diseases, and prosecutorial costs. Their estimates, however, apply only as long as drug use is prevented and therefore do not directly accrue from drug-testing programs. Consequently, there are few data in the literature that addresses the question of whether drug testing, in the most general sense, correlates with positive outcomes (increased efficiency, reduction in accidents, fewer healthcare claims, etc.). Whether the logistical advantages of POCT translate into an incremental added benefit is even less clear.

One study *(51)* compared the cost of point-of-care urine drug screening in a large manufacturing company with the cost of drug testing in a Department of Health and Human Services (DHHS)–certified reference laboratory. A total of 1101 employees were screened by the US Food and Drug Administration (FDA)–approved point-of-care device, and urine specimens from 56 employees were sent to the referral laboratory for screening. All positive screens were confirmed by GC-MS. The principal difference between the point-of-care screening and offsite laboratory is related to the elimination of administrative expenses associated with processing negative screens, which at the point of care were not subject to the same intensity of review as in the offsite laboratory. The detailed variable cost analysis includes factors representing the labor associated with collecting, processing, and reviewing negative results, and these factors principally account for the cost differential between onsite and offsite drug testing. More specifically, the authors point out that the bulk of the cost savings was due to employee time lost when subjects traveled to offsite collection centers, rather than submitting a specimen at a designated onsite location. There is no indication that the laboratory charge was different for prescreened specimens.

Are POCT devices reliable for nonclinical applications?

Guideline 105. *Although generally reliable in comparison to automated screening methods for DOA, point-of-care devices do not have sufficient specificity to be used for nonclinical applications, and results may be subject to legal challenge unless positive results are confirmed by a definitive method.*

Strength/consensus of recommendation: A

Level of evidence: I

In a medical setting, laboratory results are interpreted by licensed medical professionals, most often physicians. For the vast majority of laboratory tests, a clinically trained gatekeeper mitigates the potential for patient harm when the laboratory result has the potential to prompt an intervention that is otherwise inconsistent with medical management based on clinical indications. Such safeguards do not ordinarily exist for nonclinical drug testing, except for regulated drug-testing programs that require a medical review officer. Therefore, nonclinical drug testing demands a higher standard of reliability than is customary for laboratory applications that are used in conjunction with diagnostic medical services.

Among the SAMHSA-regulated DOA, the specificity of POCT devices varies according to the individual target drug. Cannabinoids, benzoylecgonine, and phencyclidine hydrochloride (PCP) are the most specific, whereas amphetamine and opiate assays cross-react significantly with congeners. Benzodiazepine and barbiturate assays variably detect the many drugs within those classifications. Screening devices that differ significantly in the degree of cross-reactivity with drugs within a particular classification introduce ambiguities that may create opportunities for legal challenge.

Studies in Europe *(64)* and Canada *(69)* assessed the results of POC drug-testing programs directed at impaired drivers and inmates on conditional release, respectively. In the former study, positive results of the roadside test were used only to give police additional information when drug use was already suspected, and all specimens were submitted for subsequent GC-MS analysis. There is no mention of whether the roadside testing had any impact on the legal proceedings that followed. In the Canadian study, positive screening results were likewise confirmed by GC-MS, but regrettably, no data are given concerning falsely positive screens. A recent field study of point-of-care drug testing of impaired drivers *(5)*, however, compared the results obtained by police officers with parallel analyses on the same devices performed by trained technologists, and overall, the police officers had a greater than 3-fold higher error rate than technologists. A Finnish study *(25)* also found significant differences between point-of-care tests performed by trained and untrained staff, and this disparity has been demonstrated in clinical settings, as well *(10)*. So in addition to the limited analytical specificity of point-of-care drug screening tests, nonclinical applications of these devices may introduce a higher frequency of analytical errors.

How well do nonlaboratory personnel use POCT devices for DOA in urine for definitive actions in nonclinical settings?

Guideline 106. *When used by trained laboratory personnel, there is evidence that the current POCT devices for urine drug screening produce results that are comparable to laboratory-based screening methods. When used by trained, nonlaboratory personnel, results are poorer. Policy makers need to decide the acceptable benefit/risk ratio they seek in taking definitive actions; advice from laboratorians should be sought.*

Strength/consensus of recommendation: A

Level of evidence: II

In the study by Brookoff et al. *(21),* initial screening was exclusively performed on site by a trained law enforcement officer. This study was conducted over 46 consecutive 7-h night shifts, using 1 device to screen for cocaine and marijuana. Samples giving a positive result were retested on site. Those remaining positive were submitted for rescreening (Emit) (Syva Diagnostics, Cupertino, CA, USA) and confirmation (GC-MS). One hundred fifty of 175 subjects stopped for reckless driving underwent screening, and of these, 59% were positive for either or both drugs. Of those that screened negative for cocaine or marijuana, none were subsequently found to contain cocaine using GC-MS. There were 10 found positive for THC-COOH, but using a cutoff of 50 ng/mL. All of the 38 cocaine-positive samples were confirmed, whereas 70% of the THC-positive samples were confirmed. The results of the confirmed analyses were successfully used in prosecuting the subjects.

In the study by Crouch et al. *(5),* 5 different devices were compared at 2 sites. Though the settings were not described, samples were collected from suspected drivers on Friday and Saturday nights (2200–0600 h) over a 9- to 12-month period. The devices were tested in a rotating sequence, with the first screen performed by the participating officers and all subsequent ones by a technologist; it is not clear if the technologist was on site. This individual tested each sample using the remaining 4 devices. Results were compared between devices and were confirmed using GC-MS (all positive results were confirmed, 5% of all negatives were confirmed, and any discrepant results were confirmed). The error rates reported for the officers were 2.5% (total) compared to 0.8% for the technologists. The lowest error rates were reported using the TesTcup and TesTstik (Roche Diagnostics/Boehringer Mannheim GmbH) devices. The 800 specimens collected yielded a positive rate of 36% for at least 1 drug class. The overall performance of the devices was good, with few false positives and negatives observed using any of the devices. The highest false-positive rate for THC-COOH occurred using the AccuSign (Princeton BioMeditech Corporation, Monmouth, NJ, USA) device, with 2 nonconfirmed samples out of 172 samples. The greatest numbers of "false-positive" results were obtained for the amphetamine and opiates classes and for PCP. One of the strengths of this study was that for amphetamines and opiates, effort was made to identify other drugs of the class present in the samples that had potentially contributed to the positive response, in addition to target analytes (amphetamine/methamphetamine, morphine). These data are perhaps the most interesting in that they demonstrate the presence of drugs not sought by some laboratories, e.g., 39 positive amphetamine samples: 6 had measurable amphetamine, methamphetamine, or phentermine (the target analytes), whereas 17 of the samples were found to contain MDMA. Pseudoephedrine, phenylpropanolamine, and ephedrine were also

found in samples yielding positive screening results using the Triage (Biosite Incorporated, San Diego, CA, USA) panel. Similar data are seen with the opiates in that of the 38 samples screening positive using 1 or more of the devices for opiates, only 19 contained measurable amounts of morphine or codeine, whereas all but 2 of the remaining positive samples were found to contain hydrocodone and/or hydromorphone.

Collectively, these studies suggested higher discrepancy rates for the nonlaboratory personnel. Efficiency rates of pain clinic nurses *(10)* were 82.9% (THC), 82.3% (COC), 100% (OPI) compared to laboratory technologists, 100% (THC), 98.1% (COC), and 98.4% (OPI). Though this study suggested that increased errors were more frequent with multidrug panels, details were not clearly presented. When trained law enforcement officers were compared to laboratory personnel on site and using multidrug panel devices, the overall comparison of error rates was 0.8% (27/3200 analyses) by the technologists compared to 2.5% (20/800 analyses) for the officers. In a study involving a pain clinic, the noise and distraction level of the clinic was considered as contributing to the error rate.

OTHER ISSUES

Are POCT panels of drugs preferred over single tests?

Guideline 107. *If opting to use POCT panels, consider the prevalence of use in the population to be tested for all the drug types on the panel; consider the benefits of single POCT devices in terms of flexibility and cost. Balance this against the breadth of testing available from a central laboratory.*

Strength/consensus of recommendation: I

Level of evidence: III

There is little evidence to indicate that the best panel combinations and selection should be based upon the needs of the testing setting. Some authors indicate that testers can become confused using panel devices *(10)*. However, in the Roadside Testing evaluation *(70)*, police officers clearly preferred panel tests. The same combination of tests performed singly may be more expensive than a device containing a panel of drugs

Is there evidence for an economic impact of POCT for DOA and ethanol in any context?

Guideline 108. *Independent studies to assess the economic value of POCT for drug testing are urgently needed, particularly given the multimillion dollar nature of the market.*

Strength/consensus of recommendation: I

Level of evidence: III

There are no studies of the economics of POC drug and alcohol testing vs laboratory testing in any environment.

In summary, the introduction and use of POCT for DOA is a corporate policy issue for an organization. POCT should be used within a clearly defined framework. The objective of testing should be clear and the benefits and risks recognized. Policies regarding confirmatory testing must be understood as part of an overall use strategy. Involving laboratory professionals in the decision-making process is advised and essential where definitive punitive action may result. Quality issues, maintenance, recordkeeping, and cost/benefit also require consideration.

The development of interfaceable devices with unequivocal recording of patient/client identification is needed, and they are still generally lacking. Collaboration between manufacturers, laboratory personnel, end users, and managers requires a more informed and balanced approach.

In the future, there is need for evaluation of the economic impact of immediacy of POCT testing for drugs and ethanol in a variety of clinical and nonclinical situations. Best practices for the use of POCT and CLT need to be established based on evidence. There needs to be further independent investigation as to the benefits of urine vs saliva (oral fluid) testing.

REFERENCES

1. Jenkins AJ, Darwin WD, Huestis MA, Cone EJ, Mitchell JM. Validity testing of the accuPINCH THC test. J Anal Toxicol 1995; 19:5–12.
2. Rohrich J, Schmidt K, Bratzke H. Application of the novel immunoassay TRIAGE to a rapid detection of antemortem drug-abuse. J Anal Toxicol 1994;18:407–14.
3. Beck O, Kraft M, Moeller MR, Smith BL, Schneider S, Wennig R. Frontline immunochromatographic device for on-site urine testing of amphetamines: laboratory validation using authentic specimens. Ann Clin Biochem 2000;37:199–204.
4. Crouch DJ, Frank JF, Farrell LJ, Karsch HM, Klaunig JE. A multiple-site laboratory evaluation of three on-site urinalysis drug-testing devices. J Anal Toxicol 1998;22:493–502.
5. Crouch DJ, Hersch RK, Cook RF, Frank JF, Walsh JM. A field evaluation of five on-site drug-testing devices. J Anal Toxicol 2002;26:493–9.
6. George S, Braithwaite RA. A preliminary evaluation of five rapid detection kits for on site drugs of abuse screening. Addiction 1995;90:227–32.
7. Jenkins AJ, Mills LC, Darwin WD, Huestis MA, Cone EJ, Mitchell JM. Validity testing of the Ez-Screen Cannabinoid Test. J Anal Toxicol 1993;17:292–8.
8. Kadehjian LJ. Performance of five non-instrumented urine drug-testing devices with challenging near-cutoff specimens. J Anal Toxicol 2001;25:670–9.
9. Korte T, Pykalainen J, Lillsunde P, Seppala T. Comparison of RapiTest with Emit d.a.u. and GC-MS for the analysis of drugs in urine. J Anal Toxicol 1997;21:49–53.
10. Kranzler HR, Stone J, McLaughlin L. Evaluation of a point-of-care testing product for drugs of abuse: testing site is a key variable. Drug Alcohol Depend 1995;40:55–62.
11. Leino A, Saarimies J, Gronholm M, Lillsunde P. Comparison of eight commercial on-site screening devices for drugs-of-abuse testing. Scand J Clin Lab Invest 2001;61:325–31.

12. Peace MR, Tarnai LD, Poklis A. Performance evaluation of four on-site drug-testing devices for detection of drugs of abuse in urine. J Anal Toxicol 2000;24:589–94.
13. Peace MR, Poklis JL, Tarnai LD, Poklis A. An evaluation of the OnTrak Testcup-er on-site urine drug-testing device for drugs commonly encountered from emergency departments. J Anal Toxicol 2002;26:500–3.
14. Phillips JE, Bogema S, Fu P, Furmaga W, Wu AH, Zic V, et al. Signify ER Drug Screen Test evaluation: comparison to Triage Drug of Abuse Panel plus tricyclic antidepressants. Clin Chim Acta 2003;328:31–8.
15. Ros JJW, Pelders MG, Egberts ACG. Performance of Abusign drugs-of-abuse slide tests with particular emphasis on concentrations near the cutoff: comparison with FPIA-ADx and confirmation of results with GC-MS. J Anal Toxicol 1998;22:40–4.
16. Taylor EH, Oertli EH, Wolfgang JW, Mueller E. Accuracy of five on-site immunoassay drugs-of-abuse testing devices. J Anal Toxicol 1999;23:119–24.
17. Towt J, Tsai SC, Hernandez MR, Klimov AD, Kravec CV, Rouse SL, et al. ONTRAK TESTCUP: a novel, on-site, multi-analyte screen for the detection of abused drugs. J Anal Toxicol 1995;19:504–10.
18. Yang JM, Lewandrowski KB. Urine drugs of abuse testing at the point-of-care: clinical interpretation and programmatic considerations with specific reference to the Syva Rapid Test (SRT). Clin Chim Acta 2001;307:27–32.
19. Birnbach DJ, Browne IM, Kim A, Stein DJ, Thys DM. Identification of polysubstance abuse in the parturient. Br J Anaesth 2001; 87:488–90.
20. Belfer RA, Klein BL, Boenning DA, Soldin SJ. Emergency department evaluation of a rapid assay for detection of cocaine metabolites in urine specimens. Pediatr Emerg Care 1996;12:113–5.
21. Brookoff D, Cook CS, Williams C, Mann CS. Testing reckless drivers for cocaine and marijuana. N Engl J Med 1994;331:518–22.
22. Buchan BJ, Walsh JM, Leaverton PE. Evaluation of the accuracy of on-site multi-analyte drug testing devices in the determination of the prevalence of illicit drugs in drivers. J Forensic Sci 1998; 43:395–9.
23. Eggers V, Tio J, Neumann T, Pragst F, Muller C, Schmidt LG, et al. Blood alcohol concentration for monitoring ethanol treatment to prevent alcohol withdrawal in the intensive care unit. Int Care Med 2002;28:1475–82.
24. George S, Braithwaite RA. Use of on-site testing for drugs of abuse. Clin Chem 2002;48:1639–46.
25. Gronholm M, Lillsunde P. A comparison between on-site immunoassay drug-testing devices and laboratory results. Forensic Sci Int 2001;121:37–46.
26. Koch TR, Raglin RL, Kirk S, Bruni JF. Improved screening for benzodiazepine metabolites in urine using the Triage Panel for Drugs of Abuse. J Anal Toxicol 1994;18:168–72.
27. Mastrovitch TA, Bithoney WG, Debari VA, Gold NA. Point-of-care testing for drugs of abuse in an urban emergency department. Ann Clin Lab Sci 2002;32:383–6.
28. Moore L, Wicks J, Spiehler V, Holgate R. Gas chromatography-mass spectrometry confirmation of Cozart RapiScan saliva methadone and opiates tests. J Anal Toxicol 2001;25:520–4.
29. Poklis A, Oneal CL. Potential for false positive results by the TRIAGE panel of drugs-of-abuse immunoassay. J Anal Toxicol 1996;20:209–10.
30. Schilling RF, Bidassie B, El Bassel N. Detecting cocaine and opiates in urine: comparing three commercial assays. J Psychoactive Drug 1999;31:305–13.
31. Knight SJ, Freedman T, Puskas A, Martel PA, Odonnell M. Industrial employee drug screening: a blind-study of laboratory performance using commercially prepared controls. J Occ Environ Med 1990;32:715–21.
32. Schwartz JG, Zollars PR, Okorodudu AO, Carnahan JJ, Wallace JE, Briggs JE. Accuracy of common drug screen tests. Am J Emerg Med 1991;9:166–70.
33. Jehanli A, Brannan S, Moore L, Spiehler VR. Blind trials of an onsite saliva drug test for marijuana and opiates. J Forensic Sci 2001;46:1214–20.
34. Colbert DL. Drug-abuse screening with immunoassays: unexpected cross-reactivities and other pitfalls. Br J Biomed Sci 1994;51:136–46.
35. Baden LR, Horowitz G, Jacoby H, Eliopoulos GM. Quinolones and false-positive urine screening for opiates by immunoassay technology. JAMA 2001;286:3115–9.
36. Janssen HW, Bookelman H, Dols JLS, Gerritzen WEE, de Keyzer RH. Point-of-care testing: the views of the working group of the Dutch Association of Clinical Chemistry. Clin Chem Lab Med 1999;37:675–80.
37. Caldwell JP, Kim ND. The response of the Intoxilyzer 5000 to five potential interfering substances. J Forensic Sci 1997;42:1080–7.
38. Cody JT, Valtier S. Effects of Stealth adulterant on immunoassay testing for drugs of abuse. J Anal Toxicol 2001;25:466–70.
39. Tsai JSC, ElSohly MA, Tsai SF, Murphy TP, Twarowska B, Salamone SJ. Investigation of nitrite adulteration on the immunoassay and GC-MS analysis of cannabinoids in urine specimens. J Anal Toxicol 2000;24:708–14.
40. Tsai SC, ElSohly MA, Dubrovsky T, Twarowska B, Towt J, Salamone SJ. Determination of five abused drugs in nitrite-adulterated urine by immunoassays and gas chromatography-mass spectrometry. J Anal Toxicol 1998;22:474–80.
41. Wu AHB, Bristol B, Sexton K, Cassella-McLane G, Holtman V, Hill DW. Adulteration of urine by "Urine Luck." Clin Chem 1999;45:1051–7.
42. Lafolie P, Beck O. Deficient performance of drugs of abuse testing in Sweden: an external control study. Scand J Clin Lab Invest 1994;54:251–6.
43. Dubowski KM. Quality assurance in breath-alcohol analysis. J Anal Toxicol 1994;18:306–11.
44. Badia R, Segura J, Artola A, de la Torre R. Survey on drugs-of-abuse testing in the European Union. J Anal Toxicol 1998; 22:117–26.
45. Burnett D, Lader S, Richens A, Smith BL, Toseland PA, Walker G, et al. A survey of drugs of abuse testing by clinical laboratories in the United Kingdom. Ann Clin Biochem 1990;27:213–22.
46. Cassani M, Giuliani L, Amigoni M, Buratta A, Marocchi A. Experience with external quality assessment of drugs of abuse testing in the Lombardy region in Italy. Clin Chem Lab Med 2002;40:156–64.
47. Wilson JF, Smith BL. Evaluation of detection techniques and laboratory proficiency in testing for drugs of abuse in urine: an external quality assessment scheme using clinically realistic urine samples. Ann Clin Biochem 1999;36:592–600.
48. Delaney BC, Hyde CJ, McManus RJ, Wilson S, Fitzmaurice DA, Jowett S, et al. Systematic review of near patient test evaluations in primary care. BMJ 1999; 319:824–7.
49. Wu AHB, Wong SS, Johnson KG, Callies J, Shu DX, Dunn WE, et al. Evaluation of the Triage system for emergency drugs-of-abuse testing in urine. J Anal Toxicol 1993;17:241–5.
50. Bendtsen P, Hultberg J, Carlsson M, Jones AW. Monitoring ethanol exposure in a clinical setting by analysis of blood, breath, saliva, and urine. Alcohol Clin Exp Res 1999;23:1446–51.

51. Ozminkowski RJ, Mark T, Cangianelli L, Walsh JM, Davidson R, Blank D, et al. The cost of on-site versus off-site workplace urinalysis testing for illicit drug use. Health Care Manag (Frederick) 2001;20:59–69.
52. Valentine JL, Komoroski EM. Use of a visual panel detection method for drugs of abuse: clinical and laboratory experience with children and adolescents. J Pediatr 1995;126:135–40.
53. Dasgupta A, Wahed A, Wells A. Rapid spot tests for detecting the presence of adulterants in urine specimens submitted for drug testing. Am J Clin Pathol 2002;117:325–9.
54. Burtonwood CA, Marsh A, Halloran SP, Smith BL. Sixteen Devices for the Detection of Drugs of Abuse in Urine. Norwich, UK: Medicines and Healthcare Regulatory Agency, 2005.
55. O'Neal CL, Crouch DJ, Rollins DE, Fatah AA. The effects of collection methods on oral fluid codeine concentrations. J Anal Toxicol 2000;24:536–42.
56. Barrett C, Good C, Moore C. Comparison of point-of-collection screening of drugs of abuse in oral fluid with a laboratory-based urine screen. Forensic Sci Int 2001;122:163–6.
57. Silvaggio T, Prezzia CP. There are disadvantages, too, for oral fluid, on-site urine testing. Occup Health Saf 2001;70:8.
58. Samyn N, van Haeren C. On-site testing of saliva and sweat with Drugwipe and determination of concentrations of drugs of abuse in saliva, plasma and urine of suspected users. Int J Legal Med 2000;113:150–4.
59. Kintz P, Cirimele V, Ludes B. Detection of cannabis in oral fluid (saliva) and forehead wipes (sweat) from impaired drivers. J Anal Toxicol 2000;24:557–61.
60. Yacoubian GS, Wish ED, Perez DM. A comparison of saliva testing to urinalysis in an arrestee population. J Psychoactive Drugs 2001;33:289–94.
61. Harpe KG, Yealy DM, Heller MB, Kaplan RM, Fochtman FW. Saliva alcohol reagent strips in altered response protocols. Prehospital Disaster Med 1990;5:41–3.
62. Cherpitel CJ, Soghikian K, Hurley LB. Alcohol-related health services use and identification of patients in the emergency department. Ann Emerg Med 1996;28:418–23.
63. Soderstrom CA, Dailey JT, Kerns TJ. Alcohol and other drugs: an assessment of testing and clinical practices in U.S. trauma centers. J Trauma 1994;36:68–73.
64. Steinmeyer S, Ohr H, Maurer HJ, Moeller MR. Practical aspects of roadside tests for administrative traffic offences in Germany. Forensic Sci Int 2001;121:33–6.
65. Skopp G, Potsch L. Perspiration versus saliva: basic aspects concerning their use in roadside drug testing. Int J Legal Med 1999;112:213–21.
66. Kidwell DA, Smith FP. Susceptibility of PharmChek drugs of abuse patch to environmental contamination. Forensic Sci Int 2001;116:89–106.
67. Pacifici R, Farre M, Pichini S, Ortuno J, Roset PN, Zuccaro P, et al. Sweat testing of MDMA with the Drugwipe analytical device: a controlled study with two volunteers. J Anal Toxicol 2001;25:144–6.
68. French MT, Martin RF. The costs of drug abuse consequences: a summary of research findings. J Subst Abuse Treat 1996;13: 453–66.
69. Fraser AD, Zamecnik J. Substance abuse monitoring by the Correctional Service of Canada. Ther Drug Monit 2002;24: 187–91.
70. Verstraete AG, Puddu M. Evaluation of different roadside tests. In: Verstraete AG, ed. Rosita: Roadside Testing Assessment. Ghent: Rosita Consortium, 2001:167–232pp.

PUBLIC COMMENTS

No public comments were received on the guidelines.

Chapter **8**

Infectious Disease

Sheldon Campbell, Joseph Campos, Gerri S. Hall, William D. LeBar, Wallace Greene, Donna Roush, James T. Rudrik, Barbara Russell, Robert Sautter

INTRODUCTION

A constant in an ever-changing healthcare environment is the need for fast, accurate, and reliable diagnostic testing. Point-of-care testing (POCT) technology is a relatively new science that is focused on meeting the demands for faster testing and better patient care and outcomes. Point of care (POC) is rapid testing done on site or at the bedside by trained personal such as nurses, nursing assistants, medical assistants, and patients. There are a variety of POC tests available for home use, as well as clinical settings, ranging from rapid testing for glucose, cholesterol, prothrombin time, screening for streptococcal throat, and human immunodeficiency virus (HIV). As the number of rapid tests has increased, so has the number of situations in which POC testing could apply. The development and implementation of POC testing for infectious disease would have a huge impact not only on public health concerns but also for "routine" clinical situations. Reliable and accurate POC testing may improve patient outcomes, as well as reduce inappropriate antibiotic therapy. The purpose of this manuscript is to evaluate the available literature concerning several infectious disease tests and determine whether or not the current literature supports the use of POC, near patient, testing.

BIOTERRORISM

The need to worry about the use of bioterrorism agents in the United States did not seem a reality before 2001; however, since the fall of 2001, the need for guidelines for the diagnosis and treatment of potential agents such as *Bacillus anthracis* or the virus smallpox and the need for methods to quickly recognize the agents involved in a potential bioterrorist threat are apparent. During the events in the fall of 2001, health departments on their own or with the assistance of local hospitals and healthcare facilities attempted to screen potentially exposed individuals and many thousands of environmental substances for the presence of the spores of *B. anthracis*. Not many rapid methods were available for such screening, although molecular tools, such as polymerase chain reaction (PCR), were used to provide more rapid testing than would be available with more traditional culture methods. Traditionally, POCT is performed on patients; however, in this section tests are reviewed that are used by governmental agencies to screen the environment for select agents. The reader should be aware that select agents are currently screened in approved sentinel laboratories and referred for confirmation. Some tests discussed here are done so to inform the reader about what is available on the market.

Are there tests for the detection of *B. anthracis* spores as agents of bioterrorism that are or will be available for use as POCT? Are these needed for "field" or POCT testing?

Guideline 109. *No recommendation can be made for or against routinely providing POCT because there are no data to support the fact that routine nasal swabs in each office or laboratory would provide information that would aid in determining cause or presence of a bioterrorism agent, in particular anthrax. There is no good literature with randomized studies that would allow for one to determine if the need for testing these nasal swabs at POCT would aid in the investigation.*

Strength/consensus of recommendation: I

Since 2001, there have been reports of assays that are or are being developed to detect *B. anthracis* spores, as well as assays to rapidly detect other potential agents, such as *C. botulinum* or *F. tularensis*. The Anthrax BioThreat from Tetracore (Gaithersburg, MD, USA) was shown to detect $>10^6$ spores, with a specificity of 100%. As a POCT, the claim is that the detection of anthrax spores can be done within 15 min in the field. BioWarfare Agent Detection Devices (Osborne Scientific, Lakeside, AZ, USA) claims a similar rapid test, without any instrument requirements, hence also touted as a potential "in-the-field" test. Response Biomedical Corporation (RBM, Burnaby, BC, Canada) has developed a RAMP Anthrax test that can detect at a level of 10^4 spores in 15 min, with 100% specificity. Assays for smallpox, monkeypox, cowpox, ricin, and botulinum toxins are also promised. Last, HandyLab, Inc. (Ann Arbor, MI, USA) has a "laboratory on a chip" in development, using a small

handheld reader that can be taken in the field, and the first assay will be for detection of anthrax spores. In addition, 3 of the commercially available lateral-flow devices have been evaluated in the literature to be used in detection of spores of *B. anthracis (1)*. Recently, a report in the *Morbidity and Mortality Weekly Report (MMWR)* (June 4, 2004, "Responding to Detection of Aerosolized *B. anthracis* by Autonomous Detection Systems in the Workplace") details the advantages of early detection of a release of anthrax spores. These devices are being deployed in postal offices, etc. It is clear that this is the technology of the future and may soon be available to the clinical laboratorian. So clearly the technological marketplace is responding to the potential need for such products. Whether any of these are needed for POCT testing in patient areas is the question posed.

The literature would be graded as III, following the opinions of authorities as follows. In a reference by Kiratisin et al. *(2)*, the results of large-scale screening of nasal swabs for *B. anthracis* in the midst of the Fall 2001 threats were presented. A descriptive summary of the culture methods used to screen 689 individuals from Capitol Hill and another 3247 from the Brentwood Post Office facility is given. There were a few positive cultures for *Bacillus* sp., none of which proved to be *B. anthracis*. The authors concluded that the screening was perhaps not the most effective way to detect the organism, if present, in these exposed individuals, but they suggest that time from exposure until processing may greatly affect recovery. Rapid testing was performed in this study, but results were not available for quite some time because of the incubation of the media and need for confirmation of suspect isolates. The authors do not speculate, however, whether a more rapid test might have been more effective or provided more efficient outcomes because all individuals were offered or given prophylaxis, regardless of the culture results.

In a report by Anderson and Eisoid *(3)*, summarizing the events of October 15, 2001, and subsequent days of the anthrax investigations, communications were seen to be the key factor to controlling the situation; comments were made by the authors that healthcare workers should make the decisions as to who gets screened and how, but they do not further comment on need for rapidity of testing. Byrne et al. *(4)* comment on the use of an automated aerosol collection system for constant surveillance of the environment rather than relying on collection of samples by individuals as being much more efficient, constant, and reproducible.

The need for rapid screening if another attack occurs would seem probable; however, there is no literature nor outcome studies to provide information that use of such in-the-field tests would contain any outbreak or reduce the incidence of exposure or infection. Such assays will probably continue to be investigated, however, and should be with studies done to indicate their efficacy. A rapid molecular PCR product by IDI (Infectio Diagnostic Inc., Sainte-Foy, QC, Canada) that can be performed on Cepheid's (Sunnyvale, CA, USA) Smart Cycler does have an application for detection of *B. anthracis* in post offices presently. This might be considered "at the place," or POC, although no patients are involved directly in this type of testing. "Rapid" molecular tests are or will become available, and the use of these assays as POCT may be possible *(5–7)*. Currently, you have to be a "certified" facility to identify and work with agents of bioterrorism. If the methods involve handling of potentially dangerous agents, then one would think that there would be restrictions on use of any of these assays, except by "certified" laboratories and individuals. Thus, use of any of these potential tests would have to be performed by laboratories that have been certified to handle agents of bioterrorism and not done in most laboratories that are considered Level A or sentinel laboratories. There are risks in using a test that might become available for agents of bioterrorism. Some of these agents might be involved in nonterrorist activities, and inappropriate alarms may sound if 1 of these assays is performed without benefit of determining the "bioterrorism" nature of the incident. On the other hand, handling of any of the bioterrorism agents by untrained individuals may unduly expose them and others at POC to the hazards of the agent in question.

CLOSTRIDIUM DIFFICILE

C. difficile is the causative agent of pseudomembranous colitis. The syndrome is most often associated with antibiotic use. The organism produces 2 main toxins that are associated with the disease. Toxin A, a potent enterotoxin with minimal cytotoxic capabilities, involves the erosion of the intestinal mucosa and then a fluid response in the intestine. The second, cytotoxin B, is a heat-labile toxin that causes a decrease in protein synthesis, disorganization of actin filaments, and loss of intracellular potassium.

The cytotoxin B assay has been the gold standard for the determination of *C. difficile* disease. However, many hospitals elect not to perform the assay. This choice is often made because the test is technically difficult to perform, is difficult to transport because of its sensitivity to heat, and takes time to detecting a negative sample. For these reasons, many laboratories have elected to assay for toxin A. Toxin A assays use a same-day enzyme immunoassay (EIA). In addition to these tests, toxin A/B tests and antigen tests (glutamate dehydrogenase) have been used for same-day results.

Is there research available evaluating the clinical outcomes of rapid tests for *C. difficile* toxin performed at the POC?

Guideline 110. *There is fair evidence against POCT for* C. difficile *toxin at this time.*

Strength/consensus of recommendation: C

Level of evidence: II

There are no data available to evaluate *C. difficile* tests at the POC. Many of the rapid tests used for the detection of *C. difficile* toxin involve multiple sample preparation steps such as dilutions, vortex-mixing, centrifugation, and washing *(8, 9)*.

The multiple steps required of the procedures would make this type of testing difficult to perform at the POC. In addition, an important piece that is missing in all of the rapid testing articles is the fact that the testing was not performed by individuals that typically are involved in POCT *(8, 9)*. For *C. difficile* testing to be brought to the POC, the number of procedural steps of the test would need to be reduced and studies would need to be performed comparing the POCT result to the laboratory result and ultimately to the clinical outcome.

INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis (IM) testing performed in physician office laboratories is widespread because there is a need to clinically differentiate this syndrome from other entities. Rapid card tests that detect heterophile antibodies (HA) have been available for a long time. However, the majority of research performed on the laboratory tests for the diagnosis of IM during the past 10 years has focused on specific serologies for Epstein-Barr virus. Commercially available EIA tests for immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies to the viral capsid antigen (anti-VCA-IgM, anti-VCA-IgG), antibody to the nuclear antigen (anti-EBNA), and antibody to early antigen (Anti-EA-IgG) have been compared to the gold standard method using indirect immunofluorescence assays. A few studies within the past 10 years have compared Epstein-Barr virus (EBV)-specific serologies to the commercially available HA tests.

Have patient outcome studies been performed on the rapid tests that are available to screen for IM at the POCT site, and have the studies been performed by the POCT personnel?

Guideline 111. *Recommend POCT for HA testing in patients >12 years old, fair evidence to support procedure. However, some individuals do not produce HA in IM, and if a negative test is obtained EBV-specific serologies should be performed before ruling out IM.*

Strength/consensus of recommendation: B

Level of evidence: II

Guideline 112. *Recommend against POCT for HA testing in children <13 years old, fair evidence against procedure. It is well documented in the literature that a large portion of children do not produce HA. In these patients, EBV-specific serologies should be performed before ruling out IM.*

Strength/consensus of recommendation: C

Level of evidence: II

Gartner et al. *(10)* tested 264 samples with 4 commercially available EIAs and compared these results to an indirect fluorescent antibody (IFA) reference method. Rea et al. *(11)* collected 380 samples for analysis by ELISA to detect EBV specific serologies and compared these to results obtained by using IFA methods. Fung et al. *(12)* compared a single EIA test to an IFA test in 152 patient samples. Studies performed using only the EBV-specific serologies are not used at this time at the POC.

Other studies have compared the commercially available tests for EIA and IFA EBV specific serologies, along with the commercially available HA tests. Gomez et al. *(13)* found that, when compared to EBV-specific serology, 3 rapid IM tests for HA had low sensitivity, 15%–33% in children under 13 years old and 59%–81% in patients >13 years old. The specificities ranged from 86%–100% in both age groups. The researchers recommended that EBV-specific serologies be performed on all HA-negative cases in adults and on all children *(13)*. Bruu et al. *(14)* compared 12 commercially available tests for the diagnosis of IM (6 were tests for EBV specific serologies and 6 were tests for HA). Samples from 6 groups of individuals were used in the study. Group A included samples from patients with recent primary EBV infection. Group B consisted of serial dilutions of samples from patients with recent primary IM. Group C samples were from immunocompromised patients. Group D samples were from healthy blood donors and Group E contained sera from patients with no previous EBV infection. The researchers recommended 4 of the 6 tests for HA *(14)*. Elgh and Linderholm *(15)* compared 6 HA tests with EBV-specific serology. The researchers found that the sensitivity for the rapid tests was 70%–92% and the specificity was 96%–100%. They recommended 5 of the 6 tests for confirmation of EBV-associated IM. Gerber et al. *(16)* compared 4 HA tests and 1 enzyme-linked immunosorbent assay (ELISA) EBV-specific serology test to EBV specific serology by IFA. The sensitivities for the HA tests ranged from 78% to 84%, with specificities of 89% to 100% *(16)*. These HA tests are being used at the POC as a diagnostic test for IM.

Research has been performed that compared the results of tests for HA only. Schwartz *(17)* studied the congruence of 3 rapid HA tests. He found that only 9 out of 135 specimens were incongruent among the 3 tests. Rogers et al. *(18)* compared a new dry latex preparation HA test to 3 other commercially available HA tests. Through this comparison, the authors found that the new test had a sensitivity of 87% and a specificity of 98.7%.

The research studies listed above were comparative studies. Little if any research has been performed in regard to the downstream effects of the correct or incorrect diagnosis of IM when using tests for HA at the POC. Research needs to be performed that considers the outcomes of using tests to detect the presence of HA at the POC site. (Data such as number of clinic visits or reduction of length of stay in the ED, reduction in the number of contraindicated drugs or therapies, length of time to recovery, or days of work/school lost need to be collected). In addition, research needs to be performed that studies the feasibility of performing EBV-specific serologies on all children <13 years old in place of the HA test. Also, research that compares the accuracy of IM testing at the POC site by POC personnel to the accuracy of the test performed in a Clinical Laboratory Improvement Amendments

(CLIA)-approved laboratory by certified medical technologists is essential to investigate the true outcomes of POCT.

CHLAMYDIA TRACHOMATIS AND *NEISSERIA GONORRHOEAE*

Will direct examinations for *C. trachomatis* and *N. gonorrhoeae*, delivered as POC tests, achieve high enough sensitivity for routine care?

Guideline 113. *POC* Chlamydia *tests should only be used while the patient is present for treatment and follow-up. If the results are not available until after the patient leaves, do not use POC tests. The gram stain may be used as a POC test for symptomatic men with urethral discharge.*

Strength/consensus of recommendation: A

Level of evidence: II (small analytic studies and opinions of respected authorities)

Most tests currently available for *C. trachomatis* and *N. gonorrhoeae* must be performed in a laboratory, and results are usually not available before the patient's departure *(19–25)*. This delay may lead to patients not returning for treatment and further disease transmission. Twenty percent of patients with positive tests fail to return in 30 days, and 30% fail to return in 2 weeks after notification of test results. This can lead to the spread of the disease and ultimately may result in increase cases of pelvic inflammatory disease (PID) in women. Because 30% of untreated cases of *Chlamydia* result in PID, this may result in as much as $4000 in future medical costs.

In a recent study (Swain et al. *(23)*), it was determined that using a decision analysis scheme including clinical criteria and POC (near patient) tests could increase the number of patients treated from 48.6% of those women assessed by clinical criteria to as high as 79.1% using a direct fluorescent antibody (DFA) method in the POC and 78.4% using a POC optical immunoassay (OIA) method. However, the results of the Swain et al. *(23)* study and other studies of the performance of POC *C. trachomatis* tests have shown that these products have reduced sensitivity when compared to culture or nonamplified chlamydia methods. Many studies have been assessed using culture as the gold standard; however, it is anticipated that this disparity would be even greater if POC tests were compared to nucleic acid amplification tests or to an infected patient standard. The best overall strategy for therapy in the abovementioned study was using a presumptive treatment protocol, along with selective testing (12.8% untreated patients) vs OIA POC tests and the same presumptive protocol (21.6% untreated patients).

A clear need for testing does occur because using only the presumptive treatment and not laboratory testing resulted in 51.4% of patients with disease untreated. Using universal nucleic acid amplification test (NAAT) testing with no presumptive treatment resulted in 23.6% of patients left untreated. Clearly, clinical criteria and laboratory testing are required. A proposed model including the prevalence of the disease in the population, clinical risk assessment, and the probability of infection, coupled with laboratory testing, might be the most prudent method of STD evaluation for *C. trachomatis* and *N. gonorrhoeae.* The National Chlamydia Laboratory Committee, Association of Public Health Laboratories recommendation that POC tests should only be used when the patient is available for treatment or follow-up or in specific situations such as in high-risk patients who are unlikely to return, criminal intake facilities where individuals are released within hours after detention, the homeless, or in method evaluations and projects should be followed.

The 2002 *MMWR (25)* states that the gram stain is the most reliable POC test for the presumptive identification of *N. gonorrhoeae* from urethral exudates in symptomatic men. Gram stain is not recommended for testing for infection in women.

More research and development are needed with POC tests that have increased accuracy and reliability at the POC for *C. trachomatis* and *N. gonorrhoeae*. With this increased reliability, there may be a change in the recommendations for their routine use in screening populations.

GROUP A STREPTOCOCCAL ANTIGEN TESTS

In acute care settings, Group A streptococcus (GAS) antigen testing has become a routine POC test *(26–60)*. Overall performance of the test has varied with regard to sensitivity. It is common practice to perform rapid antigen testing because ~0%–30% of office visits are concerned with the diagnosis of pharyngitis. This evaluation details the available published literature to determine whether there is enough evidenced-based research in the literature to support the use of rapid antigen tests for the diagnosis of GAS pharyngitis at the POC.

Are rapid tests for Group A streptococcal antigen performed at the POC useful for diagnosis of Group A streptococcal infections? Is there research available evaluating the clinical outcomes of rapid tests for Group A streptococcal antigen performed at the POC?

Guideline 114. *Rapid tests for diagnosis of GAS pharyngitis in general provide clinically useful, financially justified results; these tests also have utility for testing nonpharyngeal specimens. The recommendation of the American Academy of Pediatrics to confirm negative rapid GAS antigen detection results of pharyngeal specimens from children should be followed; the Infectious Diseases Society of America recommendation to perform laboratory tests (either throat culture or rapid antigen detection) on specimens from adults with clinical evidence of pharyngitis should be followed.*

Strength/consensus of recommendation: A

Level of evidence: III

GROUP B STREPTOCOCCI

By 1996, the clinical data were well documented, and the Centers for Disease Control and Prevention (CDC), along with other public health officials, published guidelines for the prevention of perinatal group B streptococcal disease (GBS) *(61)*. At that time, the CDC offered 2 different prevention systems: a risk-based approach or a culture-based screening method. The risk-based method used the following criteria: delivery at or <37 weeks' gestation, maternal temperature of greater than 100.4 °F, rupture of membranes without progressing labor of >18 h. The CDC recommendations of 1996 helped raise awareness of GBS and provided effective guidelines for prenatal screening, thereby reducing the number of neonates born with early-onset disease. Before active prevention was initiated, an estimated 7500 cases of neonatal GBS disease occurred annually, (costing $294 million in direct medical costs annually). The rate of early-onset infection has decreased from 1.7 cases per 1000 live births (1993) to 0.5 cases per 1000 live births (2000) *(62)*. The CDC continued to monitor prenatal screening for GBS and found overwhelming evidence that culture-based screening was substantially more effective than the earlier suggested risk-based approach *(63)*. As a result, several recommendations and updates were published in 2002 to help meet the needs of each of the different groups that are affected by GBS: obstetrics, pediatric care, laboratory, public health authorities, and expectant parents. The use of evidence-based practice, as well as consulting a wide spectrum of stakeholders, established a more comprehensive approach for prevention of GBS.

There are several recommendations that remain the same, as well as some major differences, when comparing the 1996 and 2002 CDC reports *(61, 62)*. Penicillin remains the antibiotic of choice, with ampicillin as an acceptable alternative. Women whose culture results are not known at delivery should be managed as before, using the risk-based approach. The most notable difference in the 2002 recommendation is replacing the risk-based assessment for universal prenatal culture-based screening. The CDC recommends culture screen of the vagina/rectum of all pregnant women at 35–37 weeks' gestation. The CDC no longer suggests using risk-based assessment as a means to prevent GBS unless the patient has not received prenatal care or if the culture results are not known at delivery. POC testing would be extremely useful to the clinician in this scenario, which may reduce inappropriate use of antibiotics. The updated guidelines specifically include recommendations against the use of antibiotics for GBS-colonized women undergoing planned cesarean deliveries where there is no rupture of membranes and labor has not begun *(62)*. There are also detailed instructions on collection, as well as expanded methods of GBS culture processing, including instructions on susceptibility testing. Currently, no POC device is recommended to be used as a screen only for GBS.

There are many factors that contribute to the accuracy of laboratory test results. Whether the sample is a blood test or culture, it is important to collect, label, and process the specimen properly. It is essential for clinicians to follow the recommended CDC guidelines for collection to improve isolation and to ensure reliability. Both the 1996 and 2002 CDC guidelines recommend collecting lower vaginal and rectal cultures at 35–37 weeks' gestation. A single swab may be used for the vagina, followed by insertion into the rectum through the anal sphincter. It is also acceptable to use 2 different swabs; however, both swabs should be processed in the same broth. It is important to note that the presence of GBS is what is important, not the site of GBS colonization. The collection of "vaginal/rectal swabs improves GBS isolation by 40% compared to use of vaginal specimens alone," and yet there are still clinicians that collect only vaginal swabs *(63)*. The CDC also specifically states that collecting cervical specimens and using a speculum are not recommended. There is documentation to support the CDC's claim that cervical collection yields 40% fewer positive cultures than single vaginal swabs. Yet, 6% of laboratories accept cervical specimens *(63)*. Because GBS colonization may be transient, proper timing of collection at 35–37 weeks' gestation is recommended to improve sensitivity and specificity and to give more reliable results. Laboratory processing of the specimen according to CDC guidelines is equally important for isolation and identification of GBS. The vagina and rectum are colonized with heavy normal flora, which can make isolation of GBS challenging. The 1996 and 2002 CDC guidelines for clinical laboratories recommend 2 different media for GBS isolation: plate media and selective broth *(61, 62)*. The plate medium suggested is trypticase soy agar with 5% sheep's blood, known as TSA, or CNA. There are 2 selective broths suggested, Todd-Hewitt or LIM broth, which are supplemented with antibiotics to suppress normal flora and allow GBS to grow. The synergist effects of using both plate and selective media improve GBS isolation. The use of plate media alone without selective broth will miss 50% of women who are GBS carriers and will give false-negative results *(62)*. "A survey of clinical laboratories in selected counties of 3 states in 1997–1998 found that only a proportion of laboratories was using the recommended selective broth media to process GBS cultures (Georgia, 39% of laboratories; Minnesota, 42%; Connecticut, 62%), suggesting that this may be an area in need of improvement." *(62)* A follow-up report was published in 2003 to determine whether clinical laboratory improvements had been made using the 2002 CDC guidelines.

Is there research available evaluating the clinical outcomes of rapid tests for group B streptococcus? Are rapid test kits reliable, and should they or should they not be used for POCT?

Guideline 115. *There is insufficient evidence to recommend POCT for group B streptococcus. There was no literature found demonstrating a link to POC testing for Group B streptococcus and outcomes data.*

Strength/consensus of recommendation: I

Rapid detection of Group B streptococcus is well documented using latex particle agglutination (LPA), EIA, and DNA testing *(64–77)*. Review of published data shows that rapid testing of LPA and EIA is not sensitive for low colonization of Group B streptococcus and therefore is not reliable for replacing the current standard of culture. Molecular testing, however, is very sensitive for detection of low to high colonization of Group B streptococcus, and is presently in development as a POC test. Currently, molecular testing is more costly when compared to culture and may not replace the current standard. POCT for Group B could potentially identify colonized women who may not have been cultured at 37 weeks or those with no prenatal care. Research is needed to determine whether POCT using newer molecular approaches will further decrease the incidence of neonatal meningitis and sepsis by detecting maternal colonization of Group B streptococcus at the time of delivery. Molecular tests have been marketed for the detection of Group POC tests.

HELICOBACTER PYLORI

Peptic ulcer disease causes chronic inflammation of the stomach and duodenum that may affect as many as 10% of all Americans at some time in their lives. Potent antiulcer medications may eliminate symptoms, but recurrence rates remain high. Approximately 80% of patients with gastric or duodenal ulcers, without other predisposing factors such as NSAID (nonsteroidal anti-inflammatory drug) use, are infected with *H. pylori*. Eradication of infection results in the resolution of gastritis and a marked decrease in the recurrence rate of ulcers *(78–89)*.

Is there research available evaluating the clinical outcomes of rapid tests for *H. pylori* at the POC?

Guideline 116. *There appear to be tests available for sensitive and specific testing at POC for* H. pylori*, but as yet no studies have been done to determine whether such POCT would have favorable clinical outcomes. Because tests including stool antigen tests, and urea breath tests have proven comparable in overall detection of* H. pylori *at the POC, studies should be conducted to determine their utility in early detection and treatment of dyspepsia-associated* H. pylori *disease.*

Strength/consensus of recommendation: I

INFLUENZA VIRUS INFECTION

Influenza infections occur in large numbers every year and are associated with increased morbidity and mortality. These infections produce a broad range of symptoms, ranging from asymptomatic infections to fulminant viral pneumonia, making diagnosis based solely on clinical presentation difficult, especially during nonpeak periods. There are numerous studies demonstrating the benefits of rapid diagnostic assays for influenza, both in directing appropriate use of antiviral drugs and in the reduction of unnecessary diagnostic tests *(90–92)*. With the availability of CLIA-waived assays for influenza, their use as POC tests needs to be addressed. Specifically, how do the sensitivity, specificity, and positive and negative predictive values of these rapid tests determine their clinical usefulness in the POCT setting?

Are there studies available for evaluating the clinical outcomes of rapid tests for influenza virus performed at the POC?

Guideline 117. *We found that the literature supports the lack of sensitivity and accuracy of clinical criteria alone for the diagnosis of influenza virus infection. Therefore, additional testing, including POCT, may be useful. These tests should only be used for POCT when the virus is prevalent in the community, and negative results should not be used to rule out influenza virus infections. Only nasopharyngeal swabs, aspirates, or washings should be used with these assays. The sensitivities of the tests using throat swabs are 60% or less. During the peak of an outbreak, not every single patient with flu symptoms needs to be tested, unless a positive result will result in the withholding of antibiotics. The greatest cost benefit is achieved when unnecessary antibiotics are not prescribed for patients with positive influenza virus test results. If treating with antivirals is being considered, the patient must be treated within the first 48 h of onset of symptoms for even a minimal effect to be achieved.*

Strength/consensus of recommendation: B

Level of evidence: I and III

One study addressed the use of a rapid influenza assay in a POC setting using nonlaboratory personnel to perform the testing at a pediatric hospital emergency department (ED) *(93)*. They studied 391 patients between 2 months and 21 years, presenting with fever, cough, coryza, myalgias, and headache. They were randomized into 2 groups: (1) physician received the rapid flu result before seeing the patient; or (2) physician did not have the result of the rapid test. The 2 influenza-positive groups were compared for laboratory and radiographic studies and their associated patient charges, prescriptions, and length of stay in the ED. There were significant reductions in unnecessary tests, prescriptions, and increase in antiviral prescriptions and a significant reduction in time spent in the ED and in the mean charge. A telephone follow-up revealed no differences between the 2 groups for return visits to the primary physician or ED, new prescriptions, length of time patient missed school or daycare, and the length of time primary caregiver missed work. These recommendations are in agreement with the recommendations of the World Health Organization for the use of rapid diagnostic tests for the detection of influenza virus *(94)*.

RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV) is an important viral pathogen most commonly seen in young children less than 1 year of age. Serious respiratory infections may also occur in elderly and immunocompromised adults. Diagnosis of RSV infections based on clinical presentation is difficult (sensitivity, 72.8%; specificity, 73.2%) *(95)*. RSV is also a significant nosocomial pathogen, making rapid diagnosis of these infections useful for infection control. RSV may be grown in cell culture; however, this usually required 4 or more days, which reduces the clinical usefulness of this method. Rapid diagnostic methods include direct fluorescent antibody staining and several rapid-antigen-detection kits. The reported sensitivity values range from 62% up to 96%. This wide range is due to multiple factors, including the age of the patients (these assays perform very poorly in adults, 10%–23% sensitivity) *(96)*, the specimen type being tested (throat swabs perform poorly), and the assay used as the gold standard (culture or molecular amplification) to which the rapid test is being compared. The use of rapid diagnostic assays for RSV by the laboratory has been documented to reduce the length of hospital stay, antibiotic use, and other tests *(97, 98)*. Reductions in nosocomial infections in a newborn nursery were reported when combined with cohorting; visitation restrictions; and gowns, gloves, and masks *(99)*.

Are there studies available for evaluating the clinical outcomes of rapid tests for RSV performed at the POC?

Guideline 118. *The literature supports the lack of sensitivity and accuracy of clinical criteria alone for the diagnosis of RSV infection; therefore, additional testing, including POCT, may be useful when used appropriately. Tests for RSV suitable for POCT have a broad range of sensitivity and specificity, and their positive and negative predictive values vary greatly, depending on the prevalence of the virus in the community. Because of these performance characteristics, these tests should only be used for POCT when the virus is prevalent in the community, and negative results should not be used to rule out RSV infections. Only nasopharyngeal swabs, aspirates, or washings should be used with these assays. The sensitivities of the tests using throat swabs are 60% or less. The greatest cost benefit is achieved when unnecessary antibiotics are not prescribed for patients with positive RSV test results.*

Strength/consensus of recommendation: B

Level of evidence: I and III

One study addresses the use of a rapid RSV assay in a POC setting using nonlaboratory personnel to perform the testing at a large pediatric hospital ED. They reported a reduction of needless antibiotic use and a reduction in hospital-acquired RSV infections *(100)*.

HIV TESTING

The prevalence of HIV infection is increasing in the United States, and many persons at risk are unaware that they are infected *(101)*. CDC goals for HIV prevention include making HIV testing a routine part of medical care, and recent publications suggest that expanded screening for HIV is a cost-effective health intervention *(102–104)*. Unfortunately, many at-risk persons have limited access to the healthcare system, and approaches to hard-to-reach populations have been limited by the logistics of conventional HIV testing, which require a follow-up visit before results of testing are available, even for seronegative patients. In addition, conventional HIV testing protocols fall short when an immediate result would optimize patient care; for example, in assessment of the source-patient in occupational blood and bodily fluid exposures and in labor and delivery settings with women of unknown HIV serostatus.

To address these issues, rapid HIV tests have been under development and being assessed in active use for more than a decade *(105, 106)*. Used both in clinical laboratories and at the POC, rapid HIV tests promise to enhance our ability to assess HIV status in situations where rapid action is necessary and to expand HIV testing to previously difficult populations and situations.

Four rapid HIV antibody tests were available as of April 2005: the Abbott Diagnostics' (Abbott Park, IL, USA) OraQuick and Trinity Biotech's (Dublin, Ireland) Uni-Gold Recombigen, both with "waived" status, and MedMira's (Halifax, NS, Canada) Reveal and Bio-Rad Laboratories' (Hercules, CA, USA) Multispot HIV-1/HIV-2, which are nonwaived. Other tests are in development; and an older kit, Abbott's Single Use Diagnostic System HIV-1 (SUDS) test, has been removed from the market, but not before extensive experience was gained with its use.

Do rapid HIV antibody tests perform as well as laboratory-based methods (a) in validation studies and (b) in field studies? Are there sources of analytic variation unique to rapid/POC HIV test kits?

Guideline 119. *Under validation conditions, currently available HIV antibody tests perform with comparable sensitivity and specificity to laboratory-based ELISA methods in patient populations that are suitable for rapid testing.*

Strength/consensus of recommendation: B

Level of evidence: I (at least 1 randomized controlled trial)

Guideline 120. *In field studies, currently available HIV antibody tests perform with comparable sensitivity and specificity to laboratory-based ELISA methods.*

Strength/consensus of recommendation: B

Level of evidence: I (at least 1 randomized controlled trial)

Guideline 121. *Rapid/POC tests for HIV should be used by personnel well trained in the method, with ongoing quality control and performance-improvement programs.*

Strength/consensus of recommendation: A

Level of evidence: II and III (small studies and opinions of respected authorities)

Guideline 122. *Rapid/POC tests should be used with caution, if at all, to follow exposed persons who are heavily antiretroviral therapy (ART) treated.*

Strength/consensus of recommendation: B

Level of evidence: II (dramatic results in uncontrolled experiments)

In US Food and Drug Administration data supporting the approval of all 4 current methods, the rapid tests appear to have comparable sensitivity to conventional EIA methods, using seroconversion panels, low-titer panels, high- and low-risk unknown panels, and known positive and negative specimens. Occasional false-positive and false-negative results were seen in large panels but never in numbers sufficient to discriminate between different kits in a significant manner. The kits vary in the number of conventional EIA methods used in the comparisons, and the particular conventional EIA method is rarely specified. Uniquely, the Multispot allows discrimination between HIV-1 and HIV-2 reactivity *(107–110)*.

Numerous published studies support the manufacturer's validation data suggesting that rapid tests perform similarly to laboratory-based EIA methods when performed by skilled staff. In the largest such study, the Mother-Infant Rapid Intervention At Delivery (MIRIAD) trial, HIV testing with OraQuick at POC had equal sensitivity to laboratory-based ELISA and had fewer false positives *(111)*. The OraQuick has also been studied in a region with transmission of multiple HIV subtypes and performs as well as a laboratory-based EIA in this setting as well *(112)*. Other rapid tests have also been evaluated in patients with non-B subtypes *(113)*, but the existing data are limited relative to the large number of HIV subtypes in the world.

In addition to the 4 currently approved methods, numerous other tests are being studied and, presumably, in the process of approval. As an expanding number of methods become available, careful postmarketing surveillance of test performance and problems will be essential.

One publication explored the rate of performance-related errors in use of rapid HIV tests by nonlaboratorians. The rate of errors decreased when the procedure was demonstrated to the users, and the authors concluded that careful training and ongoing performance assessment is important in POC HIV-testing programs. Significant levels of errors related to sample handling, inoculation, and recordkeeping were observed *(114)*. The CDC has issued extensive performance and quality-assurance guidelines for use of rapid HIV tests, which are recommended for all healthcare organizations performing testing *(115)*. The labeling of the rapid tests includes language stating that they are to be sold only to agents of a clinical laboratory; what this means in practice is not entirely clear.

The rapid HIV antibody tests have comparatively small antigen suites. In theory, this should limit sensitivity in some patients. A report has been published of a series of patients who were treated with highly active antiretroviral therapy (HAART) early after a known HIV exposure. These patients developed HIV infection with low viral loads and a declining gp 41 antibody response, which was not detected by the OraQuick method *(116)*. Although this is not a patient population for which rapid testing would be appropriate currently, this report points to a potential problem with rapid tests, particularly if used for 2-stage confirmatory testing (see below). The tests with both gp 41 and gp 120 (Table 8-1) might be less susceptible to this effect but have not been tested.

The performance of rapid HIV tests at POC under actual field conditions is still difficult to determine. The potential for substandard performance of the tests is significant, caused by human errors, kits storage problems, environmental issues in nonlaboratory testing environments, and other variables. Authors of studies that examine the use of rapid HIV tests at the POC should be encouraged to provide details of the type and training of personnel performing POC HIV testing, the location and environment in which the testing was performed, and any other information relevant to evaluating the factors affecting practical performance of rapid HIV tests. Additional studies of the quality of testing under actual conditions of routine use are difficult to perform; 1 of the desirable properties of the rapid tests is ease of sampling compared with conventional testing, but highly desirable.

Table 8-1 Rapid HIV Kit Antigens

Test	Antigens represented		Approved for HIV types
	HIV-1	HIV-2	
Abbot/Orasure OraQuick Advance Rapid HIV 1/2	gp 41	gp 36	HIV-1 and 2
Bio-Rad Multispot HIV-1/HIV-2 Rapid	Recombinant and synthetic gp41	gp 36	HIV-1 and 2, separate result for each
Trinity Uni-Gold Recombigen HIV	gp41, gp120	?	HIV-1
MedMira Reveal Rapid HIV-1 Antibody	gp41, gp120	?	HIV-1

Does HIV testing at POC improve rates and timing of ART for HIV-infected women in labor?

Guideline 123. *Rapid HIV testing in the peripartum period, laboratory-based or POC, improves antiretroviral prophylaxis and most likely reduces peripartum transmission of HIV, provided systems are in place to use the information therapeutically.*

Strength/consensus of recommendation: A

Level of evidence: II

Multiple trials have now established that rapid testing protocols can provide information to support provision of antiretroviral therapy during the perinatal period. In an uncontrolled intervention trial in Lima, Peru, 3543 women were tested with both oral fluid- and blood-based rapid methods, and 27 were positive with 1 or both. ART was provided before delivery for 17/19 women whose delivery records were available. Two of the 27 positive tests failed to confirm with a laboratory EIA, but no parallel testing was performed, making it difficult to assess the quality of the rapid HIV test results *(117)*.

In a study in Nairobi, rapid testing increased the rate of notification of pregnant women of their HIV serostatus but did not affect the (low) rate of antiretroviral prophylaxis. Rapid testing protocols must be coupled with effective posttest strategies for provision of care to be effective in affecting health *(118)*. A similar protocol in Cote d'Ivoire led to just 26.2% of HIV-infected women entering the preventive program. Entry into preventive care was adversely affected by illiteracy and by living with a partner, again demonstrating the limitations of rapid testing in addressing systemic problems in provision of care *(119)*.

One study compared the availability of HIV test results between institutions using SUDS and using conventional ELISA methods and within a single institution before and after conversion from ELISA to SUDS. The use of SUDS significantly decreased time to report, but there were major differences between institutions using the rapid test, emphasizing the need for comprehensive systems to facilitate rapid testing and use of results *(120)*.

In the MIRIAD trial, rapid testing was performed for 4849 women who presented to labor-and-delivery units in a multicenter trial. Of these, 34 were positive by a rapid test; in these women, zidovudine was started before delivery in 18, and all HIV-exposed infants received zidovudine after delivery. Of the 32 infants who were available for follow-up, 3 were HIV infected, 2 DNA positive at birth, and 1 negative at birth but positive at 6 weeks of age. In historical studies, the rate of transmission of HIV in the absence of prophylaxis is 14%–33% *(121)*. There was no control arm of this study; either standard care without rapid testing or with risk-based provision of ART *(111)*.

A cautionary note was sounded by the observation that, of 69 patients with a positive rapid EIA (of 9781 women tested peripartum), only 26 were confirmed as HIV infected by Western blot, yielding a positive predictive value for the rapid test of only 37.7%, 9.8% in Hispanic women. The authors suggested that in very-low-risk populations, the routine disclosure of rapid intrapartum HIV results should be avoided before confirmatory testing *(122)*.

No systematic study has compared laboratory-based and POC use of rapid HIV tests in the peripartum period.

The comparative value, accuracy, and operational efficiency of POC vs laboratory-based rapid HIV testing, both in the peripartum and other settings, has not been determined. Results from any such study may be difficult to generalize to different settings because of differences in institutional organization and resources. Despite the limitations of the MIRIAD trial, it will be difficult to ethically justify a truly controlled trial of rapid testing vs no or conventional testing, unless a large fraction of patients in the "no testing" or "conventional testing" arm of the study receive prophylaxis. Research is also needed on the cost-effectiveness of rapid testing in highly resource-limited environments such as the less-developed countries.

Does HIV testing at POC provide benefits for blood- and body-fluid-exposed employees?

Guideline 124. *Strongly recommend rapid testing of the source-patient for employee exposures.*

Strength/consensus of recommendation: A

Level of evidence: II

Guideline 125. *No recommendation regarding testing at POC.*

Strength/consensus of recommendation: I

In a controlled study, the use of rapid HIV testing decreased costs and self-reported stress among blood- and body-fluid-exposed healthcare workers. The rapid test was performed by nursing staff of the emergency unit, who also performed the clinical evaluation of the exposed workers. The rapid test, GENIE II (Sanofi-Pasteur, France), is not available in the United States but performed identically to the conventional EIA *(123)*.

The impact of rapid testing was assessed in a retrospective review format, estimating the costs that would have been incurred had conventional testing been performed instead. The authors estimated that more than $5000 was saved in treating 17 patients by the use of the rapid test. The costs used in the model included medication costs, lost work time, labor, and testing costs *(124)*. Another similar study in Brazil estimated a savings of nearly $3000 in 109 cases *(125)*.

In Italy, implementation of a rapid HIV test, the Capillus HIV-1/HIV-2 (Trinity Biotech; not currently available in the United States) in 2 hospitals produced a dramatic reduction in use of ART and a significant reduction in the number of source

patients who remained untested. At hospital A, of 567 workers exposed in the prerapid era, 90 received ART; only 6 source patients tested HIV positive. After implementation of the rapid test, only 3 exposed workers out of 628 received ART, and 3 source patients were HIV positive. A similarly dramatic reduction in prophylaxis was seen at hospital B. The incremental cost of rapid vs conventional testing was similar to the cost of the doses of antiretroviral drugs saved. There was also an increase in the number of exposures reported at hospital B; the authors speculate that rapid testing protocols might make reporting more likely by decreasing the likelihood of unnecessary prophylactic therapy *(126)*.

Although the available data are limited, the magnitude of the effect is impressive. Further studies of the impact of rapid testing vs risk-based protocols, even historical studies, would be useful. As in many areas, comparison of laboratory-based and POC rapid testing is desirable, though the results may be difficult to generalize.

Does HIV testing at POC improve HIV case finding, entry into comprehensive HIV care programs, or facilitate changes in risky behaviors?

Guideline 126. *No strong recommendation for rapid/POC testing in outreach settings can be supported by current literature, but there is reason to expect that certain populations could be better served by POC screening.*

Strength/consensus of recommendation: I

Level of evidence: II

Analytically, conventional HIV tests perform superbly; outside of the seroconversion "window period" and other defined areas of physiological ambiguity (e.g., the neonatal period), the sensitivity and specificity of laboratory-based testing with an EIA and confirmatory Western blot approach 100%. In many settings, however, preanalytical and postanalytical issues sharply limit the achievable performance of HIV/acquired immunodeficiency syndrome testing. When significant numbers of at-risk persons lack access to testing or fail to return for results after samples are drawn for off-site testing, the analytical performance of the test is irrelevant. In 1998, when 1.9 million publicly funded HIV tests were performed in the United States, 48% of those tested failed to receive posttest counseling *(127)*. Thus, there is a compelling rationale for rapid and POCT strategies.

In a controlled trial in public clinics, the use of an early rapid test (SUDS) increased the number of patients learning their serostatus vs conventional testing in both an anonymous testing clinic and an sexually transmitted disease (STD) clinic. Eighty-eight percent of patients who had previously been HIV tested using a conventional protocol preferred the rapid test. In the year after the testing, clients tested with rapid and standard methods were equally likely to return with a new STD *(128)*.

A study assessing the value of offering HIV testing routinely in the ED incidentally assessed the use of rapid HIV vs conventional testing. Using the SUDS test, 467 patients tested in the rapid arm of the study compared with 981 tested conventionally. Rapid tests were performed both in the main laboratory and in a satellite laboratory next to the ED. Follow-up was better for seropositive patients in the rapid test group, but the difference was not statistically significant. Turnaround time was faster in the ED satellite laboratory than in the main laboratory (107 ± 52 min vs 48 ± 37 min), and more patients received their results before leaving the ED with satellite laboratory testing (80% vs 45%). The interpretation of these results is limited by an extremely complex 4-phase protocol in which enrollment procedures changed with each phase *(129)*.

An uncontrolled descriptive study in an STD clinic enrolled 1581 patients, of whom 1357 had same-visit results and posttest counseling, whereas 209 refused rapid testing and preferred conventional testing. The test used was the SUDS assay. Of the 1357 patients who received same-visit testing and counseling, 37 were HIV positive, and 36 of these attended their first HIV clinic visit; the other patient died of HIV-related complications before the first visit. There were 6 false-positive and 1 false-negative SUDS results. In this setting, rapid testing was highly preferred by patients, and even discordant results were handled well by the recipients *(130)*.

Several studies of patient acceptance of rapid HIV testing suggest that rapid tests will be well received by the target population. A focus-group study at an inner-city hospital showed overwhelming preference for rapid testing, provided concerns about accuracy were addressed and provided the rapid testing did not prolong already long clinic waiting times *(131)*. A survey of persons aged 12–24 years showed a preference for oral sampling and for rapid testing vs blood or longer times to result *(132)*. Women in northern Thailand preferred rapid testing *(133)*. Journal and newsletter articles *(134–137)* indicate considerable interest in HIV care providers and target populations in rapid HIV testing, tempered by concerns about how rapid testing will be handled and availability of ART for newly identified patients.

Studies of rapid testing in outreach settings (gay bathhouses) showed an increase from 74% to 99% of clients receiving their test results over conventional testing. There was also an increase in the number of patients who returned for partner notification and early treatment counseling after result confirmation. The rapid test was more cost-effective. The authors noted, however, the potential problems inherent in performing testing in a dim, crowded space, including the phrase "In places where lighting is poor we recommend having a flashlight on hand to read the test results," which suggests that a more systematic approach to quality assurance would benefit these programs. Other issues identified were the bathhouse owner's level of comfort with the impact of a screening program and of giving positive results on the social atmosphere of the facility and the availability of a CLIA-certified laboratory to oversee the testing *(138, 139)*.

A randomized trial in needle exchange and bathhouse outreach testing showed that client acceptability increased both

with oral fluid testing (using an off-site laboratory for oral fluid testing) and with rapid testing relative to traditional testing. Testing strategies were randomized by offering different strategies on randomly determined shifts. Although the largest proportion of clients accepted oral fluid testing, rapid testing was preferred over traditional testing, and more persons received results with rapid testing than with traditional or oral fluid testing. Fewer than half those who agreed to be tested with the rapid test in the needle exchange environment received their results, pointing out the limitations of even rapid tests in difficult-to-reach populations *(140)*.

More trials, preferably controlled trials with careful description of testing procedures and environments, would help to assess the settings in which rapid HIV testing can be usefully performed, the performance of the tests under field conditions, the relative value of on-site laboratory-based vs POC testing for settings in which that is applicable, and the impact of rapid testing on behavior change both as it affects HIV risk and transmission of other sexually transmitted or blood-borne diseases. Quality assurance is likely to be essential to effective outreach programs; what is the role of clinical laboratories in outreach testing? How will the results of outreach testing be entered into and maintained in the medical record?

What algorithms for confirmatory testing should be used with POC HIV tests?

Guideline 127. *Confirmatory testing should go directly to Western blot/IFA, bypassing a second EIA step***.**

Strength/consensus of recommendation: A

Level of evidence: III

Guideline 128. *In some resource-limited settings, a second, different rapid test is used for confirmation; this has not been carefully studied but is promising.*

Strength/consensus of recommendation: I

Level of evidence: III

Given the overall good performance of rapid HIV tests, the CDC recommends that a second screening EIA *not* be performed before confirmation by immunofluorescent assay (IFA) or Western blot. Requiring a second positive EIA could harm the sensitivity of the overall testing scheme; a positive rapid or POC EIA should be considered equivalent to a laboratory-based EIA as a screening test. This recommendation is not based on direct trials but on the operational characteristics of the rapid tests as sufficiently similar to existing conventional EIAs to be treated as equivalent for the purpose of confirmatory testing *(141, 142)*.

There is significant interest in the use of a second, different rapid test as a sufficient confirmatory method in some settings. Such a scheme has been modeled for cost-effectiveness, even recommended, but not extensively studied in practice *(143–145)*. Results of pilot projects using varying strategies for accelerated confirmatory testing have been encouraging *(146–148)*.

Ideally, a strategy for confirmatory testing should use rapid tests with different antigen coverage. Currently approved methods use similar antigen mixes (Table 8-1). The Trinity Uni-Gold and MedMira Reveal add gp 120 to the gp 41 used by OraQuick and Multispot. No study has examined confirmatory testing using currently approved methods.

The use of a second, independent rapid test for confirmation should be assessed in systematic controlled trials. The value of rapid confirmation will vary with the prevalence of the disease in the target population.

TRICHOMONAS VAGINALIS VAGINITIS

Trichomonas vaginalis is a protozoan parasite that is 1 of the 3 most common causes of infectious vaginitis. The most commonly used diagnostic tool has been observation of motile trophozoites of this parasite in vaginal discharge; however, there is ample literature that this method is not very sensitive and is thoroughly dependent on the viability of the organism. The trophozoites are very fragile and will no longer be motile within 1–2 h or less, hence necessitating a POC test. However, it is not a very sensitive assay. Culture is the gold standard; however, this is not a rapid or POC test. Most recently, there have been some additions to the testing marketplace of assays for the detection of *T. vaginalis*, along with assays for bacterial vaginosis (BV) and *Candida*, the other 2 agents of vaginitis. The Affirm probe (Becton Dickinson, Sparks, MD, USA) can be used to detect all 3 entities with very high sensitivity in ~1 h after specimen collection. It, however, is a moderately complex test and not readily performed in every office situation. Immunochromatographic assays that do lend themselves easily to POC testing are becoming available for the detection of *T. vaginalis*.

Is there a clinical need for POC testing for the presence of *T. vaginalis* in the diagnosis of vaginitis? Will direct examinations for agents of vaginitis, delivered in POC format, achieve high enough sensitivity for routine care?

Guideline 129. *We would recommend POCT, given the fair evidence to support the procedure. Wet-mount examination of vaginal discharge for the presence of* T. vaginalis *is an insensitive procedure and should be replaced with newer methods that provide a higher level of sensitivity. Newer methods have been developed for POC that may result in better outcomes. Additionally, outcome data will need to be based on more sensitive tests that are used in pregnancy to establish an association with preterm labor/delivery and low-birth-weight deliveries.*

Strength/consensus of recommendation: B

Level of evidence: III

The literature remains controversial about the association of *T. vaginalis* with complications of pregnancy, including lower birth weight and premature labor and delivery. However the sensitivity of the methods used to document the infection in part limits the results obtained in some studies and explains the lack of consensus on any association. The literature demonstrates a 49%–89% sensitivity of the wet-mount examination in detection of *T. vaginalis*. Only a 15- to 20-min survival time has been documented when specimens are sent to laboratories on swabs. Unless the specimen can be examined immediately, the sensitivity is even lower. In studies that include more sensitive methods, such as culture for detection, the association of *T. vaginalis* with preterm labor is significant; with wet mount, the association is not always proven to be significant. There is some clinical evidence that treatment of *T. vaginalis* with metronidazole during pregnancy may have worse outcomes than not treating; however, the antibiotic appears to be the reason for this and not the elimination of the parasite.

More recently, there has been an association of *T. vaginalis* and HIV, as well as increasing reports of possible associations of *T. vaginalis* and cervical cancer. These are also in the area of controversial correlations that will require better methods of detection and more outcome studies to confirm any relationships *(149–179)*.

CANDIDA VULVOVAGINITIS

There are 3 infectious agents responsible for more than 95% of the infectious causes of vaginitis. One of these is the yeast *Candida*, most often *Candida albicans*. Yeast vaginitis is usually diagnosed clinically by the presence of a distinctive discharge, which tends to be very thick and "cheesy" in appearance and is seen in women with symptoms of extreme pruritus after use of antibiotics or other agents that would change the normal vaginal flora and increase colonization of the yeast. Laboratory or office diagnosis of yeast vaginitis is usually made by means of examination of a wet-mount preparation of the discharge. Many authors, such as Handa and Stice *(180)*, have, however, cautioned against the use of a wet mount alone because of its low sensitivity, ~61%. They and others suggest that culture is needed for a definitive diagnosis. The latter, of course, is not a rapid test. Plourd *(181)* reported a 50%–70% sensitivity of wet-mount examinations in the diagnosis of yeast vaginitis. The Affirm probe test (Becton Dickinson) does afford a 45-min test for the detection of the 3 most common agents of vaginitis, including *C. albicans*. In a recent study, 11% of samples tested were positive by the Affirm probe as compared to only 7% by wet-mount observation; however, this is ranked as a moderately to highly complex test and probably not appropriate for POCT *(182)*.

Are there POC tests that are available for the detection of yeasts in vaginal samples as cause of vaginitis, and are these tests necessary for good patient outcomes?

Guideline 130. *No recommendation for or against the need for a POC test for the detection of yeast in a vaginal specimen. This is because there are no good studies that provide information that a rapid test for the diagnosis that is more sensitive than the wet-mount tests presently available would provide a better clinical outcome than what is presently obtained.*

Strength/consensus of recommendation: I

Level of evidence: III

There is an article in 2003 by Watson and Bond *(183)* that attempts to address the need for rapid and correct diagnosis of yeast in cases of vaginitis so that appropriate antibiotics are used. It is not truly an outcomes study but comes closest to this.

BACTERIAL VAGINOSIS

There are 3 main infectious disease causes for the clinical syndrome of vaginitis: *Candida* sp., *T. vaginalis*, and the entity referred to as BV. The diagnosis of all 3 is often made with a combination of clinical criteria and observations of a wet-mount preparation of the vaginal discharge for the presence of yeast (representative of *Candida* sp.), motile trichomonads (*T. vaginalis*), or the presence of "clue cells." The latter are epithelial cells that are studded with coccobacillary bacteria, suggestive of organisms including *Gardnerella vaginalis* or *Mobiluncus* sp. BV is a result of a change in the normal vaginal flora from one of predominantly *Lactobacillus* sp. to one in which anaerobic gram-negative curved rods (*Mobiluncus* sp.) and other anaerobes predominate. *G. vaginalis*, long considered the cause of BV, is now known to be possibly involved but not the single cause. Consequently, culture specifically for the presence of *G. vaginalis* should not be used as a method of diagnosis. What is used is what is referred to as a "scored gram stain" of the vaginal discharge to discern the "flora" that is present in the vagina of the patient.

This scored gram stain *(184)*, in combination with clinical criteria *(185)*, has become widely used. The gram stain is read and quantities of organisms consistent with *Lactobacillus*, curved rods, and coccobacillary organisms are tabulated. Points are designated for each, and a "score" of 1–3 (no curved rods or coccobacillary organisms and mainly *Lactobacillus* sp. seen) is interpreted as consistent with normal vaginal flora; scores above 7 are considered consistent with BV. Scores of 4, 5, and 6 are in an intermediate category, representing a wide variety of conditions, 1 of which may be a transitional time before BV. Tam et al. *(186)* and Mota et al. *(187)* found that use of this method provided a rapid and cost-effective approach to the screening of BV patients. The sensitivity of this method in a group of 51 pregnant women was 91% vs clinical criteria alone that had a 46% sensitivity in the first study, and in the second study, out of 74 examinations, BV was diagnosed in 31% by the scored gram stain as compared to 28% by

the clinical criteria. The scored gram stain was felt to be more objective and rapid, even if the differences were not dramatic. Interobserver reliability was confirmed by Joesoef et al. *(188)* in a study in 1991 using the scored gram stain as the method of diagnosis on 225 pairs of duplicate gram-stained slides in Jakarta, Indonesia, and the University of Washington, Seattle. Correct slide preparation was emphasized for maximally good results. Experience of the individuals who read the scored gram stains is most beneficial to the effectiveness of the results. Whether this could be considered as a POCT is a question that needs to be answered.

How accurate is the diagnosis of BV using clinical criteria alone or with a wet-mount observation?

Guideline 131. *We would suggest that the literature supports the lack of sensitivity and accuracy of clinical criteria alone for the diagnosis of BV. Therefore, additional testing, including POCT, may be necessary to investigate in the future.*

Strength/consensus of recommendation: B

Level of evidence: II

What is the association of BV with complications of pregnancy, such as preterm birth?

Guideline 132. *We would recommend that clinicians routinely provide POCT for pregnant patients for the rapid diagnosis of BV because of its association with preterm birth.*

Strength/consensus of recommendation: B

Level of evidence: II

Can a POCT that involves no wet-mount observation be used to detect BV?

Guideline 133. *It would be of benefit to have other assays available that do not rely on direct wet mount or gram stain evaluations of vaginal discharge. These would potentially provide assays that could be used as POCT, especially in the pregnant woman. Some literature is available to support the use of non–wet-mount examination tests to make a laboratory diagnosis of BV. However, there are no outcomes studies using any other assays other than direct observational examination tests such as wet mounts or gram stains.*

Strength/consensus of recommendation: I

In 2002, a review of the literature since 1976 was published by the CDC Bacterial Vaginosis working group evaluating outcomes of treatment in BV positive-testing pregnant women *(189)*. The suggestion in the review was that there appeared to be a causal association between prematurity and BV, and the group felt that there was sufficient evidence to support the treatment of BV to prevent BV-associated preterm births. In addition, Hillier et al. *(190)* detected a higher rate of preterm births in women who tested positive for BV at 23–26 weeks' gestation compared to women that were negative for BV. There are opposing views about whether there is an association between BV and preterm births. A British study in 2004 has not found any relationship *(191)*. Kekki et al. *(192)* tried to determine a risk-benefit to screening and treating pregnant women at low risk for BV. Their study did not uncover a cost benefit to early screening programs, but they concluded that overall healthcare was improved when the women were screened and appropriate treatment for BV was administered.

A new rapid diagnostic kit called FemExam (CooperSurgical, Inc., Trumbull, CT, USA) was examined in Gambia, and results have been published. The Fem cards had a sensitivity of >90% as compared to clinical criteria for the diagnosis of BV. This test may afford a rapid POCT test that is less subjective than wet-mount preparations *(193)*. Use of the Affirm VPIII assay, a probe assay for the detection of *Candida* sp., *T. vaginalis*, and the entity BV, has been reviewed in the literature. For the diagnosis of BV, detection of high levels of *G. vaginalis* DNA appears to provide a rapid test that correlates well with scored gram stain and other methods to detect BV *(194, 195)*. It is listed as a moderately to highly complex assay and as such would require expertise and quality-control monitoring, as would any such assay to be used as a POCT assay. Newer EIA or lateral flow assays for the detection of BV have only recently been introduced into the clinical microbiology arena, and it will be some time before any outcome studies are done to determine their true efficacy and value in making a rapid diagnosis of BV.

REFERENCES

1. King D, Luna V, Cannons A, Cattani J, Amuso P. Performance assessment of three commercial assays for the direct detection of B. anthracis spores. J Clin Microbiol 2003;41:3454–5.
2. Kiratisin P, Fukuda CD, Wong A, et al. Large scale screening of nasal swabs for B. anthracis: descriptive summary and discussion of NIH's experience. J Clin Microbiol 2002;40:3012–5.
3. Anderson A, Eisold JF. Anthrax attack at the U.S. Capitol: Front Line thoughts. AAOHN J 2002;50:170–3.
4. Byrne KM, Fruchey IR, Bailey AM, Emanuel PA. Automated biological agents testing systems. Expert Rev Mol Diagn 2003; 3:759–68.
5. Liu RH, Yang J, Lenigk R, Bonanno J, Grodzinski P. Self-contained fully integrated biochip for sample prep, PCR and DNA microarray detection. Anal Chem 2004;76:1824–31.
6. Zuiderwijk M, Tanke HJ, Sam Niedbala R, Corstjens PL. An amplification-free hybridization based DNA assay to detect S. pneumoniae utilizing the up-converting phosphor technology. Clin Biochem 2003;36:401–3.
7. French DJ, Archard CL, Anderson MT, McDowell DG. Ultra-rapid DNA analysis using HyBeacon and direct PCR amplification from saliva. Mol Cell Probes 2002;16:319–26.

8. Lyerly DM, Neville LM, Evans DT, Fill J, Allen S, Greene W, et al. Multicenter evaluation of the Clostridium difficile TOX A/B TEST. J Clin Microbiol 1998;36:184–90.
9. Snell H, Ramos M, Longo S, John M, Hussain Z. Performance of the TechLab C. DIFF CHEK-60 enzyme immunoassay (EIA) in combination with the C. difficile Tox A/B II EIA kit, the Triage C. difficile panel immunoassay, and a cytotoxin assay for diagnosis of Clostridium difficile-associated diarrhea. J Clin Microbiol 2004; 42:4863–5.
10. Gartner BC, Hess RD, Bandt D, Kruse A, Rethwilm A, Roemer K, et al. Evaluation of four commercially available Epstein-Barr virus enzyme immunoassays with an immunofluorescence assay as the reference method. Clin Diagn Lab Immunol 2003; 10:78–82.
11. Rea TD, Ashley RL, Russo JE, Buchwald DS. A systematic study of Epstein-Barr virus serologic assays following acute infection. Am J Clin Pathol 2002;117:156–61.
12. Fung MK, Mordarski KT, Bader SA, Gronowski AM. Evaluation of the Wampole Laboratories ELISA-based assay for Epstein-Barr virus serology. Clin Chim Acta 2002;319:43–8.
13. Gomez MC, Nieto JA, Escribano MA. Evaluation of two slide agglutination tests and a novel immunochromatographic assay for rapid diagnosis of infectious mononucleosis. Clin Diagn Lab Immunol 2000;7:840–1.
14. Bruu AL, Hjetland R, Holter E, Mortensen L, Natas O, Petterson W, et al. Evaluation of 12 commercial tests for detection of Epstein-Barr virus-specific and heterophile antibodies. Clin Diagn Lab Immunol 2000;7:451–6.
15. Elgh F, Linderholm M. Evaluation of six commercially available kits using purified heterophile antigen for the rapid diagnosis of infectious mononucleosis compared with Epstein-Barr virus-specific serology. Clin Diagn Virol 1996;7:17–21.
16. Gerber MA, Shapiro ED, Ryan RW, Bell GL. Evaluations of enzyme-linked immunosorbent assay procedure for determining specific Epstein-Barr virus serology and of rapid test kits for diagnosis for infectious mononucleosis. J Clin Microbiol 1996; 34:3240–1.
17. Schwartz RH. Comparison of three rapid, in-office mononucleosis tests. Pediatr Infect Dis J 1999;18:80–1.
18. Rogers R, Windust A, Gregory J. Evaluation of a novel dry latex preparation for demonstration of infectious mononucleosis heterophile antibody in comparison with three established tests. J Clin Microbiol 1999;37:95–8.
19. Mabley D, Peeling, RW, Perkins MD. Rapid and simple point of care diagnostics for STIs. Sex Transm Infect 2001;77:397–401.
20. Mabey D, Peeling RW. Rapid diagnostic tests for sexually transmitted infection. IPPF Med Bull 2002;36:1–3.
21. Vickerman P, Watts C, Alary M, Mabey D, Peeling RW. Sensitivity requirements for point of care diagnosis of Chlamydia trachomatis and Neisseria gonorrhoeae in women. Sex Transm Infect 2003;79:363–8.
22. Ford CA, Viadro CL, Miller WC. Testing for chlamydial and gonorrheal infections outside of clinic settings. Sex Transm Dis 2004;31:38–51.
23. Swain GR, McDonald RA, Pfister JR, Gradus MS, Sedmak GV, Singh A. Decision analysis: point-of-care chlamydia testing vs. laboratory based methods. Clin Med Res 2004;2:29–35.
24. General consensus from the National Chlamydia Laboratory Committee, Association of Public Health Laboratories: recommendations for single use devices for point of care chlamydia tests. http://www.APHL.org\docs\NCCPOC.pdf (Accessed July 2004).
25. MMWR Recommendations and Reports. Screening tests to detect Chlamydia trachomatis and Neisseria gonorrhoeae infections: 2002. MMWR Morb Mortal Wkly Rep 2002;51:1–27.
26. Chapin KC, Blake P, Wilson CD. Performance characteristics and utilization of rapid antigen test, DNA probe, and culture for detection of group A streptococci in an acute care clinic. J Clin Microbiol 2002;40:4207–10.
27. McIsaac WJ, Kellner JD, Aufricht P, Vanjaka A, Low DE. Empirical validation of guidelines for the management of pharyngitis in children and adults. JAMA 2004;291:1587–95.
28. Clegg HW, Dallas SD, Roddey OF, Martin ES, Swetenburg RL, Koonce EW, et al.; Presbyterian Pediatric Research Group. Extrapharyngeal group A streptococcus infection: diagnostic accuracy and utility of rapid antigen testing. Pediatr Infect Dis J 2003;22:726–31.
29. Hart AP, Buck LL, Morgan S, Saverio S, McLaughlin JC. A comparison of the BioStar Strep A OIA rapid antigen assay, group A Selective Strep Agar (ssA), and Todd-Hewitt broth cultures for the detection of group A streptococcus in an outpatient family practice setting. Diagn Microbiol Infect Dis 1997;29:139–45.
30. Heelan JS, Wilbur S, Depetris G, Letourneau C. Rapid antigen testing for group A streptococcus by DNA probe. Diagn Microbiol Infect Dis 1996;24:65–9.
31. Kawakami S, Ono Y, Yanagawa Y, Miyazawa Y. [Basic and clinical evaluation of the new rapid diagnostic kit for detecting group A streptococci with the immunochromatographical method] [article in Japanese]. Rinsho Biseibutshu Jinsoku Shindan Kenkyukai Shi 2003;14:9–16.
32. Armengol CE, Schlager TA, Hendley JO. Sensitivity of a rapid antigen detection test for group A streptococci in a private pediatric office setting: answering the Red Book's request for validation. Pediatrics 2004;113:924–6.
33. Santos O, Weckx LL, Pignatari AC, Pignatari SS. Detection of group A β-hemolytic streptococcus employing three different detection methods: culture, rapid antigen detecting test, and molecular assay. Braz J Infect Dis 2003;7:297–300.
34. Neuner JM, Hamel MB, Phillips RS, Bona K, Aronson MD. Diagnosis and management of adults with pharyngitis: a cost-effectiveness analysis. Ann Intern Med 2003;139:113–22.
35. Gieseker KE, Roe MH, MacKenzie T, Todd JK. Evaluating the American Academy of Pediatrics diagnostic standard for Streptococcus pyogenes pharyngitis: backup culture versus repeat rapid antigen testing. Pediatrics 2003;111:e666–70.
36. Uhl JR, Adamson SC, Vetter EA, Schleck CD, Harmsen WS, Iverson LK, et al. Comparison of LightCycler PCR, rapid antigen immunoassay, and culture for detection of group A streptococci from throat swabs. J Clin Microbiol 2003;41:242–9.
37. Dale JC, Novak R, Higgens P, Wahl E. Testing for group a streptococci. Arch Pathol Lab Med 2002;126:1467–70.
38. Gieseker KE, Mackenzie T, Roe MH, Todd JK. Comparison of two rapid Streptococcus pyogenes diagnostic tests with a rigorous culture standard. Pediatr Infect Dis J 2002;21:922–7.
39. Sheeler RD, Houston MS, Radke S, Dale JC, Adamson SC. Accuracy of rapid strep testing in patients who have had recent streptococcal pharyngitis. J Am Board Fam Pract 2002; 15:261–5.
40. Bisno AL, Peter GS, Kaplan EL. Diagnosis of strep throat in adults: are clinical criteria really good enough? Clin Infect Dis 2002;35:126–9.
41. Dimatteo LA, Lowenstein SR, Brimhall B, Reiquam W, Gonzales R. The relationship between the clinical features of pharyngitis and the sensitivity of a rapid antigen test: evidence of spectrum bias. Ann Emerg Med 2001;38:648–52.

42. Mayes T, Pichichero ME. Are follow-up throat cultures necessary when rapid antigen detection tests are negative for group A streptococci? Clin Pediatr (Phila) 2001;40:191–5.
43. Kurtz B, Kurtz M, Roe M, Todd J. Importance of inoculum size and sampling effect in rapid antigen detection for diagnosis of Streptococcus pyogenes pharyngitis. J Clin Microbiol 2000; 38:279–81.
44. Pitetti RD, Drenning SD, Wald ER. Evaluation of a new rapid antigen detection kit for group A β-hemolytic streptococci. Pediatr Emerg Care 1998;14:396–8.
45. Schlager TA, Hayden GA, Woods WA, Dudley SM, Hendley JO. Optical immunoassay for rapid detection of group A β-hemolytic streptococci: should culture be replaced? Arch Pediatr Adolesc Med 1996;150:245–8.
46. Roe M, Kishiyama C, Davidson K, Schaefer L, Todd J. Comparison of BioStar Strep A OIA optical immune assay, Abbott TestPack Plus Strep A, and culture with selective media for diagnosis of group A streptococcal pharyngitis. J Clin Microbiol 1995;33:1551–3.
47. Joslyn SA, Hoekstra GL, Sutherland JE. Rapid antigen detection testing in diagnosing group A β-hemolytic streptococcal pharyngitis. J Am Board Fam Pract 1995;8:177–82.
48. Dale JC, Vetter EA, Contezac JM, Iverson LK, Wollan PC, Cockerill FR 3rd. Evaluation of two rapid antigen assays, BioStar Strep A OIA and Pacific Biotech CARDS O.S., and culture for detection of group A streptococci in throat swabs. J Clin Microbiol 1994;32:2698–701.
49. Ehrlich TP, Schwartz RH, Wientzen R, Thorne MM. Comparison of an immunochromatographic method for rapid identification of group A streptococcal antigen with culture method. Arch Fam Med 1993;2:866–9.
50. Majeed HA, al-Doussary L, Moussa MM, Yusuf AR, Suliman AH. Office diagnosis and management of group A streptococcal pharyngitis employing the rapid antigen detecting test: a 1-year prospective study of reliability and cost in primary care centres. Ann Trop Paediatr 1993;13:65–72.
51. Anhalt JP, Heiter BJ, Naumovitz DW, Bourbeau PP. Comparison of three methods for detection of group A streptococci in throat swabs. J Clin Microbiol 1992;30:2135–8.
52. Tenjarla G, Kumar A, Dyke JW. TestPack Strep A kit for the rapid detection of group A streptococci on 11,088 throat swabs in a clinical pathology laboratory. Am J Clin Pathol 1991;96:759–61.
53. Stillstrom J, Schwan A, Bjorklind A. Streptococcal throat infection: calculation of test standards and a comparison between an antigen detection test and culture. Scand J Prim Health Care 1991;9:149–54.
54. Meier FA, Howland J, Johnson J, Poisson R. Effects of a rapid antigen test for group A streptococcal pharyngitis on physician prescribing and antibiotic costs. Arch Intern Med 1990; 150:1696–700.
55. Kaplan EL, Reid HF, Johnson DR, Kunde CA. Rapid antigen detection in the diagnosis of group A streptococcal pyoderma: influence of a "learning curve effect" on sensitivity and specificity. Pediatr Infect Dis J 1989;8:591–3.
56. Kaplan EL. Rapid detection of group A streptococcal antigen for the clinician and the epidemiologist: accurate? cost-effective? useful? N Z Med J 1988;101:401–2.
57. Berwick DM, Gorss E, Macone AB, O'Rourke EJ, Goldmann DA. Impact of rapid antigen tests for group A streptococcal pharyngitis on physician use of antibiotics and throat cultures. Pediatr Infect Dis J 1987;6:1095–102.
58. Gerber MA, Markowitz M. Management of streptococcal pharyngitis reconsidered. Pediatr Infect Dis 1985;4:518–26.
59. Gerber MA, Markowitz M. Management of streptococcal pharyngitis reconsidered. Pediatr Infect Dis 1985;4:518–26.
60. Otero JR, Reyes S, Noriega AR. Rapid diagnosis of group A streptococcal antigen extracted directly from swabs by an enzymatic procedure and used to detect pharyngitis. J Clin Microbiol 1983; 18:318–20.
61. Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease: a public health perspective. MMWR Morb Mortal Wkly Rep 1996;45:1–24.
62. Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC. MMWR Morb Mortal Wkly Rep 2002;51:1–28.
63. Centers for Disease Control and Prevention. Laboratory practices for prenatal group B streptococcal screening: United States, 2003. MMWR Morb Mortal Wkly Rep 2004;53:506–9.
64. Samadi R, Stek A, Greenspoon JS. Evaluation of a rapid optical immunoassay-based test for group B streptococcus colonization in intrapartum patients. J Matern Fetal Med 2001;10:203–8.
65. Auvray C, Decaux J, Deliege R, Delesalle S, Reveil JC. Value of a rapid screening technique for vaginal carriage of group B streptococcus during high-risk pregnancies. Pathol Biol 1999;47:494–6.
66. Baker CJ. Inadequacy of rapid immunoassays for detection of group B streptococcal carriers. Obstet Gynecol 1996;88:51–5.
67. Carroll KC, Ballou D, Varner M, Chun H, Traver R, Salyer J. Rapid detection of group B streptococcal colonization of the genital tract by a commercial optical immunoassay. Eur J Clin Microbiol Infect Dis 1996;15:206–10.
68. Park CH, Ruprai D, Vandel NM, Hixon DL, Mecklenburg FE. Rapid detection of group B streptococcal antigen from vaginal specimens using a new optical immunoassay technique. Diagn Microbiol Infect Dis 1996;24:125–8.
69. Nguyen TM, Gauthier DW, Myles TD, Nuwayhid BS, Viana MA, Schreckenberger PC. Detection of group B streptococcus: comparison of an optical immunoassay with direct plating and broth-enhanced culture methods. J Matern Fetal Med 1998;7:172–6.
70. Thinkhamrop J, Limpongsanurak S, Festin MR, Daly S, Schuchat A, Lumbiganon P, et al. Infections in international pregnancy study: performance of the optical immunoassay test for detection of group B streptococcus. J Clin Microbiol 2003;41:5288–90.
71. Haberland CA, Benitz WE, Sanders GD, Pietzsch JB, Yamada S, Nguyen L, et al. Perinatal screening for group B streptococci: cost benefit analysis of rapid polymerase chain reaction. Pediatrics 2002;110:471–80.
72. Isada NB, Grossman JH. A rapid screening test for the diagnosis of endocervical group B streptococci in pregnancy: microbiologic results and clinical outcome. Obstet Gynecol 1987;70:139–41.
73. Ke D, Bergeron MG. Molecular methods for rapid detection of group B streptococci. Expert Rev Mol Diagn 2001;1:175–83.
74. Reardon EP, Bonle MA, Luther ER, Wort AJ, Bent J, Swift M. Evaluation of a rapid method for the detection of vaginal group B streptococci in women in labor. Am J Obstet Gynecol 1984; 148:575–8.
75. Wang E, Rochardson H. A rapid method for detection of group B streptococcal colonization: testing at the bedside. Obstet Gynecol 1990;76:882–5.
76. Artz LA, Kempf VA, Autenrieth IB. Rapid screening of S. agalactiae in vaginal specimens for pregnant women by fluorescent in situ hybridization. J Clin Microbiol 2003;41:2170–3.
77. Williams-Bouyer N, Resiner BS, Woods GL. Comparison of genprobe AccuProbe group B streptococcus culture identification test with conventional culture for the detection of group B streptococci in broth cultures of vaginal-rectal specimens from pregnant women. Diagn Microbiol Infect Dis 2000;36:159–62.

78. Lehmann FS, Beglinger C. Current role of Helicobacter pylori stool tests. Digestion 2003;68:119–23.
79. Delaney BC, Holder RL, Allan TF, Kenkre JE, Hobbs FD. A comparison of Bayesian and maximum likelihood methods to determine the performance of a point of care test for Helicobacter pylori in the office setting. Med Decis Making 2003;23:21–30.
80. Conwell CF, Lyell R, Rodney WM. Prevalence of Helicobacter pylori in family practice patients with refractory dyspepsia: a comparison of tests available in the office. J Fam Pract 1995;41:245–9.
81. Glupczynski Y. Microbiological and serological diagnostic tests for Helicobacter pylori: an overview. Acta Gastroenterol Belg 1998;61:321–6.
82. Basset C, Holton J, Ricci C, Gatta L, Tampieri A, Perna F, et al. Review article: diagnosis and treatment of Helicobacter: a 2002 updated review. Aliment Pharmacol Ther 2003;17:89–97.
83. Opekun AR, Abdalla N, Sutton FM, Hammoud F, Kuo GM, Torres E, et al. Urea breath testing and analysis in the primary care office. J Fam Pract 2002;51:1030–2.
84. Weijnen CF, Hendriks HA, Hoes AW, Verweij WM, Verheij TJ, de Wit NJ. New immunoassay for the detection of Helicobacter pylori infection compared with urease test, 13C breath test and histology: validation in the primary care setting. J Microbiol Methods 2001;46:235–40.
85. Fujisawa T, Kaneko T, Kumagai T, Akamatsu T, Katsuyama T, Kiyosawa K, et al. Evaluation of urinary rapid test for Helicobacter pylori in general practice. J Clin Lab Anal 2001;15:154–9.
86. Hicks JM, Haeckel R, Price CP, Lewandrowski K, Wu AH. Recommendations and opinions for the use of point-of-care testing for hospitals and primary care: summary of a 1999 symposium. Clin Chim Acta 2001;303:1–17.
87. Duggan AE, Elliott C, Logan RF. Testing for Helicobacter pylori infection: validation and diagnostic yield of a near patient test in primary care. BMJ 1999;319:1236–9.
88. Klein PD, Malaty HM, Martin RF, Graham KS, Genta RM, Graham DY. Noninvasive detection of Helicobacter pylori infection in clinical practice: the 13C urea breath test. Am J Gastroenterol 1996;91:690–4.
89. Ladabaum U, Fendrick AM, Glidden D, Scheiman JM. Helicobacter pylori test-and-treat intervention compared to usual care in primary care patients with suspected peptic ulcer disease in the United States. Am J Gastroenterol 2002;97:3007–14.
90. Noyola DE, Demmler GJ. Effect of rapid diagnosis on management of influenza infections. Pediatr Infect Dis J 2000;19:303–7.
91. Harnden A, Brueggeman A, Shepperd S, White J, Hayward A, Zambon M, et al. Near patient testing for influenza in children in primary care: comparison with laboratory test. BMJ 2003;326:480.
92. Church DL, Davies HD, Mitton C, Semeniuk H, Logue M, Maxwell C, et al. Clinical and economic evaluation of rapid influenza A virus testing in nursing homes in Calgary, Canada. Clin Infect Dis 2003;34:790–5.
93. Bonner AB, Monroe KW, Talley LI, Klasner AE, Kimberlin DW. Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: results of a randomized, prospective, controlled trial. Pediatrics 2003;112:363–7.
94. World Health Organization. WHO recommendations on the use of rapid testing for influenza diagnosis. http:// www.who.int/entity/csr/disease/avian_influenza/guidelines/RapidTestInfluenza_web.pdf (Accessed September 2005).
95. Weigl JA, Puppe W, Schmitt HJ. Can respiratory syncytial virus etiology be diagnosed clinically? a hospital-based case-control study in children under two years of age. Eur J Epidemiol 2003;18:431–9.
96. Casiano-Colon AE, Hulbert BB, Mayer TK, Walsh EE, Falsey AR. Lack of sensitivity of rapid antigen tests for the diagnosis of respiratory syncytial virus infection in adults. J Clin Virol 2003;28:169–74.
97. Woo PC, Chiu S, Seto W, Peiris M. Cost-effectiveness of rapid diagnosis of viral respiratory tract infections in pediatric patients. J Clin Microbiol 1997;35:1579–81.
98. Barenfanger J, Drake C, Leon N, Mueller T, Troutt T. Clinical and financial benefits of rapid detection of respiratory viruses: an outcomes study. J Clin Microbiol 2000;38:2824–8.
99. Abels S, Nadal D, Stroehle A, Bossart W. Reliable detection of respiratory syncytial virus infection in children for adequate hospital infection control management. J Clin Microbiol 2001; 39:3135–9.
100. Mackie PL, Joannidis PA, Beattie J. Evaluation of an acute point-of-care system screening for respiratory syncytial virus infection. J Hosp Infect 2001;48:66–71.
101. Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report. Washington, DC: US Department of Health and Human Services, 2002:1–48.[2]
102. Paltiel AD, Weinstein MC, Kimmel AD, Seage GR 3rd, Losina E, Zhang H, et al. Expanded screening for HIV in the United States: an analysis of cost-effectiveness. N Engl J Med 2005;352:586–95.
103. Beckwith CG, Flanigan TP, del Rio C, Simmons E, Wing EJ, Carpenter CJ, et al. It is time to implement routine, not risk-based, HIV testing. Clin Infect Dis 2005; 40:1037–40.
104. Rothman RE, Ketlogetswe KS, Dolan T, Wyer PC, Kelen GD. Preventive care in the emergency department: should emergency departments conduct routine HIV screening? a systematic review. Acad Emerg Med 2003;10:278–85.
105. Irwin K, Olivo N, Schable CA, Weber JT, Janssen R, Ernst J, and the CDC-Bronx-Lebanon HIV Serosurvey Team. Performance characteristics of a rapid HIV antibody assay in a hospital with a high prevalence of HIV infection. Ann Intern Med 1996; 125:471–5.
106. Spielberg F, Kassler WJ. Rapid testing for HIV antibody: a technology whose time has come. Ann Intern Med 1996;125:509–11.
107. US Food and Drug Administration, Center for Biologics Evaluation and Research. Summary of Safety and Effectiveness, CBER: Oraquick Rapid HIV-1. http://www.fda.gov/cber/pmasumm/P010047S.pdf (Accessed April 2005).
108. US Food and Drug Administration, Center for Biologics Evaluation and Research.Summary of Safety and Effectiveness, CBER. Unigold Recombigen HIV. http://www.fda.gov/cber/pmasumm/ P0300250S.pdf (Accessed April 2005).
109. US Food and Drug Administration, Center for Biologics Evaluation and Research. Summary of Safety and Effectiveness, CBER. MedMira Reveal Rapid HIV-1 Antibody Test. http://www.fda.gov/ cber/pmasumm/P000023S.htm (Accessed March 2005).
110. US Food and Drug Administration, Center for Biologics Evaluation and Research. Summary of Safety and Effectiveness, CBER. Bio-Rad Multispot HIV-1/HIV-2 Rapid Test. http://www.fda.gov/cber/ pmasumm/P040046S.pdf (Accessed April 2005).
111. Bulterys M, Jamieson DJ, O'Sullivan MJ, Cohen MH, Maupin R, Nesheim S, et al. Rapid HIV-1 testing during labor. JAMA 2004;292:219–23.
112. Reynolds SJ, Ndongala LM, Luo CC, Mwandagalirwa K, Losoma AJ, Mwamba KJ, et al. Evaluation of a rapid test for the detection of antibodies to human immunodeficiency virus type 1 and 2 in the setting of multiple transmitted viral subtypes. Int J STD AIDS 2002;13:171–3.

113. Holguin A. Evaluation of three rapid tests for detection of antibodies to HIV-1 non-B subtypes. J Virol Methods 2004;115:105–7.
114. Granade TC, Parekh BS, Phillips SK, McDougal JS. Performance of the Oraquick and Hema-strip rapid HIV antibody detection assays by non-laboratorians. J Clin Virol 2004;30:229–32.
115. Centers for Disease Control and Prevention. Quality Assurance Guidelines for Testing Using the OraQuick Rapid HIV-1 Antibody Test. Washington, DC: US Department of Health and Human Services, 2003.
116. O'Connell RJ, Merritt TM, Malia JA, VanCott TC, Dolan MJ, Zahwa H, et al. Performance of the OraQuick rapid antibody test in diagnosis of human immunodeficiency virus type 1 infection in patients with various levels of exposure to highly active antiretroviral therapy. J Clin Microbiol 2003;41:2153–5.
117. Melvin AJ, Alarcon J, Velasquez C, Rodriguez C, Piscoya J, Giraldo A, et al. Rapid HIV type 1 testing of women presenting in late pregnancy with unknown HIV status in Lima, Peru. AIDS Res Hum Retroviruses 2004;20:1046–52.
118. Malonza IM, Richardson BA, Kreiss JK, Bwayo JJ, John Stewart GC. The effect of rapid HIV-1 testing on uptake of perinatal HIV-1 interventions: a randomized clinical trial. AIDS 2003;17:113–8.
119. Dabis F, Bequet L, Ekouevi DK, Viho I, Rouet F, Horo A, et al.; ANRS 1201/1202 DITRAME PLUS Study Group. Acceptability and uptake of a package to prevent mother-to-child transmission using rapid HIV testing in Abidjan, Cote d'Ivoire. AIDS 2004;18:697–700.
120. Forsyth BWC, Barringer SR, Walls TA, Landry ML, Ferguson D, Tinghitella TJ, et al. Rapid HIV testing of women in labor: too long a delay. J Acquir Immune Defic Syndr 2004;35:151–4.
121. Cohn SE, Clark RA. Human immunodeficiency virus infections of women. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 6th ed. Philadelphia, PA: Elsevier, 2005:1617–38.
122. Zacharias NM, Athanassaki ID, Sangi-Haghpeykar H, Gardner MO. High false-positive rate of human immunodeficiency virus rapid serum screening in a predominantly Hispanic prenatal population. J Perinatol 2004;24:743–7.
123. King AM, Osterwalder JJ, Vernazza PL. A randomized prospective study to evaluate a rapid HIV-antibody assay in the management of cases of percutaneous exposure amongst health care workers. Swiss Med Wkly 2001;131:10–13.
124. Kallenborn JC, Price TG, Carrico RC, Davidson AB. Infect Control Hosp Epidemiol 2001;22:289–93.
125. Machado AA, Martinez R, Haikal AA, Rodriguez da Silva MCV. Advantages of the rapid HIV-1 test in occupational accidents with potentially contaminated material among health workers. Rev Inst Med Trop Sao Paulo 2001;43:199–201.
126. Puro V, Fraincisci D, Sighinolfi L,Civljak R, Belfori B, Deparis P, et al. Benefits of a rapid HIV test for evaluation of the source patient after occupational exposure of healthcare workers. J Hosp Infect 2004;57:179–82.
127. Centers for Disease Control and Prevention. HIV counseling and testing in publicly funded sites annual report, 1997 and 1998. http://www.cdc.gov/hiv/pubs/cts98.pdf (Accessed April 2005).
128. Kassler WJ, Dillon BA, Haley C, Jones WK, Goldman A. On-site, rapid HIV testing with same-day results and counseling. AIDS 1997;11:1045–51.
129. Kelen GD, Shahan JB, Quinn TC, and the Project Educate Work Group. Emergency department-based HIV screening and counseling: experience with rapid and standard serologic testing. Ann Emerg Med 1999;33:147–55.
130. Kendrick SR, Kroc KA, Withum D, Rydman RJ, Branson BM, Weinstein RA. Outcomes of offering rapid point-of-care HIV testing in a sexually transmitted disease clinic. J Acquir Immune Defic Syndr 2005;38:142–6.
131. Hutchinson AB, Corbie-Smith G, Thomas SB, Mohanan S, del Rio C. Understanding the patient's perspective of rapid and routine HIV testing in an inner-city urgent care center. AIDS Ed Prev 2004;16:101–14.
132. Peralta L, Constantine N, Griffin-Deeds B, Martin L, Ghalib K. Evaluation of youth preferences for rapid and innovative human immunodeficiency virus antibody tests. Arch Pediatr Adolesc Med 2001;155:838–43.
133. Liu A, Kilmars PH, Supawitkul S, Chaowanachan T, Yanpaisarn S, Chaikkumao S, et al. Rapid whole-blood finger-stick test for HIV antibody: performance and acceptability among women in northern Thailand. J Acquire Immune Defic Syndr 2003;33:194–8.
134. Galvan FH, Brooks RA, Leibowitz AA. Rapid HIV testing: issues in implementation. AIDS Patient Care STD 2004;18:15–8.
135. Rapid HIV test yields counseling, referrals. AIDS Alert 2003;18:127–8.
136. Rapid tests could mean trouble for ADAPS. AIDS Alert 2003;18:129–30.
137. Jones JP. In the culture of now: the arrival of the OraQuick rapid HIV test. Posit Aware 2004;15:35–6.
138. Spielberg F, Branson BM, Goldbaum GM, Lockhart D, Kurth A, Celum CL, et al. Overcoming barriers to HIV testing: preferences for new strategies among clients of a needle exchange, a sexually transmitted disease clinic, and sex venues for men who have sex with men. J Acquire Immune Defic Syndr 2003;32:318–28.
139. Spielberg F, Branson BM, Goldbaum GM, Kurth A, Wood RW. Designing an HIV counseling and testing program for bathhouses: the Seattle experience with strategies to improve acceptability. J Homosex 2003;44:203–20.
140. Spielberg F, Branson BM, Goldbaum GM, Lockhart D, Kurth A, Rossini A, et al. Choosing HIV counseling and testing strategies for outreach settings. J Acquire Immune Defic Syndr 2005;38:348–55.
141. Centers for Disease Control and Prevention. Notice to readers: protocols for confirmation of reactive rapid HIV tests. MMWR Morb Mortal Wkly Rep 2004;53:221–2.
142. Centers for Disease Control and Prevention. Quality assurance guidelines for testing using the OraQuick® Rapid HIV-1 Antibody Test [US Department of Health and Human Services Web site]. http://www.cdc.gov/hiv/rapid_testing/ materials/QA-Guide.htm (Accessed March 2005).
143. Wright RJ, Stringer JSA. Rapid testing strategies for HIV-1 serodiagnosis in high-prevalence African settings. Am J Prev Med 2004;27:42–8.
144. Ekwueme DU, Pinkerton SD, Holtgrave DR, Branson BM. Cost comparison of three HIV counseling and testing technologies. Am J Prev Med 2003;25:112–21.
145. World Health Organization. The importance of simple/rapid assays in HIV testing. Wkly Epidemiol Rec 1998;73:321–6. http://www.who.int/docstore/wer/pdf/1998/wer7342.pdf (Accessed April 2005).
146. Menard D, Mavolomade EE, Mandeng MJ, Talarmin A. Advantages of an alternative strategy based on consecutive HIV

serological tests for detection of HIV antibodies in Central African Republic. J Virol Methods 2003;111:129–34.
147. Urassa W, Nozohoor S, Jaffer S, Karama K, Mhalu F, Biberfeld G. Evaluation of an alternative confirmatory strategy for the diagnosis of HIV infection in Dar Es Salaam, Tanzania, based on simple rapid assays. J Virol Methods 2002;100: 115–20.
148. Rouet F, Ekouevi DK, Inwoley A, Chaix ML, Burgard M, Bequet L, et al. Field evaluation of a rapid human immunodeficiency virus (HIV) serial serologic testing algorithm for diagnosis and differentiation of HIV type 1 (HIV-1), HIV-2, and dual HIV-1-HIV-2 infections in West African pregnant women. J Clin Microbiol 2004;42: 4147–53.
149. Fernandez Limia O, Lantero MI, Betancourt A, de Armas E, Villoch A. Prevalence of Candida albicans and Trichomonas vaginalis in pregnant women in Havana City by an immunologic latex agglutination test. Med Gen Med 2004;6:50.
150. Pillay A, Lewis J, Ballard RC. Evaluation of Xenostrip-Tv, a rapid diagnostic test for Trichomonas vaginalis infection. J Clin Microbiol 2004;42:3853–6.
151. Adu-Sarkodie Y, Opoku BK, Danso KA, Weiss HA, Mabey D. Comparison of latex agglutination, wet preparation, and culture for the detection of Trichomonas vaginalis. Sex Transm Infect 2004;80:201–3.
152. Riggs MA, Klebanoff MA. Treatment of vaginal infections to prevent preterm birth: a meta-analysis. Clin Obstet Gynecol 2004;47:796–807.
153. Brown D. Clinical variability of bacterial vaginosis and trichomoniasis. J Reprod Med 2004;49:781–6.
154. Kigozi GG, Brahmbhatt H, Wabwire-Mangen F, Wawer MJ, Serwadda D, Sewankambo N, et al. Treatment of Trichomonas in pregnancy and adverse outcomes of pregnancy: a subanalysis of a randomized trial in Rakai, Uganda. Am J Obstet Gynecol 2003;189:1398–400.
155. Buchmayer S, Sparen P, Cnattingius S. Signs of infection in Pap smears and risk of adverse pregnancy outcome. Paediatr Perinat Epidemiol 2003;17:340–6.
156. Carey JC, Klebanoff MA, National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. What have we learned about vaginal infections and preterm birth? Semin Perinatol 2003;27:212–6.
157. Cram LF, Zapata MI, Toy EC, Baker B. Genitourinary infections and their association with preterm labor. Am Fam Physician 2002;65:241–8.
158. Huppert JS, Batteiger BE, Braslins P, Feldman JA, Hobbs MM, Sankey HZ, et al. Use of an immunochromatographic assay for rapid detection of Trichomonas vaginalis in vaginal specimens. J Clin Microbiol 2005;43:684–7.
159. Amindavaa O, Kristensen S, Pak CY, Khalzan D, Chultemsuren B, Randall AS, et al. Sexually transmitted infections among pregnant women attending antenatal clinics in Mongolia: potential impact on the Mongolian HIV epidemic. Int J STD AIDS 2005;16:153–7.
160. Blake DR, Duggan A, Joffe A. Use of spun urine to enhance detection of Trichomonas vaginalis in adolescent women. Arch Pediatr Adolesc Med 1999;153:1222–5.
161. Chesson HW, Blandford JM, Pinkerton SD. Estimates of the annual number and cost of new HIV infections among women attributable to trichomoniasis in the United States. Sex Transm Dis 2004;31:547–51.
162. Cotch MF, Pastorek JG 2nd, Nugent RP, Hillier SL, Gibbs RS, Martin DH, et al. Trichomonas vaginalis associated with low birth weight and preterm delivery: the Vaginal Infections and Prematurity Study Group. Sex Transm Dis 1997;24:353–60.
163. Diclemente RJ, Wingood GM, Crosby RA, Rose E, Lang D, Pillay A, et al. A descriptive analysis of STD prevalence among urban pregnant African-American teens: data from a pilot study. J Adolesc Health 2004; 34:376–83.
164. Donders GG. Treatment of sexually transmitted bacterial diseases in pregnant women. Drugs 2000;59:477–85.
165. Hardick J, Yang S, Lin S, Duncan D, Gaydos C. Use of the Roche LightCycler instrument in a real-time PCR for Trichomonas vaginalis in urine samples from females and males. J Clin Microbiol 2003;41:5619–22.
166. Kaydos SC, Swygard H, Wise SL, Sena AC, Leone PA, Miller WC, et al. Development and validation of a PCR-based enzyme-linked immunosorbent assay with urine for use in clinical research settings to detect Trichomonas vaginalis in women. J Clin Microbiol 2002;40:89–95.
167. Klebanoff MA, Carey JC, Hauth JC, Hillier SL,Nugent RP, Thom EA, et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic Trichomonas vaginalis infection. N Engl J Med 2001;345:487–93.
168. Knox J, Tabrizi SN, Miller P, Petoumenos K, Law M, Chen S, et al. Evaluation of self-collected samples in contrast to practitioner-collected samples for detection of Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis by polymerase chain reaction among women living in remote areas. Sex Transm Dis 2002;29:647–54.
169. Lawing LF, Hedges SR, Schwebke JR. Detection of trichomoniasis in vaginal and urine specimens from women by culture and PCR. J Clin Microbiol 2000;38:3585–8.
170. Leutscher P, Jensen JS, Hoffmann S, Berthelsen L, Ramarakoto CE, Ramaniraka V, et al. Sexually transmitted infections in rural Madagascar at an early stage of the HIV epidemic: a 6-month community-based follow-up study. Sex Transm Dis 2005;32: 150–5.
171. Magnus M, Clark R, Myers L, Farley T, Kissinger PJ. Trichomonas vaginalis among HIV-Infected women: are immune status or protease inhibitor use associated with subsequent T. vaginalis positivity? Sex Transm Dis 2003;30:839–43.
172. Mason PR, Fiori PL, Cappuccinelli P, Rappelli P, Gregson S. Seroepidemiology of Trichomonas vaginalis in rural women in Zimbabwe and patterns of association with HIV infection. Epidemiol Infect 2005;133:315–23.
173. Mayta H, Gilman RH, Calderon MM, Gottlieb A, Soto G, Tuero I. 18S Ribosomal DNA-based PCR for diagnosis of Trichomonas vaginalis. J Clin Microbiol 2000;38:2683–7.
174. Mohamed OA, Cohen CR, Kungu D, Kuyoh MA, Onyango JA, Bwayo JJ, et al. Urine proves a poor specimen for culture of Trichomonas vaginalis in women. Sex Transm Infect 2001; 77:78–9.
175. Nusbaum MR, Wallace RR, Slatt LM, Kondrad EC. Sexually transmitted infections and increased risk of co-infection with human immunodeficiency virus. J Am Osteopath Assoc 2004; 104:527–35.
176. Sayed el-Ahl SA, el-Wakil HS, Kamel NM, Mahmoud MS. A preliminary study on the relationship between Trichomonas vaginalis and cervical cancer in Egyptian women. J Egypt Soc Parasitol 2002;32:167–78.

177. Soper D. Trichomoniasis: under control or undercontrolled? Am J Obstet Gynecol 2004;190:281–90.
178. Sullivan EA, Koro S, Tabrizi S, Kaldor J, Poumerol G, Chen S, et al. Prevalence of sexually transmitted diseases and human immunodeficiency virus among women attending prenatal services in Apia, Samoa. Int J STD AIDS 2004;15:116–9.
179. van Der Schee C, van Belkum A, Zwijgers L, van Der Brugge E, O'Neill EL, Luijendijk A, et al. Improved diagnosis of Trichomonas vaginalis infection by PCR using vaginal swabs and urine specimens compared to diagnosis by wet mount microscopy, culture, and fluorescent staining. J Clin Microbiol 1999;37:4127–30.
180. Handa VL, Stice CW. Fungal culture findings in cyclic vulvitis. Obstet Gynecol 2000;96:301–3.
181. Plourd DM. Practical guide to diagnosing and treating vaginitis. Medscape Womens Health 1997;2:2.
182. Brown HL, Fuller DD, Jasper LT, Davis TE, Wright JD. Clinical evaluation of the Affirm VPIII in the detection and identification of Trichomonas vaginalis, Gardnerella vaginalis, and Candida sp. in vaginitis/vaginosis. Infect Dis Obstet Gynecol 2004; 12:17–21.
183. Watson MC, Bond CM, Grampian Evidence Based Community Pharmacy Guidelines Group. Evidence based guidelines for non-prescription treatment of vulvovaginal candidiasis (VVC). Pharm World Sci 2003;25:129–34.
184. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol 1991;29:297–301.
185. Holmes KK. Nonspecific vaginosis. Scand J Infect Dis 1981;26(Suppl):110–4.
186. Tam MT, Yungbluth M, Myles T. Gram stain method shows better sensitivity than clinical criteria for detection of bacterial vaginosis in surveillance of pregnancy, low-income women in a clinical setting. Infect Dis Obstet Gynecol 1998;6:204–8.
187. Mota A, Prieto E, Carnall V, Exposto F. Evaluation of microscopy methods for the diagnosis of bacterial vaginosis. Acta Med Port 2000;13:77–80.
188. Joesoef MR, Hillier SL, Josodiwondo S, Linnan M. Reproducibility of a scoring system for gram stain diagnosis of bacterial vaginosis. J Clin Microbiol 1991;29:1730–1.
189. Koumans EH, Markowitz LE, Hogan V, The CDC BV Working Group. Indications for therapy and treatment recommendations for bacterial vaginosis in nonpregnant and pregnant women: a synthesis of data. Clin Infect Dis 2002;35:S152–72.
190. Hillier SL, Nugent RP, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. N Engl J Med 1995;333:1737–42.
191. Oakeshott P, Kerry S, Hay S, Hay P. Bacterial vaginosis and preterm birth: a prospective community-based cohort study. Br J Gen Pract 2004;54:119–22.
192. Kekki M, Kurki T, Kotomaki T, Sintonen H, Paavonen J. Cost-effectiveness of screening and treatment for bacterial vaginosis in early pregnancy among women at low risk for preterm birth. Acta Obstet Gynecol Scand 2004;83:27–36.
193. West B, Morison L, van der Loeff MS, Gooding E, Awasana AA, Demba E, et al. Evaluation of a new rapid diagnostic kit (FemExam) for bacterial vaginosis in patients with vaginal discharge syndrome in The Gambia. Sex Transm Dis 2003; 30:483–9.
194. Witt A, Petricevic L, Kaufmann U, Gregor H, Kiss H. DNA hybridization test: rapid diagnostic tool for excluding bacterial vaginosis in pregnant women with symptoms suggestive of infection. J Clin Microbiol 2002;40:3057–9.
195. Briselden AM, Hillier SL. Evaluation of AFFIRM VP Microbial Identification Test for Gardnerella vaginalis and Trichomonas vaginalis. J Clin Microbiol 1994;32:148–52.

PUBLIC COMMENTS

No public comments were received on the guidelines.

Chapter **9**

Occult Blood

Stacy Foran Melanson, John Petersen, and Kent B. Lewandrowski

INTRODUCTION

This document summarizes our review of the literature on fecal occult blood and gastric occult blood. Occult blood is the unexpected presence of nonvisible blood in the stool or other body fluids. A daily loss of 2–3 mL of blood is generally considered the lower limit for abnormal bleeding that may be indicative of gastrointestinal pathology. Increased sensitivity of fecal occult blood tests (FOBT) beyond this limit is associated with higher rates of false positives and decreased test specificity. Fecal occult blood testing is commonly used in outpatient settings to screen for colorectal neoplasia in asymptomatic individuals. FOBT has also been used to monitor gastrointestinal bleeding in high-risk hospitalized patients and to detect upper gastrointestinal bleeding. In emergency department settings, FOBT can indicate bleeding caused by trauma or other conditions. Three methodologies are currently used for FOBT, including chemical or peroxidase-based methods, heme-porphyrin assays, and immunological methods. FOBT is not reliable for detecting occult blood in gastric fluid, so other methods such as Gastroccult (Beckman Coulter, Fullerton, CA, USA) have been developed for this purpose. These guidelines will focus on the use of FOBT for detecting colorectal neoplasia and other gastrointestinal lesions. We will also review data concerning the preferred methodology for FOBT in these settings. The utility of Gastroccult testing in an inpatient setting will be addressed. The literature search performed for occult blood testing is seen in Literature Search 60.

Does annual or biennial guaiac-based FOBT, in the average-risk asymptomatic outpatient population older than 50 years (no family history or other risk factors for colorectal cancer [CRC]), reduce mortality from colorectal cancer compared to no FOBT screening?

Guideline 134. *We strongly recommend that clinicians routinely provide guaiac-based FOBT for asymptomatic individuals older than 50 years at least biennially to reduce mortality from colorectal cancer. Three large randomized controlled trials have illustrated a 15%–33% reduction in mortality from annual or biennial FOBT. FOBT is easy and inexpensive and poses no risk to the patient.*

Strength/consensus of recommendation: A

Level of evidence: I and II (randomized controlled trials and case-control studies)

CRC is the second leading cause of cancer death in the United States, with more than 570,000 new cases per year. The lifetime incidence in the US population is ~6%, a rate that justifies mass screening. Colorectal carcinoma has a well-defined natural progression, and survival correlates strongly with the stage of the tumor. Screening can change the overall prognosis and outcome in patients with early disease. FOBT detects blood loss in the stool arising from colorectal neoplasms and has become a standard practice to screen for CRC. However, the optimal approach for the prevention of CRC remains uncertain *(1–4)*.

Three randomized controlled trials, Minnesota Colon Cancer Control Study, Nottingham, United Kingdom (UK), and Funen, Denmark, enrolled more than 250,000 participants and demonstrated a 15%–33% reduction in mortality from annual or biennial FOBT *(5–14)*. The Minnesota Colon Cancer Control Study enrolled 46,551 volunteers aged 50–80 years, randomized to annual FOBT, biennial FOBT, or control (no intervention) *(5)*. Participants were asked to submit 6 guaiac-impregnated paper slides (slides contained 2 smears from each of 3 consecutive stools). Dietary restrictions, such as avoidance of aspirin, red meat, and vitamin C, were in place but were not verified. The Hemoccult II (HO) method (Beckman Coulter), with rehydration for most samples, was used in the hospital laboratory. All volunteers with positive results were encouraged to obtain a full examination and colonoscopy. After a 13-year follow-up, the volunteers receiving annual FOBT had a 33% reduction in mortality compared to controls. This remained unchanged after 18 years. The volunteers receiving biennial FOBT for 13 years had a 6% reduction in mortality compared to controls. The results in the biennial group were not significant after 13 years; however, after an 18-year follow-up, the mortality reduction in the biennial group was statistically significant, at 21% *(6)*.

The European studies were similar in design to the Minnesota study, with a few exceptions. The Nottingham, UK, trial recruited 152,850 people aged 45–74 years who lived in Nottingham between 1981 and 1991 *(7)*. The participants were

randomly assigned to biennial FOBT or no screening. No dietary restrictions were used, except in cases of borderline results. Participants received the original Hemoccult home test kit (single slide rather than triple slides), with instructions from their primary care physician. The specimens were shipped to the medical center and results analyzed without rehydration by 1 of 3 investigators. A 15% reduction in cumulative CRC mortality was found in participants who received biennial screening, with a median follow-up of 7.8 years. This mortality reduction was still apparent after an 11-year follow-up *(8)*. In Funen, Denmark, 140,000 people aged 45–75 years who lived in Funen were allocated to biennial FOBT or no screening *(9)*. The HO assay was used with dietary restrictions but without rehydration. Biennial screening for 10 years decreased CRC mortality by 18%. Further delineation in this study illustrated that the mortality reduction was most pronounced in patients with lesions above the sigmoid colon *(10)*. The Denmark study is still in progress.

The conclusions in the 3 randomized trials were similar, although the magnitude of mortality reduction differed. These differences have been attributed to multiple factors, including variations in compliance rates, study population, test sensitivity, and length of follow-up. Compliance is a major impediment to FOBT, and it has been estimated that <25% of the population undergoes FOBT despite aggressive publicity *(15)*. The European trials may have better external validity because they enrolled all eligible members of the population as opposed to volunteers. The Minnesota study has also been criticized for rehydrating test samples, which increases test sensitivity *(16, 17)*. In the Minnesota study, 28%–38% of the volunteers in the test group received colonoscopy, whereas only 4% of the participants in the European trials underwent colonoscopy for a positive fecal occult blood result. Both annual and biennial screening techniques were used. Although annual testing in the Minnesota trial further decreased mortality compared with biennial testing, it occurred at the expense of additional testing *(1)*. The follow-up periods were also not consistent between trials.

The randomized studies have also shown that patients who receive annual or biennial FOBT have both a longer survival time than patients who are not screened or are at an earlier stage of CRC on detection *(5–10, 13, 14)*. However, these conclusions are made with caution because of lead-time bias. The increased survival may be due to the detection of cancer at an earlier stage.

Other studies corroborate the results of the 3 randomized controlled trials. A recent large controlled trial including 91,999 individuals aged 45–74 years was performed in Burgundy, France *(18)*. Individuals received either biennial FOBT using a guaiac-based method (without diet restriction or rehydration) or no screening. The population was followed up for 11 years. CRC mortality was 33% lower in the population that had at least 1 FOBT screening than in the control group. O'Leary et al. *(19)* examined the efficacy, as well as the cost-effectiveness, of FOBT compared to more invasive methods. Colonoscopy averted the greatest number of deaths from CRC (31%), followed by annual FOBT (29%), flexible sigmoidoscopy (21%), and biennial FOBT (19%). However, flexible sigmoidoscopy was the most cost-effective. Several case-control studies have confirmed the ability of annual or biennial FOBT to lower mortality from CRC by 25%–80% *(20–25)*. These studies typically compared patients who died from CRC to age- and sex-matched controls and retrospectively determined whether they had received FOBT. Case-control studies provide direct estimates of efficacy of screening uninfluenced by noncompliance; however, screened patients may differ from nonscreened patients in terms of CRC risks. A recent abstract at the *Digestive Disease of the Week* (DDW) by Bampton et al. *(26)* illustrated that screening patients with an immunoassay for hemoglobin (InSure, Enterix, NJ), after an initial colonoscopy, detected additional pathology.

The utility of FOBT in combination with sigmoidoscopy for the detection of CRC has been examined by several studies, including 2 randomized controlled trials *(11, 27, 28)*. One study randomized 24,465 volunteers to either 16 years of biennial Hemocccult II testing or a single flexible sigmoidoscopy and HO test *(11)*. Screening with HO biennially for 16 years detected more CRCs than single screening, but the difference in length of follow-up makes mortality rates difficult to compare. At 13 Veterans Administration centers, 2885 asymptomatic individuals aged 50–75 years received a colonoscopy to detect neoplasia, in addition to flexible sigmoidoscopy and FOBT *(27)*. In those patients with CRC, a combination of flexible sigmoidoscopy and FOBT identified 75.8% of the cancers. FOBT detected 5% of cancers that were not seen on flexible sigmoidoscopy. In the Colon Project, Winawer et al. *(28)* enrolled 21,756 patients aged 40 years or older to either a study group (annual rigid sigmoidoscopy and FOBT) or control group (annual sigmoidoscopy alone). They found an increased survival in the study group but no significant effect on mortality. More studies with similar designs will be necessary to determine whether the addition of flexible sigmoidoscopy to FOBT is warranted. Although the evidence is not clear, based on currently available studies, the American Gastroenterological Association (AGA) recommends combining the tests and performing FOBT every year and sigmoidoscopy every 5 years *(29)*. FOBT should be performed first because a positive test warrants a colonoscopy and sigmoidoscopy can be avoided.

Two randomized control studies showed no reduction in mortality from CRC screening. Kewenter et al. *(12)* reported a study of 68,308 participants in Goteborg, Sweden, randomized into screening or control groups. More CRCs were detected in the screened group, but no significant differences in mortality rate were found. These participants were only followed up for 2–7 years, which may not have been long enough to detect a statistical difference in mortality rates. In another study, all residents of Jiashan County, China, aged 30 years or older were enrolled in a randomized controlled trial to screen for CRC *(30)*. The screening method was immunological FOBT. The study showed a reduction in mortality from rectal cancer but no reduction in mortality from colon cancer. These results may differ from other randomized controlled trials because of the study population, screening method, or other disparities in the study design.

Most studies illustrate that FOBT reduces CRC mortality at minimal risk to the patient *(1–14)*. Studies performed in the UK, using the knowledge gained from the Nottingham trial, also

illustrated that screening for CRC with FOBT can be successfully implemented in a population between 50 and 69 years old *(31, 32)*. The 2003 AGA guidelines recommend yearly FOBT of 2 samples from each of 3 consecutive stools in all average-risk men and women starting at age 50. Currently, the AGA recommends against rehydration because it substantially increases the false-positive rate. Either an immunochemical test without dietary restrictions or guaiac-based tests with dietary restriction are advocated *(29)*. In contrast to the AGA, there is 1 meta-analysis showing that dietary restriction does not significantly affect the positivity rate for nonrehydrated guaiac-based FOBT and advises against dietary restriction *(33)*.

Although there is strong evidence to support FOBT for colorectal screening, studies have not addressed several key points. No trials have shown the preferred methodology for FOBT screening in CRC, including whether the guaiac-based assays should be rehydrated or nonrehydrated. Other issues include the need for dietary restrictions, the recommended length of follow-up, the most beneficial frequency of screening, and the strategy for follow-up of positive fecal occult blood results.

Does annual or biennial guaiac-based FOBT, in the asymptomatic population older than 50 years, significantly decrease the incidence of CRC?

Guideline 135. *We cannot currently recommend for or against the use of guaiac-based FOBT to reduce the incidence of CRC. Randomized control studies addressing this question are conflicting; however, the differences in length of follow-up make it difficult to draw direct comparisons. More studies need to be performed to resolve this question.*

Strength/consensus of recommendation: I

Level of evidence: I and II (randomized controlled trials and case-control studies)

The concept that FOBT may lower the incidence of CRC has been debated. Some experts have postulated that screening for CRC with FOBT will decrease the incidence of cancer. Patients with positive fecal occult blood results may receive colonoscopy, and in a percentage of cases precursor lesions (i.e., adenomatous polyps and villous adenomas) will be detected and removed, preventing cancer from developing. On the other hand, small benign adenomatous polyps are less likely to bleed than carcinomas, and they may not be efficiently detected by mass screening. In many cases, FOBT will discover early-stage cancers without necessarily decreasing the incidence of disease but rather only the rate of mortality *(1, 2, 4)*.

The 3 randomized controlled trials addressing the use of FOBT made different conclusions concerning the effect of FOBT on the incidence of CRC *(5, 7, 9)*. The Minnesota Colon Cancer Control Study involved 46,551 volunteers tested annually or biennially for fecal occult blood. This study found a decreased incidence of CRC in both screened groups at 13 and 18 years of follow-up *(34)*. After 18 years, the number of cases of CRC was 417, 435 and 507 in the annual, biennial, and control groups, respectively. In the Nottingham, UK, study 4.3% more cancers were detected in the biennially screened population after 7.8 years of follow-up *(7)*. In the Funen, Denmark trial an equal number of cancers were seen in the screened and control populations, which included a 10-year follow-up period *(9)*. The different conclusions in the 3 studies have been attributed to the variation in length of follow-up (7.8 years in the UK, 10 years in Denmark, and 18 years in Minnesota). The Denmark trial, which is ongoing, may answer this question. In addition, hydrated fecal occult blood samples were used in the Minnesota trial, which increases test sensitivity and may help detect more precursor lesions. The design of the Minnesota study may actually have underestimated the true effect on the incidence of CRC in each group *(34)*. The subjects in the control group were not prevented from undergoing screening through their personal physicians. Compliance with the protocol was also not optimal and may have attenuated the true effect. Finally, a hiatus occurred in the screening program (4.5 years for the annual group and 3.6 years for the biennial group), which may have masked the true incidence.

Other studies investigating the effect of FOBT on the incidence of CRC are also conflicting. A randomized controlled trial was performed on 27,000 inhabitants of Goteberg, Sweden, aged 60–64 years *(35)*. After the original randomized controlled trial was completed *(12)*, a subsequent study determined the incidence of CRC in the test and control group during a 7-year follow-up. The control group had more colorectal neoplasms than the test group, with the greatest effect during the first 2 years. However, if the entire length of screening and follow-up was included, the incidence of CRC in the 2 groups was similar. The increased incidence of cancer in the control group during rescreening may have been due to a lead-time effect. Niv et al. *(36)* did not find any difference in the incidence of CRC in screened vs nonscreened volunteers during a 3-year screening and 8-year follow-up period. A similar incidence of CRC in the screened and control group was also found in a study done in Burgundy, France *(18)*. In contrast, a case-control study done on 357 patients with advanced CRC and age- and sex-matched controls strongly suggested that screening reduced the incidence of advanced CRC *(37)*.

In conclusion, although randomized controlled trials have been performed to determine whether FOBT decreases the incidence of CRC, the results to date are unclear. Ongoing studies with longer lengths of follow-up may clarify this issue.

Should FOBT be performed in the central laboratory or at the point of care for asymptomatic patients who require screening for CRC?

Guideline 136. *We cannot recommend for or against FOBT performed in the central laboratory or at the point of care to screen for CRC in asymptomatic patients. Experts suggest that home collection of specimens with analysis either in the physician office or laboratory is*

Continued on next page

Continued from previous page

recommended over traditional point-of-care testing (POCT) for occult blood by digital rectal examination (DRE). In addition, the randomized controlled trials illustrating CRC mortality reduction used the central laboratory to perform FOBT. However, no trials have compared these methodologies and addressed the benefits of POCT, which include convenience and an increase in compliance.

Strength/consensus of recommendation: I

Level of evidence: III (retrospective trial, expert opinion)

methodology. Although guaiac-based testing is not extremely sensitive, it is reasonably specific, cheap, and easy to use and poses no risk to the patient. In addition, 3 large randomized controlled trials used guaiac-based methods to illustrate a reduction in CRC mortality. Although guaiac-based methods are widely used in the United States, there is insufficient evidence to recommend guaiac-based methods over other types of assays.

Strength/consensus of recommendation: I

Level of evidence: II and III (prospective comparative trials, descriptive studies, and opinion)

The validity of testing for occult blood at the point of care vs the central laboratory has not been adequately addressed. Specimens for FOBT may be obtained at home, by the patient, or in association with a DRE. Specimens can then be mailed to a central laboratory for testing, delivered to an outpatient clinic for analysis, or collected at the bedside during examination for immediate FOBT. Home collection of samples with physician office analysis is neither traditional POCT (i.e., immediate collection, with prompt results at the bedside) nor central laboratory testing. Categorization of nontraditional POCT techniques is controversial.

The AGA and other experts imply that traditional FOBT at point of care is not recommended, because of lack of sensitivity *(29, 38)*. The significance of a single positive FOBT obtained during DRE compared to the recommended home collection of 6 specimens has also not been evaluated. In addition, specimens received by DRE may be affected by the lack of dietary and medication restrictions in these patients. In a study by Fisher et al. *(39)*, published as an abstract in the DDW, only 5% of patients with significant pathology by colonoscopy had a positive FOBT result by DRE. Some clinicians believe that induced rectal trauma at the time of digital examination leads to a high false-positive rate. However, Eisner and Lewis *(40)* performed a retrospective study on 270 patients who underwent colonoscopy for any positive FOBT. The frequency of colonic abnormalities was similar with both collection methods, which argues against a high false-positive rate with DRE. Many clinicians perform DRE as part of a routine physical or hospital admission, in part because it may be the only opportunity to screen for CRC in certain patients. However, no large prospective trials have compared the accuracy of central laboratory testing to nontraditional or traditional POCT.

Which FOBT method, guaiac-based, heme-porphyrin assay, or immunological, is the most accurate (sensitivity, specificity, positive predictive value [PPV]) in an outpatient setting for the detection of CRC in asymptomatic individuals older than 50 years?

Guideline 137. *We cannot currently recommend an ideal fecal occult blood method for the detection of CRC according to the current literature and available*

Three main categories of FOBT are available in the United States, guaiac-based/chemical methods, immunological assays, and heme-porphyrin methods *(38)*. Guaiac-based methods such as the HO detect pseudoperoxidase activity in hemoglobin. The pseudoperoxidase present in hemoglobin interacts with guaiac, impregnated in a card, producing a blue color. False-positive results can occur in patients taking certain medication or in patients who consume rare red meat, turnips, and horseradish, which contain peroxidase. High doses of vitamin C can produce false-negative results. The sample used for guaiac-based methods can be rehydrated to increase sensitivity at the expense of specificity and PPV *(17)*. The Hemoccult SENSA (HOS) (Beckman Coulter) is also a guaiac-based method with acceptable sensitivity and specificity and fewer false positives than the rehydrated HO. Guaiac-based methods are inexpensive and easy to perform and can be interpreted in the physician's office (POCT). However, dietary and drug restrictions are required, and there will still be a delay in processing the test if rehydration is performed *(1, 3, 15)*.

The immunological and heme-porphyrin methods were developed to improve sensitivity. Immunological methods include the HemeSelect (HSel; Beckman Coulter), which uses reverse passive hemagglutination and detects intact hemoglobin and globin. It was designed to specifically detect colonic lesions (but not upper gastrointestinal bleeding). These methods are more expensive than guaiac-based methods and require more involved interpretation. The HemoQuant (HQ; SmithKline Diagnostics; no longer available) is a heme-porphyrin test, which detects porphyrin. Patients with CRC generally have fecal hemoglobin concentrations >2 mg/g feces. The test has a high sensitivity for bleeding both from upper and lower gastrointestinal sources, but this compromises its specificity for CRC *(1, 3, 15)*. (Sensitivity and specificity are dependent on the study and population examined; analytically, this test has better sensitivity because it is touted to be able to detect 1.5 mg hemoglobin per gram of stool, whereas the guaiac cards do not begin to turn positive until levels of 5 mg/g of stool are reached. In studies, Hemoccult using rehydrated stool has sensitivities of 30%–50%, with specificities around 95%, whereas HQ has sensitivity of 40%–60%, but much lower specificities accordingly.)

A large study was done on 8104 asymptomatic patients scheduled for routine physicals at Kaiser Permanent Medical

Center to compare the ability of HO, HSel, HOS, and a combination of HOS and HSel to detect CRC *(41)*. Each patient received all 3 testing methods. Dietary restrictions were in place but not confirmed, and no rehydration of samples was performed. Patients with positive results by any testing method received a colonoscopy, and all patients were followed up for 2 years. The HOS had the highest sensitivity for the detection of CRC, at 79.4%, but the lowest specificity, at 86.7%. HO had the highest specificity (97.7%) but a poor sensitivity (37.1%). The HSel was neither the most sensitive nor the most specific. All had PPV $< 9.0\%$. Combination testing was also performed. If a positive HOS result was obtained by screening, it was confirmed with the HSel method. This resulted in a sensitivity of 65.6%, a specificity of 97.3%, and a PPV of 9.0%. The value of combination testing in an outpatient setting beyond this study is uncertain.

Several other studies have been performed to determine the accuracy of FOBT methods in asymptomatic individuals eligible for CRC screening *(16, 41–50)*. A wide range for sensitivities, specificities, and PPVs is obtained when the results of different studies are compiled. The variations could be the result of differences in study population, age of participants, dietary requirements, preparation of specimens (i.e., rehydration), endpoints measured, screening intervals, and years of follow-up. The large discrepancies in the ranges for sensitivity, specificity, and PPV make the data in the literature difficult to interpret. Immunological methods (i.e., HSel) are generally more sensitive and less specific, but interpretation of the available literature suggests that the differences are not striking. Guaiac-based methods such as HO are more specific and for their convenience tend to be the method of choice. All methods have poor PPVs because of the relatively low prevalence of CRC in the asymptomatic screened population.

A few articles have examined the accuracy of FOBT in symptomatic or high-risk patients with family histories of CRC *(51–54)*. Similar to the studies done with asymptomatic patients, these studies are also not consistent. Four studies on symptomatic patients compared HO to the heme porphyrin method, HQ *(51–54)*. Barber et al. *(52)* compared the HQ and HO methods in 184 patients with bleeding as a result of iron deficiency and concluded that the HQ had an overall better performance for detecting gastrointestinal lesions. On the other hand, St. John et al. *(54)* reported that HO was more sensitive than HQ for the detection of CRC in a cross-sectional study. The range of sensitivities for the detection of CRC or gastrointestinal lesions was between 26% and 89.5% for HO and 26% and 74.2% for HQ. Specificities ranged from 32.4% to 99.3% for HO and 81%–94.7% for HQ. Most of the authors question the added benefit of quantitative HQ, especially because of the increased cost and inconvenience *(51, 52, 54)*. Ahlquist et al. *(51)* suggested that neither HO nor HQ is optimal for screening high-risk patients.

Patient and physician compliance is a major obstacle in FOBT. Averages from the literature estimate that only 50% of the eligible population undergoes FOBT for CRC screening, but in reality the numbers may be $<25\%$ *(15)*. Cole et al. *(55)* performed a study on 1818 residents aged between 50 and 69 years to determine compliance rates with different FOBT methodologies. Participation was higher with immunological methods that involve more convenient sampling and remove the need for dietary and drug restrictions. By contrast, a meta-analysis found that moderate dietary restrictions did not affect completion rates *(33)*. In addition to providing optimal sensitivity and specificity, the preferred methodology for FOBT should maximize patient participation.

The literature does not demonstrate that any 1 FOBT method is superior for the detection of CRC. After a review of the literature, Young et al. *(56)* also concluded that no FOBT method fulfills the needs of all target populations. This study recommends using the patient population and colonoscopy resources to determine the most reliable method. No studies incorporated a cost analysis into their study design to aid in the differentiation of methodologies. In general, guaiac-based methods are used clinically because they are easy to use and inexpensive and have been shown to decrease mortality from CRC in at least 3 randomized controlled trials. The AGA recommends either guaiac-based testing with dietary restriction or an immunochemical method *(29)*.

Is FOBT useful in symptomatic patients to differentiate bleeding caused by upper gastrointestinal lesions (including gastroesophageal cancer) from bleeding caused by lower gastrointestinal lesions?

Guideline 138. *We cannot currently recommend FOBT to differentiate upper from lower sources of gastrointestinal bleeding. A limited number of cohort and case-control studies have demonstrated that FOBT can detect bleeding caused by upper gastrointestinal lesions, but there is no evidence to support that guaiac-based FOBT can determine the origin of bleeding.*

Strength/consensus of recommendation: I

Level of evidence: II (case-control and cohort studies)

Both upper and lower gastrointestinal lesions can result in positive FOBTs. Traditionally, guaiac-based FOBT was designed to detect lower gastrointestinal sources of bleeding by monitoring intact hemoglobin. In the case of upper gastrointestinal bleeding, hemoglobin undergoes degradation by intestinal enzymes as it passes through the gastrointestinal tract, which frequently causes a false-negative result with guaiac-based tests. However, in patients with significant bleeding (5–10 mL per day) from an upper gastrointestinal source, intact hemoglobin can still be detected in the stool. The ability of guaiac-based tests to detect bleeding is variable and depends on anatomic, physiologic, and dietary factors. Immunochemical tests are very sensitive for colonic bleeding but do not detect blood from the upper gastrointestinal tract. In contrast, the heme-porphyrin test, which measures porphyrin, the breakdown product of hemoglobin, can quantify bleeding from any gastrointestinal source. However, most

immunological and porphyrin methods require laboratory processing *(38)*.

Studies have shown that guaiac-based FOBT can detect upper GI sources of bleeding *(57, 58)*. However, these studies do not suggest that FOBT can differentiate the source of bleeding and have questioned the utility of FOBT for detecting bleeding caused by gastric or esophageal lesions. A prospective study was published using 248 patients with positive guaiac-based FOBTs (HO) *(58)*. All of the patients were referred for further evaluation (colonoscopy or upper endoscopy). Of all patients, 48% had gastrointestinal lesions identified; 21.8% were colonic and 28.6% were upper gastrointestinal, illustrating that guaiac-based FOBT can detect bleeding throughout the gastrointestinal tract, but without discrimination. A study done in high-risk inpatient pediatric patients with known upper and lower gastrointestinal sources of bleeding suggested the use of highly sensitive guaiac-based methods for suspected upper gastrointestinal bleeding in children. However, the authors did not suggest that this method may be used to differentiate the source of bleeding *(59)*. In 178 patients starting dialysis, guaiac-based FOBT detected more CRCs than upper gastrointestinal tumors *(57)*.

Heme-porphyrin methods have also been shown to detect bleeding from upper gastrointestinal sources. Harewood et al. *(60)* tested 56 patients with known upper gastrointestinal lesions and found that heme-porphyrin methods detected upper gastrointestinal blood loss more frequently than guaiac-based or immunological-based assays. Another study compared guaiac-based methods with heme-porphyrin methods in 106 healthy volunteers, 170 patients with gastrointestinal symptoms, 44 patients with gastrointestinal cancer, 75 patients with benign polyps, and 374 patients with other benign gastrointestinal lesions *(61)*. The heme-porphyrin based method was more sensitive for gastrointestinal bleeding and was better in detecting bleeding from proximal lesions.

Immunological FOBT are insensitive for upper gastrointestinal sources of bleeding *(62, 63)*. Nakama et al. *(62, 63)* performed 2 studies using patients with documented upper and lower digestive tract diseases and healthy controls. In 1 study, immunological FOBT was performed on 226 subjects (124 with upper gastrointestinal disease, 34 with CRC, and 68 healthy controls) *(63)*. The sensitivity for upper digestive tract disease was only 19%. In the other study, immunological FOBT was performed on 150 patients with gastric cancer, 150 patients with CRC, and 300 healthy volunteers *(62)*. FOBT was positive in 8% of patients with gastric cancer and 7% of patients without gastric cancer. In these studies, immunochemical occult blood tests could detect only a low percentage of patients with upper gastrointestinal bleeding. These studies recommended against the use of immunological FOBT to screen for suspected upper gastrointestinal lesions.

In an article by Rockey et al. *(64)*, groups of 10 healthy volunteers drank blood mixed with tomato juice for 3 consecutive days and were tested for fecal occult blood by a variety of methodologies. The highly sensitive guaiac-based method (HOS) detected blood in all subjects after ingestion of 20 mL of blood and in 50% of subjects after ingestion of 10 mL and was more sensitive than the HO for detecting upper gastrointestinal bleeding. Immunochemical assays did not detect occult blood in any of the subjects. These data raised "the possibility that a combination of a highly sensitive guaiac-based FOB test plus an immunochemical method could aid in differentiating occult upper from lower GI bleeding."

Evidence supports the fact that upper gastrointestinal bleeding can be detected by FOBT, but no in vivo human studies have addressed the ability of FOBT to differentiate the source of bleeding. Although clinicians would find a rapid, easy-to-use, sensitive method to differentiate upper from lower sources of gastrointestinal bleeding useful, there is no evidence to suggest that the guaiac-based FOBT can make this distinction.

Can guaiac-based FOBT be used in patients receiving therapeutic anticoagulation to predict whether a patient is at high risk for gastrointestinal bleeding?

Guideline 139. *We cannot currently recommend for or against the use of guaiac-based FOBT to predict gastrointestinal bleeding in patients receiving anticoagulation. Although the current literature is sparse, it suggests that positive fecal occult blood results do not correlate with the level of anticoagulation. From these data, it can be extrapolated that FOBT would not be predictive of bleeding risk. More studies need to be done to directly address this issue.*

Strength/consensus of recommendation: I

Level of evidence: II and III (prospective trials and expert opinion)

Many inpatients and outpatients receive anticoagulation for cardiovascular-related events. Bleeding is a significant risk for patients receiving anticoagulation. A few studies have investigated the effects of anticoagulants on FOBT results. A prospective crossover study of 100 patients older than 40 years was done *(65)*. Patients were assigned to groups taking no aspirin or warfarin, daily aspirin (81 mg or 325 mg), or warfarin but no aspirin. Each patient collected stool at home, and occult blood testing was done in the central laboratory by the HQ or HO methods. No increase in the rate of positive FOBT was seen in the patients taking warfarin. In addition, the international normalized ratio (INR) level, which is used to monitor anticoagulation therapy, was not associated with occult blood by HQ. A small dose-dependent increase in gastrointestinal blood loss was seen in patients taking aspirin; however, the quantity detected was still within the normal limits of 2 mg hemoglobin per gram of stool.

A study by Blackshear et al. *(66)* investigated 117 patients receiving anticoagulation for atrial fibrillation. The patients received either standard warfarin (INR 2–3), warfarin (INR < 1.5) and 325 mg of aspirin, or aspirin alone. After 1 month of therapy, the patients mailed specimens to the laboratory for HQ FOBT. The patients taking warfarin and aspirin had slightly more fecal hemoglobin than those taking standard

warfarin. None of the results were significantly different from the reference population without atrial fibrillation. In a prospective study, 256 patients receiving anticoagulation were screened with HO with no rehydration *(67)*. The positive rate was higher in the patients receiving anticoagulation (12% vs 3%), but the patients with positive results had previously undiagnosed lesions of the gastrointestinal tract. This study postulated that anticoagulants might unmask bleeding from preexisting lesions.

The few trials examining FOBT on anticoagulated patients are consistent. Fecal blood level in patients treated with anticoagulation or low-dose aspirin are normal or minimally increased compared to controls *(38, 65–68)*. Some recommendations suggest stopping aspirin before FOBT is performed, but Greenberg et al. *(65)* suggested that aspirin and warfarin do not compromise the accuracy of FOBT and that the cardiovascular disadvantages of discontinuing anticoagulation outweigh the minimal FOBT benefits. In addition, the INR does not correlate with positive FOBT results *(65–67)*. These studies conclude that a positive FOBT should not be attributed solely to anticoagulation therapy and should lead to a formal evaluation. Whether qualitative or quantitative hemoglobin monitoring in the stool may predict bleeding events is not known, but the studies described imply otherwise. FOBT can be done at the point of care (i.e., DRE at inpatient bedside) or by home collection (i.e., presumably in outpatients). No study has described the effect of anticoagulation on guaiac-based FOBT results done on inpatients after DRE. Although clinicians use FOBT at the point of care to predict gastrointestinal (GI) bleeding in inpatients or outpatients receiving anticoagulation, this practice cannot be substantiated by the literature.

Can Gastroccult testing of gastric fluid from a nasogastric tube be used to detect gastrointestinal bleeding in high-risk intensive care unit (ICU) patients receiving antacid prophylaxis?

Guideline 140. *We cannot currently recommend for or against the use of Gastroccult to detect gastric bleeding in ICU patients receiving antacid prophylaxis. Only 1 study to our knowledge has indirectly addressed this issue. No randomized controlled trials have been performed.*

Strength/consensus of recommendation: I

Level of evidence: III (small study and clinical evidence)

FOBT should not be used to measure occult blood in gastric fluid, because of interferences from low pH, certain medications (antacids and vitamin C lead to false-negative results), and metal ions (iron and copper salts lead to false-positive results). The presence or absence of occult blood in gastric fluid is useful in emergency department or ICU settings for the detection of bleeding caused by trauma or a deteriorating gastric condition (stress ulcer syndrome). Gastroccult tests are used for this purpose. The pseudoperoxidase in hemoglobin reacts with guaiac and a buffered, stabilized hydrogen peroxide solution, producing a blue color in the presence of blood. Two in vitro studies have illustrated that Gastroccult is a simple, rapid, and convenient method for the evaluation of patients with suspected occult blood in gastric fluid. Gastroccult, unlike Hemoccult, is not influenced by pH or sucralfate *(69, 70)*.

Derrida et al. *(71)* used Gastroccult every 4 h to identify blood in gastric juice of 41 ICU patients at risk for gastrointestinal bleeding (patients with overt gastrointestinal bleeding were excluded) and receiving antacid prophylaxis; 27% (14/41) had at least 1 positive Gastroccult reading and received an upper endoscopy. No endoscopy was performed in patients with negative Gastroccult findings. In 13/14 patients, a source of gastric bleeding was detected. This study suggests that Gastroccult testing may aid in detecting occult bleeding in critically ill patients. However, this small study did not perform upper endoscopy on negative-testing patients, which would have documented the false-negative results obtained with the Gastroccult test.

Current data are insufficient to recommend the use of Gastroccult for ICU patients to detect upper gastrointestinal bleeding. Although this practice is widespread, more studies will be necessary to document the utility of Gastroccult testing for this application.

In summary, FOBT is rapid, inexpensive, easy to use, and useful in a variety of practice settings to assist clinicians in detecting gastrointestinal bleeding and to guide the selection of appropriate follow-up testing. Annual or biennial FOBT on 2 samples from each of 3 consecutive stools is recommended for all average-risk men and women beginning at age 50 to reduce mortality from CRC. Most experts agree that FOBT, although reducing CRC mortality, does not affect the incidence of CRC. This issue remains controversial because the literature conclusions are not consistent. Although FOBT is inexpensive and poses minimal risk to the patient, many patients with no pathology will incur the discomfort, cost, and risk of colonoscopy if a positive result is obtained. Despite consensus among expert groups that FOBT reduces mortality from CRC, the screening rates remain low and the follow-up of positive FOBT is inadequate. The medical community should not only optimize the clinical utility of FOBT but also improve patient and physician compliance and enforce regular FOBT to maximize the benefit for patients. No studies have investigated the role of FOBT, if any, in the treatment of patients with CRC.

The use of FOBT at the point of care cannot be advocated, because of lack of medical evidence, although its convenience and the opportunity for greater compliance are appealing. The randomized controlled trials performed FOBT in the central laboratory, and no clinical trials have investigated the role of POCT vs the central laboratory.

Currently, no specific FOBT methodology can be recommended. However, the most recent AGA recommendation suggests either yearly guaiac-based tests with dietary restriction or an immunochemical test without dietary restriction. The AGA also recommended against rehydrating FOBT because it leads

to substantially higher false-positive rates. Guidelines on the preferred methodology in specific settings, including a cost analysis, need to be published.

The use of FOBT in hospitalized patients has not been thoroughly explored. Studies suggest that FOBT results do not correlate with the level of anticoagulation; however, the utility of FOBT to monitor anticoagulation has not been addressed. According to current evidence, the use of FOBT to differentiate upper and lower gastrointestinal lesions also cannot be advocated. Furthermore, the role of occult blood testing on nongastrointestinal specimens such as nipple discharge and sputum is unknown. The small numbers of studies that have examined the role of occult blood in nipple discharge or sputum for the diagnosis of breast or lung cancer have shown that occult blood testing is neither a sensitive nor a specific method *(72–75)*.

Gastroccult is frequently used in the inpatient setting to detect blood in gastric fluid or vomitus. Studies on Gastroccult testing are sparse, and no definitive guidelines on the clinical utility of Gastroccult at the point of care can be determined from the literature.

Finally, new methodology has recently been developed to detect DNA mutations in the stool that are associated with CRC. Studies are currently in progress that compare FOBT to DNA-based methods.

REFERENCES

1. Walsh JM, Terdiman JP. Colorectal cancer screening: scientific review [review]. JAMA 2003;289:1288–96.
2. Rex DK. Current colorectal cancer screening strategies: overview and obstacles to implementation [review]. Rev Gastroenterol Disord 2002; 2(Suppl 1):S2–11.
3. Ahlquist DA, Shuber AP. Stool screening for colorectal cancer: evolution from occult blood to molecular markers. Clin Chim Acta 2002;315:157–68.
4. Otto S, Eckhardt S. Early detection for colorectal cancer: new aspects in fecal occult blood screening. J Surg Oncol 2000; 75:220–6.
5. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood: Minnesota Colon Cancer Control Study. N Engl J Med 1993;328:1365–71.
6. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst 1999;91:434–7.
7. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472–7.
8. Scholefield JH, Moss S, Sufi F, Mangham CM, Hardcastle JD. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 2002;50: 840–4.
9. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996;348:1467–71.
10. Jorgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002;50:29–32.
11. Rasmussen M, Fenger C, Kronborg O. Diagnostic yield in a biennial Hemoccult-II screening program compared to a once-only screening with flexible sigmoidoscopy and Hemoccult-II. Scand J Gastroenterol 2003;38:114–8.
12. Kewenter J, Brevinge H, Engaras B, Haglind E, Ahren C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing: results for 68,308 subjects. Scand J Gastroenterol 1994;29:468–73.
13. Mapp TJ, Hardcastle JD, Moss SM, Robinson MH. Survival of patients with colorectal cancer diagnosed in a randomized controlled trial of faecal occult blood screening. Br J Surg 1999;86:1286–91.
14. Robinson MH, Hardcastle JD, Moss SM, Amar SS, Chamberlain JO, Armitage NC, et al. The risks of screening: data from the Nottingham randomised controlled trial of faecal occult blood screening for colorectal cancer. Gut 1999;45:588–92.
15. Simon JB. Fecal occult blood testing: clinical value and limitations [review]. Gastroenterologist 1998;6:66–78.
16. Levin B, Hess K, Johnson C. Screening for colorectal cancer: a comparison of 3 fecal occult blood tests. Arch Intern Med 1997;157:970–6.
17. Castiglione G, Biagini M, Barchielli A, Grazzini G, Mazzotta A, Salvadori P, et al. Effect of rehydration on guaiac-based faecal occult blood testing in colorectal cancer screening. Br J Cancer 1993;67:1142–4.
18. Faivre J, Dancourt V, Lejeune C, Tazi MA, Lamour J, Gerard D, et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. Gastroenterology 2004;126:1674–80.
19. O'Leary BA, Olynyk JK, Neville AM, Platell CF. Cost-effectiveness of colorectal cancer screening: comparison of community-based flexible sigmoidoscopy with fecal occult blood testing and colonoscopy. J Gastroenterol Hepatol 2004;19:38–47.
20. Saito H, Soma Y, Nakajima M, Koeda J, Kawaguchi H, Kakizaki R, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. Oncol Rep 2000;7:815–9.
21. Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS. Effect of fecal occult blood testing on mortality from colorectal cancer: a case-control study. Ann Intern Med 1993;118:1–6.
22. Zappa M, Castiglione G, Grazzini G, Falini P, Giorgi D, Paci E, et al. Effect of faecal occult blood testing on colorectal mortality: results of a population-based case-control study in the district of Florence, Italy. Int J Cancer 1997;73:208–10.
23. Faivre J, Tazi MA, El Mrini T, Lejeune C, Benhamiche AM, Dassonville F. Faecal occult blood screening and reduction of colorectal cancer mortality: a case-control study. Br J Cancer 1999;79:680–3.
24. Lamah M, Norris J, Caffarey SM, Broughton M, Marks CG. Effect of faecal occult blood testing on colorectal cancer mortality in the surveillance of subjects at moderate risk of colorectal neoplasia: a case-control study. Int J Colorectal Dis 2001;16:313–7.
25. Bertario L, Russo A, Crosignani P, Sala P, Spinelli P, Pizzetti P, et al. Reducing colorectal cancer mortality by repeated faecal occult blood test: a nested case-control study. Eur J Cancer 1999;35:973–7.
26. Bampton P, Sandford J, Cole S. Interval fecal occult blood testing in a colonoscopy-based colorectal cancer surveillance program detects additional pathology [abstract]. Digestive Disease Week 2004;126:A-25.
27. Lieberman DA, Weiss DG. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. N Engl J Med 2001;345:555–60.

28. Winawer SJ, Flehinger BJ, Schottenfeld D, Miller DG. Screening for colorectal cancer with fecal occult blood testing and sigmoidoscopy. J Natl Cancer Inst 1993;85:1311–8.
29. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale: update based on new evidence. Gastroenterology 2003;124:544–60.
30. Zheng S, Chen K, Liu X, Ma X, Yu H, Yao K, et al. Cluster randomization trial of sequence mass screening for colorectal cancer. Dis Colon Rectum 2003;46:51–8.
31. Group UCCSP. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. BMJ 2004;329:133–135.
32. Steele RJ, Parker R, Patnick J, Warner J, Fraser C, Mowat NA, et al. A demonstration pilot trial for colorectal cancer screening in the United Kingdom: a new concept in the introduction of healthcare strategies. J Med Screen 2001;8:197–202.
33. Pignone M, Campbell MK, Carr C, Phillips C. Meta-analysis of dietary restriction during fecal occult blood testing. Eff Clin Pract 2001;4:150–6.
34. Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603–7.
35. Kewenter J, Brevinge H, Engaras B, Haglind E, Ahren C. Follow-up after screening for colorectal neoplasms with fecal occult blood testing in a controlled trial. Dis Colon Rectum 1994;37:115–9.
36. Niv Y, Lev-El M, Fraser G, Abuksis G, Tamir A. Protective effect of faecal occult blood test screening for colorectal cancer: worse prognosis for screening refusers. Gut 2002;50:33–7.
37. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. Br J Cancer 2003;89:23–8.
38. Rockey DC. Occult gastrointestinal bleeding [review]. N Engl J Med 1999;341:38–46.
39. Fisher DA, Jeffreys A, Coffman C. Barriers to full colon evaluation for a positive fecal occult blood test [abstract]. Digestive Dis Week 2004;126:A-58.
40. Eisner MS, Lewis JH. Diagnostic yield of a positive fecal occult blood test found on digital rectal examination: does the finger count? Arch Intern Med 1991;151:2180–4.
41. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med 1996;334:155–9.
42. Allison JE, Feldman R, Tekawa IS. Hemoccult screening in detecting colorectal neoplasm: sensitivity, specificity, and predictive value: long-term follow-up in a large group practice setting. Ann Intern Med 1990;112:328–33.
43. Castiglione G, Zappa M, Grazzini G, Mazzotta A, Biagini M, Salvadori P, et al. Immunochemical vs guaiac faecal occult blood tests in a population-based screening programme for colorectal cancer. Br J Cancer 1996;74:141–4.
44. Ko CW, Dominitz JA, Nguyen TD. Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. Am J Med 2003;115:111–4.
45. Rozen P, Knaani J, Samuel Z. Performance characteristics and comparison of two immunochemical and two guaiac fecal occult blood screening tests for colorectal neoplasia. Dig Dis Sci 1997;42:2064–71.
46. Rozen P, Knaani J, Samuel Z. Comparative screening with a sensitive guaiac and specific immunochemical occult blood test in an endoscopic study. Cancer 2000;89:46–52.
47. Church TR, Ederer F, Mandel JS. Fecal occult blood screening in the Minnesota study: sensitivity of the screening test. J Natl Cancer Inst 1997;89:1440–8.
48. Jouve JL, Remontet L, Dancourt V, Lejeune C, Benhamiche AM, Faivre J, et al. Estimation of screening test (Hemoccult) sensitivity in colorectal cancer mass screening. Br J Cancer 2001;84:1477–81.
49. Thomas WM, Pye G, Hardcastle JD, Walker AR. Screening for colorectal carcinoma: an analysis of the sensitivity of haemoccult. Br J Surg 1992;79:833–5.
50. Rennert G, Rennert HS, Miron E, Peterburg Y. Population colorectal cancer screening with fecal occult blood test. Cancer Epidemiol Biomarkers Prev 2001;10:1165–8.
51. Ahlquist DA, Wieand HS, Moertel CG, McGill DB, Loprinzi CL, O'Connell MJ, et al. Accuracy of fecal occult blood screening for colorectal neoplasia: a prospective study using Hemoccult and HemoQuant tests. JAMA 1993;269: 1262–7.
52. Barber MD, Abraham A, Brydon WG, Waldron BM, Williams AJ. Assessment of faecal occult blood loss by qualitative and quantitative methods. J R Coll Surg Edinb 2002;47:491–4.
53. Gopalswamy N, Stelling HP, Markert RJ, Maimon HN, Wahlen SD, Haddy RI. A comparative study of eight fecal occult blood tests and HemoQuant in patients in whom colonoscopy is indicated. Arch Fam Med 1994;3:1043–8.
54. St. John DJ, Young GP, McHutchison JG, Deacon MC, Alexeyeff MA. Comparison of the specificity and sensitivity of Hemoccult and HemoQuant in screening for colorectal neoplasia. Ann Intern Med 1992;117:376–82.
55. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. J Med Screen 2003;10:117–22.
56. Young GP, St. John DJ, Winawer SJ, Rozen P. Choice of fecal occult blood tests for colorectal cancer screening: recommendations based on performance characteristics in population studies: a WHO (World Health Organization) and OMED (World Organization for Digestive Endoscopy) report. Am J Gastroenterol 2002;97:2499–507.
57. Ito T, Tanaka I, Kadoya T, Kimura M, Ooshiro T, Ooishi K, et al. Screening for gastroenterological malignancies in new and maintenance dialysis patients. J Gastroenterol 1999;34:35–40.
58. Rockey DC, Koch J, Cello JP, Sanders LL, McQuaid K. Relative frequency of upper gastrointestinal and colonic lesions in patients with positive fecal occult-blood tests. N Engl J Med 1998;339: 153–9.
59. Rosenthal P, Jennings MT. Comparison of fecal occult blood tests for detection of gastrointestinal bleeding in pediatric patients. Am J Gastroenterol 1992;87:1575–9.
60. Harewood GC, McConnell JP, Harrington JJ, Mahoney DW, Ahlquist DA. Detection of occult upper gastrointestinal tract bleeding: performance differences in fecal occult blood tests. Mayo Clin Proc 2002;77:23–8.
61. Ahlquist DA, McGill DB, Schwartz S, Taylor WF, Owen RA. Fecal blood levels in health and disease: a study using HemoQuant. N Engl J Med 1985;312:1422–8.
62. Nakama H, Kamijo N, Fujimori K, Fattah AS, Zhang B. Diagnostic accuracy of immunochemical faecal occult blood test for gastric cancer. J Med Screen 1996;3:113–4.
63. Nakama H, Kamijo N, Fattah AS, Zhang B. Immunologic detection of fecal occult blood from upper digestive tract diseases. Hepatogastroenterology 1998;45:752–4.
64. Rockey DC, Auslander A, Greenberg PD. Detection of upper gastrointestinal blood with fecal occult blood tests. Am J Gastroenterol 1999;94:344–50.

65. Greenberg PD, Cello JP, Rockey DC. Asymptomatic chronic gastrointestinal blood loss in patients taking aspirin or warfarin for cardiovascular disease. Am J Med 1996;100:598–604.
66. Blackshear JL, Baker VS, Holland A, Litin SC, Ahlquist DA, Hart RG, et al. Fecal hemoglobin excretion in elderly patients with atrial fibrillation: combined aspirin and low-dose warfarin vs conventional warfarin therapy. Arch Intern Med 1996;156:658–60.
67. Jaffin BW, Bliss CM, LaMont JT. Significance of occult gastrointestinal bleeding during anticoagulation therapy. Am J Med 1987; 83:269–72.
68. Meyer BH, Luus HG, Muller FO, Badenhorst PN, Lotter MG, Rothig HJ, et al. Recombinant hirudin, a new anticoagulant, has no effect on faecal blood loss. Br J Clin Pharmacol 1992;33:524–6.
69. Rosenthal P, Thompson J, Singh M. Detection of occult blood in gastric juice. J Clin Gastroenterol 1984;6:119–21.
70. Holman JS, Shwed JA. Influence of sucralfate on the detection of occult blood in simulated gastric fluid by two screening tests. Clin Pharm 1992;11:625–7.
71. Derrida S, Nury B, Slama R, Marois F, Moreau R, Soupison T, et al. Occult gastrointestinal bleeding in high-risk intensive care unit patients receiving antacid prophylaxis: frequency and significance. Crit Care Med 1989;17:122–5.
72. Simmons R, Adamovich T, Brennan M, Christos P, Schultz M, Eisen C, et al. Nonsurgical evaluation of pathologic nipple discharge. Ann Surg Oncol 2003;10:113–6.
73. Okazaki A, Hirata K, Okazaki M, Svane G, Azavedo E. Nipple discharge disorders: current diagnostic management and the role of fiber-ductoscopy. Eur Radiol 1999;9:583–90.
74. Qin DX, Li JY, Sun LQ, Gu M, Wang GS, Cong JW, et al. Sputum occult blood screening for lung cancer: stage II screening of 14,431 subjects. Cancer 1991; 67:1960–3.
75. Chaudary MA, Millis RR, Davies GC, Hayward JL. The diagnostic value of testing for occult blood. Ann Surg 1982; 196: 651–5.

PUBLIC COMMENTS

1. Received during the AACC presentation: Can you address the utility of digital rectal examination for point of care fecal occult blood? *We added a recommendation addressing the use of FOBT in the central laboratory or at the point of care. This recommendation states that although most experts advise against testing for occult blood by DRE, the evidence to support this is insufficient.*
2. Dr. Callum G. Fraser wrote a letter suggesting that several points and references be added to the discussion. *We added discussions pertaining to the following references (31–33, 38, 55, 56) that can be found throughout the guidelines.*
3. Dr. Gary Lee Utz wrote: "The POC issue in FOBT does not appear to be adequately addressed in the draft guidelines." *In response to his comment, we added a separate recommendation discussing the utility of FOBT at the point of care vs the central laboratory. Evidence to recommend FOBT at the point of care is insufficient.*
4. Brenda L. M. Franks asked, "Do you have any plans to address FOB testing for patients on intensive anticoagulant therapy?" *We added a recommendation on the use of FOBT in patients receiving therapeutic anticoagulation. The evidence was insufficient to recommend for or against the use of FOBT to predict gastrointestinal bleeding in patients receiving anticoagulation.*

Chapter **10**

Intraoperative Parathyroid Hormone

Lori J. Sokoll, Alan T. Remaley, Salvador F. Sena, Frank H. Wians, Jr., Jiaxi Wu, Steven K. Libutti, and Robert Udelsman**

INTRODUCTION

In the late 1980s, intact parathyroid hormone (PTH) was proposed as an intraoperative monitor to the already successful surgery for primary hyperparathyroidism to provide guidance about extent of neck exploration and removal of parathyroid tissue *(1)*. The utility of PTH lies in its specificity to the parathyroid glands and a half-life of the full-length 84-residue molecule of <5 min. Modifications to intact PTH assays allowed for results available in 15 min or less, and commercialization of assays in the mid-1990s expanded the application of the intact PTH assay to allow for real-time testing during parathyroid surgery. Although PTH may not be thought of as a typical point-of-care test or analyte, measurement in the operating and angiography suites qualifies it as such. Detailed reviews providing background on intraoperative PTH testing have been published previously *(2–4)*. This document will explore clinical questions on the applications of the rapid PTH assay and the impact of the assay on patient health and operational and financial outcomes. Development of practice guidelines was based on literature searched from the PubMed database (1966, November week 2, 2003) and was limited to articles in English and those with abstracts (Literature Searches 61–74).

PRIMARY HYPERPARATHYROIDISM

Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the accuracy of identifying multiglandular disease compared to bilateral exploratory surgery? Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in patients with primary hyperparathyroidism? Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve morbidity or complication rate compared to bilateral exploratory surgery alone in patients with primary hyperparathyroidism?

Does the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improve use of local or regional anesthesia or extent of exploration (unilateral vs bilateral) compared to standard bilateral exploration? Does the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improve use of frozen sections compared to standard bilateral exploration? Does the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improve operating room time, operating room fees, overall hospital costs, or length of stay compared to standard bilateral exploration? Does the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improve incision size/cosmetic result or patient satisfaction/pain compared to standard bilateral exploration?

Guideline 141. *According to evidence for improved patient health and operational and economic outcomes, we recommend routine use of intraoperative PTH testing for patients undergoing surgery for primary hyperparathyroidism and strongly recommend routine use in minimally invasive or directed procedures.*

Strength/consensus of recommendation: A/B

Level of evidence: I, II, and III (randomized controlled trials, controlled trials, cohort study, case series, models and simulations, opinion)

Literature Search 61 investigated the following questions: (1) Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the accuracy of identifying multiglandular disease compared to bilateral exploratory surgery? and (2) Does the addition of intraoperative PTH

*Steven K. Libutti, M.D., National Cancer Institute, Bethesda, MD, USA, and Robert Udelsman, M.D., M.B.A., Yale University, New Haven, CT, USA, served as consultants on this chapter.

measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in patients with primary hyperparathyroidism?

Of the >200 publications on intraoperative PTH, fewer than 10 have any type of control group for comparison. The idealized randomized controlled trial with blinding to patient and surgeon may not be applicable to all surgical procedures. Also, as techniques become well known, it is difficult to perform prospectively controlled trials *(5)*. This may be the case for intraoperative PTH, in which, in a discussion of study design, this was noted: "the fact that quick parathormone early on was so useful . . . it seemed a disservice to limit the use of the technique" *(6)*. The limited controlled studies on intraoperative PTH have typically compared different operative strategies, of which intraoperative PTH was a component. In these studies, cure rates were uniformly very high in all of the studies in both the control and experimental groups (Table 10-1).

Two studies used a prospective randomized design *(7, 8)*. In the study by Bergenfelz et al. *(7)*, 91 patients undergoing first-time exploration for primary hyperparathyroidism were randomized to either the experimental unilateral group with limited exploration, preoperative localization with sestamibi scintigraphy radiologic scans, and intraoperative PTH testing with sampling at, before, and 5 and 15 min after gland excision (n = 47) or the control bilateral group with no preoperative localization, bilateral exploration with 4-gland visualization, and frozen section (n = 44) *(7)*. Groups were equivalent with respect to age, sex distribution, preoperative laboratory values, clinical signs and symptoms, and, at surgery, the incidence of multiglandular disease. The overall cure rate was 97% according to normocalcemia 1 year postsurgery, with 2 patients with persistent disease in the unilateral group and 1 in the bilateral group. With respect to intraoperative PTH, there was 1 false-positive result and 1 true-negative result for the operative failures. A false-positive result is defined as a 50% decrease in PTH concentrations from baseline in a patient who is not cured, whereas a true-negative result is an appropriate lack of a 50% decrease in PTH concentrations from baseline because of existing hyperfunctioning tissue.

In the second study, 48 patients with primary hyperparathyroidism were evaluated for video-assisted parathyroidectomy (VAP) according to clinical history and preoperative ultrasonography suggestive of a solitary parathyroid adenoma *(8)*. Thirty-eight patients were eligible for the study, and patients were randomized through the flip of a coin. Sex distribution was similar, although the mean age in the control group (n = 18) was 60 ± 14 (mean ± SD) years compared to 48 ± 13 years in the experimental group (n = 20). Preoperative serum calcium and intact PTH concentrations and location and size of adenoma according to preoperative findings were similar between the 2 groups. At 6 months, all patients were normocalcemic regardless of surgical approach. In a prospective longitudinal cohort study, Carty et al. *(6)* compared the palpation method for selective unilateral exploration (n = 61) to use of preoperative 99mTc sestamibi single photon emission computed tomography (SPECT, n = 67) with intraoperative PTH monitoring in 128 consecutive patients during a 19-month period. Ninety-five percent of patients in the control group and 96.9% of all patients were deemed to have a successful outcome, using a criterion of normocalcemia at 6 months postsurgery.

Several studies have evaluated intraoperative PTH testing, with comparisons to historical control groups *(5, 9–11)*. A potential confounder of this type of control group may be an effect on surgical outcome as a result of surgical experience. Henry et al. *(5)* performed a case-control study comparing endoscopic VAP modified via a lateral approach in 68 patients with sporadic primary hyperparathyroidism and a single adenoma suggested by ultrasonography and sestamibi scan. The control group consisted of 68 patients matched for age and sex who underwent conventional parathyroidectomy with bilateral exploration and general anesthesia. The study was conducted during a 2-year period. A rapid intact PTH assay, method not described, was used during surgery on the VAP group. All patients were biochemically cured 1 year after surgery.

In another study, by Johnson et al. *(9)*, the experimental group consisted of 49 patients with primary hyperparathyroidism who underwent preoperative imaging with 99mTc-sestamibi scanning and in whom the Immulite turbo PTH

Table 10-1 Comparison of Cure Rates Between Control and Experimental Groups in Studies Using Intraoperative PTH in Patients With Primary Hyperparathyroidism

		Control group		Experimental group with IO PTH	
Study	**Design**	**Approach**	**Cure rate**	**Approach**	**Cure rate**
Bergenfelz, 2002 (7)	RCT	Bilateral (*n* = 44)	98%	Unilateral (*n* = 47)	96%
Miccoli, 1999 (8)	RCT	Bilateral (*n* = 18)	100%	Video-assisted (*n* = 20)	100%
Carty, 1997 (6)	Cohort	Unilateral w/palpation (*n* = 61)	95%	Unilateral w/preoperative imaging (*n* = 67)	97%
Henry, 2001 (5)	Historical controls	Bilateral (*n* = 68)	100%	Video-assisted (*n* = 68)	100%
Chen, 1999 (10)	Historical controls	Bilateral (*n* = 184)	97%	Minimally invasive (MIP) (*n* = 33)	100%
Udelsman, 2003 (11)	Historical controls	Bilateral (*n* = 401)	97%	Minimally invasive (MIP) (*n* = 255)	99%

RCT, randomized controlled trial.

(Diagnostic Products Corporation, Los Angeles, CA, USA) was performed in the central laboratory. The control group was made up of 55 historical cases who underwent parathyroidectomy before the introduction of these 2 technologies. There was no statistical difference between groups in the outcome measure, postoperative calcium concentrations.

In a study by Chen et al. *(10)*, an outpatient minimally invasive parathyroidectomy technique (MIP), consisting of preoperative sestamibi-SPECT imaging, surgeon-administered local or regional anesthesia, exploration though small incisions of 1 to 4 cm, and intraoperative PTH measurements at 5 to 10 min after parathyroid resection, was used in 33 consecutive patients with primary hyperparathyroidism. The control group consisted of 184 consecutive patients who underwent bilateral exploration with general anesthesia. The MIP patients and control patients were similar with respect to age, preoperative calcium and PTH levels, cause of primary hyperparathyroidism, and weight of resected glands. Patient outcomes were also similar with respect to cure rates of 100% and 97.3%, respectively (*P* not significant). Surgical cure was indicated by a serum calcium concentration of 8.4–10.5 mg/dL 4 months postoperatively, with follow-up to 6 months when possible. This series has recently been expanded to 656 consecutive parathyroid explorations by a single surgeon during an 11-year period *(11)*. Of the 656 patients explored for primary hyperparathyroidism, 61% were performed with the standard technique and 39% were selected for MIP. The success rate for the entire series was 98%, with no significant difference between the 2 techniques (97% standard, 99% MIP).

In Canada, a Consensus Development Task Force on Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism *(12)* stated in their recommendations that intraoperative PTH assays are necessary for patients undergoing MIP. In the US, operative failure rates were examined in 447 consecutive cases of primary hyperparathyroidism during a 30-year period *(13)*. Rates were 5% (14/275, 1969–1989), 10% (4/39, 1990–1993), and 1.5% (2/133, 1993–1998), with operative approaches of bilateral neck exploration with excision of large glands and biopsy of normal glands, bilateral neck exploration with excision of large glands with intraoperative PTH, and limited dissection with preoperative localization and intraoperative PTH, respectively. The failure rate significantly decreased from 6% to 1.5% ($P < 0.05$) in the last 5 years.

Approximately 50 case series, both retrospective and prospective, have examined the use of intraoperative PTH in patients operated on for primary hyperparathyroidism *(1, 14–58)*. Studies in which assay results were used in real time to guide the operation have in general found the assay to be useful in cases of uniglandular disease. Accuracy in detecting multiglandular disease is more controversial. In the most focused study, Gauger et al. *(59)* retrospectively examined 20 patients from 2 institutions, undergoing conventional parathyroidectomy, who had exactly 2 glands excised based principally on size greater than an estimated 70 mg. Specimens were taken postinduction and at 5 and 10 min after removal of the first gland; however, PTH values were not used to guide exploration. Nine of 20 patients had a true-negative result, with PTH values failing to fall below the 50% threshold. The false-positive rate with PTH values falling >50% compared to baseline was 55%. It has been questioned, however, in patients with double adenomas whether the second gland is hyperfunctioning with 1 parathyroid functionally dominant and other enlarged gland relatively quiescent *(60)* or whether the larger gland can suppress smaller yet abnormal glands that could become hypersecretory if not removed *(25)*.

In a similarly designed study in which PTH measurements were not used in real time, Weber and Ritchie *(60)* found 15 false positive results in 112 patients undergoing conventional parathyroid exploration, specifically 1 of 71 single adenomas, 4 of 6 double adenomas, 7 of 15 primary hyperplasias, and 3 of 17 tertiary hyperplasias. Gordon et al. *(25)* also used morphologic criteria, not intraoperative PTH values, to guide tissue resection. Twenty-four percent of the 72 patients with primary hyperparathyroidism had multiglandular disease. Using intraoperative PTH, 6% would have had extended explorations and 6% may have required reoperation for unidentified multiglandular disease. The authors concluded the results validated the accuracy of the intraoperative PTH assay. False-positive rates of 50% in primary hyperparathyroidism were observed in very small series when intraoperative PTH was used in real time *(35, 61)*. Persistent hypercalcemia was present in 1 study *(61)* and, in the other, morphologically abnormal glands were found during contralateral thyroidectomy *(35)*. In contrast, in several additional studies in primary hyperparathyroidism the intraoperative PTH assay was accurate in correctly identifying multiglandular disease *(53, 56)*.

The incidence of multiglandular disease has been used as an argument that parathyroid glands excised according to morphologic criteria may be nonfunctioning and therefore not identified biochemically. For example, in contrast to the overall frequency of multiglandular disease in reported series of 8%–33%, Molinari et al. *(62)* found an incidence of multiglandular disease in primary hyperparathyroidism of 5% using intraoperative PTH in 105 consecutive patients. In another study *(63)*, the multiglandular disease rate was 15% with bilateral exploration and 0% with focal neck exploration in patients with sporadic primary hyperparathyroidism with 1 gland identified preoperatively. Intraoperative PTH was measured in both groups.

A concern in excising hyperfunctioning glands determined by intraoperative PTH without visualizing remaining glands is that there will be a higher late recurrence rate *(64)*. This was addressed in 2 studies *(56, 64)*. The accuracy of intraoperative PTH measurements to predict late postoperative normocalcemia was 95% in 80 patients followed up for 5 years after primary exploration *(56)*. In the second study, 320 consecutive patients with primary hyperparathyroidism were followed 6 to 313 months after successful parathyroidectomy *(64)*. The experimental group (n = 144) had glands excised according to intraoperative PTH measurements, and the historical control group (n = 176) had bilateral neck exploration with excision of enlarged glands. The number of patients with more than 1 gland excised in the control group was 3 times higher than in the experimental group ($P < 0.05$). However, there was no significant difference in the incidence of recurrent hyperfunctioning glands between the 2 operative approaches.

Literature Search 62 addressed whether the addition of intraoperative PTH measurements to surgery for parathyroid disease improves morbidity or complication rate compared to bilateral exploratory surgery alone in patients with primary hyperparathyroidism.

In general, in the small number of studies in which surgeries were performed with and without intraoperative testing, morbidity and complication rates were similar to or lower than the rate for the control group. Eleven percent of patients in the bilateral group and 4% of patients in the unilateral group had a significant complication in the randomized study by Bergenfelz et al. *(7)* ($P = 0.27$), whereas in the subset of patients with a solitary adenoma, patients operated on with a unilateral approach consumed less oral calcium during the first 4 postoperative days and had less incidence and severity of symptomatic and biochemical hypocalcemia ($P = 0.04$). Complications totaled 1 of 68 patients (inferior laryngeal nerve palsy) for the VAP procedure and 4 of 68 patients with conventional parathyroidectomy (transient systematic hypocalcemia, n = 3; wound hematoma, n = 1), which was not statistically significant *(5)*. Concise parathyroidectomy with intraoperative PTH and preoperative imaging *(6)* had less frequent minor morbidity compared to controls ($P < 0.00001$), with no major morbidity such as permanent vocal cord injury, as observed in the controls (n = 1). Morbidity was equally low for MIP (0%, n = 33) vs bilateral exploration (2.2%; n = 184; *P* value, not significant) *(10)*. Complications in the larger patient group *(11)* were similarly low, at 3.0% and 1.2% for standard and MIP explorations, respectively, as was the incidence of ipsilateral recurrent laryngeal nerve injury in both groups (<1%).

Literature Search 63 addressed whether the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improves use of local or regional anesthesia or extent of exploration (unilateral vs bilateral) compared to standard bilateral exploration.

In the study by Johnson et al. *(9)*, described previously, the impact of intraoperative PTH in conjunction with preoperative imaging and concise parathyroidectomy on use of local vs general anesthesia and unilateral vs bilateral neck explorations was evaluated. There was significantly increased use of local anesthesia in the experimental group compared to the control group (33% vs 0%; $P < 0.001$), as well as increased unilateral exploration (65% vs 0%; $P < 0.001$). Carty et al. *(6)* also observed increased unilateral exploration in a prospective cohort study comparing the palpation method for selective unilateral exploration (n = 61) to use of preoperative 99mTc sestamibi SPECT (n = 67) with the intraoperative PTH assay. Unilateral exploration was possible in 41% of patients with the first strategy and in 63% of patients with the operative technique, including intraoperative PTH ($P = 0.014$). In this study, a modification of the Nichols immunochemiluminometric assay (ICMA) assay, with a sensitivity of 40 pg/mL, was performed in the operating room, with a total turnaround time of <15 min. Unilateral exploration has been described as the major advantage of intraoperative PTH measurements *(15)*.

Literature Search 64 investigated whether the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improves use of frozen sections compared to standard bilateral exploration.

Two studies have examined the effect of intraoperative PTH on frozen-section use in comparison to a historical control groups of patients undergoing parathyroidectomy before the introduction of the technique. In 1 study *(51)* comparing 2 groups of patients undergoing parathyroidectomy with bilateral exploration, an average of 3.4 (range, 1–9) frozen sections was sent in the group of patients before introduction of the assay and 2.0 frozen sections (range, 0–6; $P < 0.01$) in the patients for whom the PTH assay was used in the operating room. In patients undergoing reoperation (n = 2), 3.0 (mean) frozen sections sent were in the group without PTH measurements and 2.12 frozen sections sent in the group with PTH measurements (n = 8), although statistical significance was not reached in this small sample set. In this study, operative times were similar, as were cure rates. Costs were not directly examined.

In the second study *(9)*, the experimental group consisted of 49 patients who underwent preoperative imaging with 99mTc-sestamibi scanning and for whom intraoperative PTH was used, whereas the control group was made up of 55 historical cases operated on consecutively, with a concise, minimally invasive approach. Frozen section use was significantly greater ($P < 0.0001$) in the control group, with a mean of 2.5 sections (range, 1–7), and all patients had at least 1 frozen section. The mean in the experimental group was 1.4 (range, 0–6), and 10 of the 49 patients had no frozen sections sent. According to a cost of $203 per frozen section, it was estimated that there was an average savings of >$200 in surgical pathology costs. The authors speculated in this 2001 report that as surgeons become more accustomed to the intraoperative PTH assay, frozen-section use will almost disappear when expected decreases in PTH values are achieved *(9)*.

A novel application for the rapid PTH assay as a substitute for tissue frozen section has been suggested in 1 report *(65)*. In this retrospective study, intraoperative parathyroid aspirates from histologically confirmed parathyroid adenomas were compared to thyroid and other nonparathyroid tissue aspirates. A sensitivity and specificity of 100% was achieved with a cutoff of >1500 pg/mL, the upper limit of the QuiCk-Intraoperative Intact PTH assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA).

Literature Search 65 investigated whether the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improves operating room time, operating room fees, overall hospital costs, or length of stay compared to standard bilateral exploration.

The majority of evidence suggests financial savings to the institution as a result of the use of intraoperative PTH, often incorporated with other techniques and surgical approaches. Most evidence incorporates historical controls for comparison, however. Outcomes examined include operating room time and fees, hospital lengths of stay, and overall hospital charges or costs. In one of the first studies combining preoperative localization of parathyroid tumors via 99mTc sestamibi (MIBI)

scintigraphy with a rapid PTH assay, cost-effectiveness was evaluated by comparing operating times for 18 patients with primary hyperparathyroidism to operating time for patients not subjected to these procedures *(33)*. Operative times decreased to an average of 36 min from 90 min. In a subsequent prospective study by the same surgeon in a consecutive series of 85 patients *(34)*, the mean operative time was 55 min (range, 21–130 min) with intraoperative PTH. In 42 of 57 patients eligible for surgery in an ambulatory setting, same-day discharge was possible. At that institution, parathyroidectomy performed in an ambulatory setting was charged at a rate 39% less than the rate for patients requiring an overnight admission.

In 2 studies of VAP compared to conventional parathyroidectomy *(5, 8)*, operative time was shorter in the randomized study (57 vs 70 min; $P < 0.05$) *(8)* and similar in the case-control study, with 64.9 min for the VAP group and 67.5 min for the standard operation *(5)*. Unfamiliarity with the new technique was an explanation. Operative time directly affected the cost per procedure charge in the first study ($1720 vs $1910) because other costs for anesthesia and frozen section or intraoperative assays were similar between the VAP and bilateral neck exploration procedures *(8)*. Operative times and surgical procedure costs were not different between the unilateral (with intraoperative PTH) and bilateral groups in the randomized prospective trial by Bergenfelz et al. *(7)* for all 88 patients; however, when patients with only a solitary parathyroid adenoma were compared, mean operative times were significantly shorter in the unilateral group (62 ± 29 min; n = 41) compared to the bilateral group (84 ± 38 min; n = 40; $P < 0.01$). Similarly, in a subset analysis comparing directed operations using the intraoperative PTH assay (n = 30) to conventional bilateral explorations (n = 31) in a case series, total hospital costs were similar ($3847 vs $3949), as was the mean length of hospitalization (1 day), whereas mean operating times tended to be shorter, at 72 vs 97 min *(66)*.

In a cohort study comparing 2 methods for selective unilateral exploration for sporadic primary hyperparathyroidism, one of which included intraoperative PTH and preoperative imaging, operative times were similar *(6)*. This was explained by the study protocol requiring biopsy of a normal parathyroid gland post–adenoma excision. Perioperative costs also did not differ; however, the mean length of hospital stay was significantly shorter in the intraoperative PTH group (1.07 ± 0.82 days vs 1.9 ± 0.94 days; $P < 0.00001$). Similarly, Johnson et al. *(9)* observed more same-day surgeries (35%) and fewer overnight stays (59%) and stays ≥48 h (6%) in the intraoperative PTH/imaging experimental group than in the control group ($P < 0.0001$), which had 87% of patients stay overnight and 13% stay ≥48 h.

The ability to perform parathyroidectomy on an outpatient basis with a minimally invasive approach incorporating intraoperative PTH resulted in shorter operative times and accounted for the significant decrease in length of hospital stay and therefore decreased hospital charges compared to patients who underwent bilateral parathyroid exploration in the study by Chen et al. *(10)*. Lengths of stay were MIP (n = 33) 0.3 ± 0.2 days, controls (n = 184) 1.8 ± 0.1 days, $P < 0.001$; whereas hospital charges in 1998 were MIP $3174 ± $386, controls $6328 ± $292 ($P < 0.001$). In an expansion of this series of patients operated on by a single surgeon during an 11-year period, comparing MIP with conventional bilateral exploration, durations of surgery (1.3 h vs 2.4 h; $P < 0.001$) and anesthesia (1.6 h vs 3.1 h; $P < 0.001$) were lower, as again were lengths of stay (0.24 days vs 1.64 days; $P < 0.0001$) *(11)*. There was a significant overall mean savings of $2693, which represented 49% of the total hospital charges ($P < 0.0001$). When stratified by new or redo procedures, lengths of stay and hospital charge outcomes followed the same significant pattern.

Flynn et al. *(24)* compared charges for a minimally invasive radioguided parathyroidectomy (MIRP), with discharge within 23 h, to a historical standard neck exploration group with minimum 23-h hospital admission. Operating room time (83 min vs 128 min), operating room charges ($1612 vs $2486), and anesthesia charges ($868 vs $1165) were less in the MIRP group, and frozen sections were eliminated. However, overall savings of $965 ($7451 vs $8416) with the outpatient procedure was characterized as modest by the authors. Wilkinson et al. *(67)* reported an analysis of hospital expenses for consecutive parathyroidectomies performed in 1994 without intraoperative PTH testing (n = 40), surgeries performed during 1997 to 1998 in hospitalized patients with intraoperative PTH and preoperative imaging studies (n = 20), and surgeries performed on an outpatient basis with both imaging and PTH studies (n = 20). Average costs were $5830, $4061, and $3420, respectively.

Fahy et al. *(68)* performed a cost-benefit analysis of localizing strategies, including intraoperative PTH and other techniques, by developing a clinical outcome model to simulate the surgical management of primary hyperparathyroidism according to charges from their surgical practice and the literature. Average total charges for bilateral neck exploration were $17,358, whereas charges for a limited neck exploration with intraoperative PTH were $14,962, and charges combining intraoperative PTH and preoperative technetium 99mTc sestamibi scanning were $13,854. Another study defined cost-effectiveness as the true cost of avoiding a failed operation as opposed to the cost of performing 1 test *(69)*. Their model was based on a study in 88 patients who underwent MIP with intraoperative PTH, although values were not used intraoperatively but only used as part of the study in comparison to short-term serum calcium concentrations up to 3 months postsurgery. They calculated a cost of $19,801 to avoid a failed operation in 7 patients who would be converted to a bilateral exploration procedure. Use of same-day routine PTH and calcium measurements instead would cost $625, although cost to repeat the operation was not included.

Literature Search 66 investigated whether the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improves incision size/cosmetic result or patient satisfaction/pain compared to standard bilateral exploration.

Several studies of varying design have examined the impact of intraoperative PTH on patient-reported aspects of parathyroid surgery, including postoperative pain, cosmetic result, and

other patient satisfaction issues. In the prospective randomized control trial by Miccoli et al. *(8)*, postoperative pain assessed using a visual analog scale was significantly less in the VAP with intraoperative PTH group during the 48-h postoperative period ($P < 0.03$), with a score approximately half that in the control group. The authors attributed the decreased pain to a shorter skin incision, as well as decreased neck hyperextension. Patients were also asked to complete a questionnaire at 1, 3, and 6 months postsurgery, describing time to return to normal activities and personal opinion on esthetics of the scar, with a 10-point score. The postoperative inactivity period was significantly shorter in the experimental group (12 ± 5.5 days vs 16 ± 6 days; mean ± SD). Personal satisfaction was also greater in the experimental group with respect to cosmetic result, with a score averaging ~3 points higher ($P < 0.03$).

In the case-control study by Henry et al. *(5)*, patients in the VAP experimental group with a 12-mm skin incision were paired with patients who had a classic transverse cervicotomy. Patients in the control group required analgesic (paracetamol) administration during the postoperative period an average of 1.66 times compared to 0.46 times for the VAP group ($P < 0.05$). Satisfaction with the cosmetic results was slightly but significantly higher in the VAP group ($P < 0.05$), as assessed during telephone questioning. Follow-up was obtained in 89% of patients, with a shorter mean follow-up of 9.2 ± 6.3 months in the VAP group compared to 23.2 ± 13.5 months in the control group. In a final study in which patient satisfaction was assessed by telephone, Burkey et al. *(66)* found no difference in overall satisfaction, satisfaction with anesthesia, length of stay, pain after discharge, and scar among patients in a prospective study using a gamma probe, intraoperative PTH, or neither. Patients in all 3 groups were explored through a collar incision ranging from 3–6 cm. Follow-up surveys were attempted in only 50% of patients (n = 75). A limitation to the study was lack of uniform treatment protocols, as described by the authors.

OTHER PARATHYROID DISEASES

Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in patients with secondary or tertiary hyperparathyroidism? (Literature Search 67)

Guideline 142. *Numerous case series suggest a role for intraoperative PTH in secondary or tertiary hyperparathyroidism, yet no studies compared outcomes to surgical procedures in which intraoperative PTH testing was not used. In addition, criteria for expected changes in PTH concentrations after total or subtotal parathyroidectomy require further study. Therefore, we make no recommendation for or against routinely providing intraoperative PTH testing for this application.*

Strength/consensus of recommendation: I

Level of evidence: III (multiple case series, opinion)

In contrast to primary hyperparathyroidism, the use of intraoperative PTH to ensure adequacy of resection in secondary (compensatory hyperplasia caused by low calcium concentrations primarily because of renal failure) and tertiary (autonomous PTH production in the presence of corrected calcium levels, which usually follows secondary disease) hyperparathyroidism has been less frequently studied. Existing studies primarily consist of observational case series. The first study to address use of intraoperative PTH was published in 1997 *(70)* and retrospectively examined 13 consecutive patients with secondary hyperparathyroidism who were undergoing total parathyroidectomy with autotransplantation or subtotal parathyroidectomy. PTH concentrations decreased an average of 84.6% after resection of 3½ or 4 glands compared to the highest of 2 baselines. In limited early follow-up, symptoms were improved in all patients, and PTH concentrations were below preoperative values. The authors speculated that use of a 50% guideline similar to primary hyperparathyroidism may not be adequate because, at minimum, subtotal parathyroidectomy is required for successful treatment. Differing rates of decline between renal and nonrenal hyperparathyroidism may also play a role. The authors also stated that long-term follow-up and increasing the number of patients would be crucial to define the role of the PTH assay in this setting. A decline of 50% in PTH values at 20 min after resection was highly predictive of cure in a large series of consecutive patients undergoing neck exploration for renal hyperparathyroidism (73 secondary, 7 tertiary), in which cure was defined as the absence of hypercalcemia and a PTH concentration less than 4 times normal. The positive predictive value was 93% and sensitivity was 96% in that study *(71)*. They authors also determined that a decrease in PTH values of <40% compared to baseline suggested a missed or hyperfunctioning supernumerary gland and is predictive of failure, with a decrease between 40% and 50% representative of variability in PTH half-life among patients. The 7 patients with tertiary hyperparathyroidism demonstrated declines in PTH similar to that of patients with primary hyperparathyroidism.

Pellitteri *(45)* retrospectively investigated 346 patients during a 7-year period in which all patients had intraoperative PTH measurements, with the study hypothesis to evaluate a directed exploration protocol. In that group, 13 of 16 patients with secondary hyperparathyroidism and 3 of 3 patients with tertiary hyperparathyroidism had therapeutic success, as determined by normocalcemia or resolution of symptoms postoperatively. Three other studies *(40, 72, 73)* that specifically studied a series of patients with secondary or tertiary hyperparathyroidism found relevant decreases in PTH concentrations similar to those previously documented in patients with primary hyperparathyroidism, although 1 report stated that addition of the assay seemed to change the operative procedure very little *(72)*. Intraoperative PTH was accurate and a useful aid in a number of studies in which secondary and tertiary hyperparathyroid patients were studied as part of a larger series of patients; however, numbers of patients were typically 10 or fewer, and follow-up was <6 months *(30, 44, 49, 50, 52, 74)*, with the exception of 1 study in which median follow-up was 8 months *(53)*. In a similarly designed retrospective study of 107

consecutive parathyroidectomies, 11 patients with secondary or tertiary hyperparathyroidism were included *(46)*. There were 2 late-operative failures in dialysis-dependent patients with postoperative hypercalcemia at 18 and 34 months after a period of normocalcemia. Postexcision PTH concentrations in these patients decreased 84% and 86%, respectively. Failures were theorized to be attributed to small nonfunctional or hypofunctional supernumerary parathyroid glands that became hyperfunctional after seemingly definitive surgery.

Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in patients with reoperative disease? (Literature Search 68)

Guideline 143. *Evidence with respect to successful surgical outcome shows utility of intraoperative PTH in patients undergoing reoperation, and therefore we recommend that the assay be used routinely in this patient population.*

Strength/consensus of recommendation: B

Level of evidence: II and III (controlled trials, multiple case series)

The recommendation for use of intraoperative PTH is based on evidence from studies in which reoperative cases were specifically studied, as well as studies in which these cases were part of a larger series of primarily new cases. Reoperations may be necessary as the result of persistent or recurrent parathyroid disease, or patients may have had previous neck surgery for thyroid disease. Fibrosis and scarring from initial procedures make subsequent surgeries more difficult; thus, repeated procedures for primary hyperparathyroidism have higher complication rates and lower success rates compared to initial explorations. A study by Irvin et al. *(75)* investigated reoperative parathyroidectomy with (n = 33) and without (n = 17) intraoperative PTH in 50 consecutive patients with persistent or recurrent primary hyperparathyroidism. Groups were similar in age and symptoms, although the controls preceded the cases in time. A successful outcome was defined in the controls as a serum calcium concentration <11 mg/dL for 6 months or longer, whereas in the intraoperative PTH group, successful outcome was defined as a return to a calcium level of 10.2 mg/dL or less. The success rate was 76% in the control group and 94% in the intraoperative PTH group, in which the assay was also used in 42% of cases to lateralize the hypersecreting gland via direct venous sampling.

The large consecutive series of primary hyperparathyroid patients by Udelsman *(11)*, comparing bilateral cervical exploration to MIP with intraoperative PTH, included 72 redo cases in the standard operation group (18% of total) and 12 redo cases in the MIP group (5% of total). In this subgroup, cure rates were favorable and indistinguishable, comparing new and redo explorations. Reoperative surgeries were 100% successful in another prospective group of 11 patients with primary hyperparathyroidism, previously operated on 1 to 3 times with a directed surgical approach consisting of preoperative imaging, intraoperative technetium 99m sestamibi scanning, and intraoperative PTH with normocalcemia at 3 to 6 postoperation *(76)*.

Thompson et al. *(77)* performed a retrospective study of 124 patients with primary hyperparathyroidism undergoing reoperative parathyroid surgery, of whom 16 were monitored intraoperatively with PTH testing. Curative results were confirmed with PTH in 5 patients with suspected single-gland disease and 9 of 11 patients with multigland disease, with a criterion of a 50% decrease at 20 min postexcision and curative results in all patients with a 70% guideline. This compared to sensitivities of 75%–90% with various preoperative imaging techniques in the entire 124-patient group. A number of other case series included reoperative patients in their studies but did not perform subgroup analyses *(16, 17, 22, 24, 31, 35, 40, 71, 78)*. Primary hyperparathyroid patients were principally studied, although patients with secondary/tertiary disease and patients with previous neck surgery for thyroid disease were also included. In studies in which subgroup analyses were performed in both reoperative primary hyperparathyroidism and secondary/tertiary hyperparathyroidism, cure rates were equal to or greater than cure rates in initial surgeries *(39, 49, 50, 52)*.

Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in patients with multiple endocrine neoplasia (MEN) I? (Literature Search 69)

Guideline 144. *We make no recommendation for use of intraoperative PTH testing in patients with MEN I. Results were positive in several case studies and several larger retrospective series; however, the studies lacked control groups.*

Strength/consensus of recommendation: I

Level of evidence: III (multiple case series)

During a 6-year period, Tonelli et al. *(79)* used intraoperative PTH measurements with a modified immunoradiometric assay (IRMA) in 16 patients with MEN I who underwent total parathyroidectomy with autotransplantation for their multiglandular hyperplasia. MEN I is one of a family of genetic disorders that results in multiple endocrine gland neoplasias. Bilateral exploration is required in these patients *(80)*. In the Tonelli et al. *(79)* study, PTH values decreased in a stepwise fashion after the removal of each gland, with an average PTH 22.3% of baseline 2 min after removal of the last gland, with values below the upper limit of the reference range. No patients were hypercalcemic after an average follow-up of 35 months. Patterns of PTH decay differed between a comparison group of 20 patients

who had a single adenoma resected compared to removal of the first gland in these MEN I patients, with declines of 21% and 74% of baseline at 10 min postexcision, respectively *(79)*.

In another series of 20 patients with MEN I, a subset of a larger group operated on during a 29-year period, intraoperative PTH was used, with a criterion of a 50% decrease at 5 min after subtotal parathyroidectomy with thymectomy *(81)*. Cure, defined as euparathyroid or hypoparathyroid, with a mean follow-up of 13 ± 11 months, was predicted with a sensitivity of 95% and an accuracy of 95%. It has been suggested *(22, 81)* that in these patients, an 80% decrease overall is more reasonable as a target and that final PTH concentrations should be within the reference range or barely detectable. Several case studies have also found positive results with intraoperative PTH monitoring in this population of patients *(12, 22, 30, 47)*.

Despite the success of the previous 2 studies with respect to recurrence of disease, rates of recurrence in patients with MEN I are higher than in patients with sporadic hyperparathyroidism, which is attributed to inadequate initial surgery, presence of supernumerary and ectopic glands, regrowth of remnant tissue, or autograft hyperfunction *(82)*. The utility of intraoperative PTH was explored in 14 patients as part of a 25-year series (1975–2000) of 94 patients with MEN I, reoperated on for hyperparathyroidism *(82)*. With respect to removal of the first gland and an expected decrease of 50%, in 12 cases PTH did not decline and additional glands were resected, or PTH did decline and no additional tissue was found. There were 2 false-positive cases as second glands were found. Ninety-three percent of cases had normal calcium and PTH values at a median follow-up of 11 months. The authors commented that the potential of the assay in the reoperative MEN I setting was encouraging *(82)*.

Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in patients with parathyroid cancer? (Literature Search 70)

Guideline 145. *We conclude that the evidence is insufficient to recommend for or against use of intraoperative PTH measurements in patients with parathyroid cancer.*

Strength/consensus of recommendation: I

Level of evidence: III (multiple case series)

Parathyroid cancer is very rare, accounting for 1% of cases of hypercalcemia and hyperparathyroidism. It is usually diagnosed during surgery for hyperparathyroidism, although plasma calcium concentrations tend to be higher than in patients with adenomas or hyperplasia *(83)*. Because of the very low prevalence of the disease, it is not surprising there are few data on the role of intraoperative PTH in such cases, with only 1 or 2 patients included in various case series *(23, 30, 39, 47, 52, 63, 78, 84)*.

LOCALIZATION

Does performing intraoperative PTH measurements in the angiography suite aid in identifying PTH gradients and result in a diagnostic study during venous localization compared to performing PTH measurements in the central laboratory? (Literature Search 71)

Guideline 146. *Despite limited evidence, we recommend that intraoperative PTH measurements be considered as a replacement for traditional laboratory measurements of PTH during venous localization to provide real-time results to the angiography team to guide sampling.*

Strength/consensus of recommendation: B

Level of evidence: III (case reports and series, and opinion)

Guideline 147. *We make no recommendation for use of rapid PTH tests in the operating suite for tumor localization because of conflicting studies. Although this may be a promising application for the rapid assay, additional studies are needed to determine whether this approach is better than more current and improved preoperative scanning techniques and the most appropriate population for use, such as reoperative cases, because routine use is not justified.*

Strength/consensus of recommendation: I

Level of evidence: III (case series)

In patients undergoing repeated exploration for primary hyperparathyroidism, studies to localize abnormal tissue are performed with noninvasive imaging techniques; however, these studies will be noninformative in a small number of patients. These patients may be referred for selective venous sampling with PTH analysis and arteriography *(85)*. Typically, specimens collected from catheterized veins in the neck and mediastinum are sent to the laboratory and analyzed for PTH in batch. Results are matched to sampling location to potentially determine the general area of the adenoma via a venous gradient. After introduction of rapid assays for PTH, it was hypothesized by endocrine surgeon Dr. Robert Udelsman that real-time analysis of PTH in the angiography suite would be beneficial to the angiographer and the patient, allowing the angiographer to obtain additional specimens when a subtle gradient in PTH concentrations is detected *(86)*. This would not be possible using the standard approach. A case report from 2000 in a patient undergoing venous localization for persistent hyperparathyroidism used the rapid PTH assay (QuiCk-Intraoperative Intact PTH assay) in the angiography suite, with comparisons analytically and clinically to samples analyzed as a batch in the

clinical laboratory with an IRMA method *(86)*. The real-time benefits were manifested in this case by the ability to repeat a questionable sample. In this case and in a subsequent series of 7 patients, the cure rate was 100% when a venous gradient was demonstrated *(86, 87)*. Despite the lack of case-controlled studies, it has been noted that angiographic localization may prove to be the most beneficial application of the rapid/intraoperative PTH assay *(86)*.

Several studies *(39, 88–90)* have examined use of the rapid PTH assay in the operating suite for venous localization to aid in locating hyperfunctioning glands by sampling veins on either side of the neck or through tissue massage. In 1996, Saharay *(89)* studied 15 consecutive patients undergoing parathyroidectomy for primary hyperparathyroidism to assess whether a locally increased PTH level during selective venous sampling accurately predicted the site of the adenoma. Using a modification of the Nichols Institute Diagnostics ICMA assay with a turnaround time of 25 min, PTH was analyzed in specimens from the superior, middle, and inferior thyroid veins on both sides of the neck. In all 15 patients, the PTH concentration accurately indicated the location of the abnormal parathyroid gland, including 1 case in which equivalent results suggested an ectopic location, although in 10 of the cases, the adenoma was identified before the PTH results were available. Postoperative calcium concentrations were normal in all cases. Sensitivity of this approach was superior to ultrasound and thallium/technetium scanning, which identified 5 of 15 abnormal parathyroids.

In another study, a lateralizing gradient comparing peripheral and internal jugular veins was found in 63% of 20 consecutive patients with primary hyperparathyroidism *(88)*. Similarly *(90)*, adenomas were correctly lateralized in 76% of primary hyperparathyroid patients (n = 23) compared to 41% for thallium/technetium scanning ($P < 0.02$). In a more recent study *(39)*, localization of the side of the hyperfunctioning tissue was successful in only 3 of 9 patients with negative preoperative sestamibi scan results. Although this may be a promising application for the rapid assay, additional studies are needed to determine whether this approach is better than more current and improved preoperative scanning techniques and the most appropriate population for use, such as reoperative cases, because it has been stated that routine use is not justified *(88)*. Therefore, we make no recommendation for use of the rapid PTH assay in the operating suite for venous localization.

SECONDARY QUESTIONS

Is there evidence to support use of a specific assay? (Literature Search 72)

Guideline 148. *There is no evidence to suggest superiority of an intraoperative intact PTH assay from a particular manufacturer compared to available assays. We do not recommend the use of a specific assay for intraoperative PTH monitoring. Additional studies comparing bio-intact or whole PTH rapid intraoperative assays to intact rapid intraoperative assays need to be performed to determine whether improved benefit exists.*

Strength/consensus of recommendation: I

Level of evidence: III (comparative studies)

Since the introduction of the first US Food and Drug Administration– (FDA) cleared assay for intraoperative PTH testing in the mid-1990s, several other assays have become commercially available. Assays are available in both automated and manual formats. PTH assays on traditional immunoassay platforms with appropriately short assay times have also been used successfully. Because the Nichols QuiCk-IntraOperative Intact PTH assay was the first rapid PTH assay developed, the majority of studies reviewed for these guidelines have used this assay. Rapid intraoperative assays have been compared to standard-length assays, as well as to each other, analytically in numerous studies, although head-to-head clinical comparisons are sparse. However, clinical studies have been published individually with all commercially available rapid intact PTH assays, and there are no results to suggest that assays do not perform in a comparable manner. Two small studies in parathyroidectomy patients, 1 comparing the Nichols QuiCk-IntraOperative Intact PTH assay and the Immulite Turbo Intact PTH assay (n = 10) *(57)* and 1 comparing the Nichols QuiCk-IntraOperative Intact PTH assay to the Elecsys 1010 (Roche Diagnostics, Indianapolis, IN, USA) intact PTH assay (n = 13) *(91)*, showed complete diagnostic agreement. Models generated using data from minimally invasive surgery in 20 patients with primary hyperparathyroidism showed differences in calculated half-lives and residual PTH concentrations among the Nichols QuiCk-IntraOperative Intact PTH, Immulite Turbo Intact PTH, and Roche Elecsys 1010 intact PTH assays. However, differences were clinically irrelevant *(92)*.

Studies reviewed here have been performed with intact PTH assays that can cross-react with amino-terminally truncated PTH fragments, in addition to the full-length PTH molecule. Subsequently, an automated bio-intact (1-84) PTH assay for intraoperative use was developed. Use of a traditional, not rapid, assay for PTH 1-84 was examined for intraoperative use in a simulated study *(93)*. Plasma specimens analyzed from 29 patients with a single adenoma and 7 patients with secondary hyperparathyroidism obtained intraoperatively were frozen at –70°C for subsequent analysis using nonrapid intact and bio-intact PTH IRMAs. Results were similar in the single-adenoma population. In real time, the ICMA intact assay PTH values declined to <50% of initial values at 10 min post–total parathyroidectomy in the secondary hyperparathyroid group, as did results with the bio-intact assay. According to the standard intact assay in the frozen samples, 3 patients had values slightly above the 50% benchmark at 10 min, with all results <50% of baseline at 15 min. Additional studies comparing bio-intact or whole PTH rapid intraoperative assays to intact rapid intraoperative assays need to be performed to determine whether improved benefit exists.

Is there evidence to support a recommended sampling protocol with respect to timing and number of samples or recommended criteria for interpretation of intraoperative PTH values? (Literature Search 73)

Guideline 149. *We recommend in patients undergoing parathyroidectomy for primary hyperparathyroidism that baseline samples be obtained at preoperation/exploration and preexcision of the suspected hyperfunctioning gland. Specimens for PTH should be drawn at 5 and 10 min postresection, with a 50% reduction in PTH concentrations from the highest baseline as a criterion. Additional samples may be necessary. Kinetic analyses appear promising; however, more work needs to done to confirm their utility.*

Strength/consensus of recommendation: A

Level of evidence: III (comparative studies and opinion)

Outcomes of studies using PTH intraoperatively in primary hyperparathyroidism can vary, depending on timing of samples and criteria used for expected change in PTH values. Timing and criteria appear to be surgeon dependent. According to the half-life of intact PTH, a >50% decline in PTH concentrations after removal of the hyperfunctioning parathyroid gland(s) is a generally accepted guideline for the interpretation of PTH levels *(33)*. This was described at a recent workshop on asymptomatic primary hyperparathyroidism updating a 1990 consensus development panel *(94)*. However, limits of 40% *(55)*, 65% *(51)*, and 75% (specific for the Immulite assay) *(36)* have been proposed. Using a threshold for decline of 75% at 10 min as opposed to 50% resulted in decreased accuracy for uni- and multiglandular disease in 1 study *(25)*.

Characteristics such as timing and number of samples and sampling location are less clearly defined. Initial baseline samples may be drawn preincision and may occur in the preoperative area, in the operating room, and before, after, or at introduction of anesthesia. Drawing a second baseline specimen preexcision, when the affected gland is identified, has been recommended *(20, 31, 55, 58)* to account for any nonspecific release of PTH from potential tumor manipulation during surgery. Samples are typically drawn from peripheral veins, although internal jugular veins have also been used intraoperatively. A concern raised with samples obtained from the jugular vein is that the PTH concentration may be influenced by parathyroid tumors up- or downstream from the sampling site *(56)*.

The highest baseline value for PTH has been recommended for calculating the percentage of change in PTH concentration. Use of preexcision samples has been suggested to reduce the number of false-negative results in patients with a single adenoma. Comparing use of the initial baseline instead of the highest preexcision value would increase the number of false negatives from 2 to 34 in a study of 206 patients *(55)*. Also, PTH concentrations have been observed to increase after general anesthesia *(95)*. A recent protocol has suggested an immediate post–gland excision sample may also be useful *(58)*.

Timing of postexcision samples is generally at 5 or 10 min, although timings of 7, 15, and 20 min have been used in reported studies *(6, 44, 77)*. Sensitivity can increase with time *(16)*, as shown in 1 study in which sensitivity, specificity, and accuracy were 86%, 100%, and 85% at 5 min and 97%, 100%, and 97% at 15 min, respectively. Sensitivity and accuracy were poorer at 5 vs 10 min in a second study *(35)*, although in a third study 10 and 15 min postexcision operative success results were similar *(46)*. In a small study of reoperative primary hyperparathyroidism, it was claimed changing the degree of decline from baseline PTH from 50% to 70% at 20 min postresection increased accuracy for patients with multiglandular disease *(77)*. Whether the postexcision sample should also fall below the lowest baseline or the upper limit of the reference range in addition to a prescribed percentage change has also been debated, with a recent study *(35)* advocating a 50% change from the highest baseline with a result lower than the lowest baseline at any given time point.

A commonly used criterion to predict postoperative calcium concentrations, now termed the Miami QPTH (quick intraoperative PTH assay) criterion, was introduced in the early 1990s by George Irvin, MD, an endocrine surgeon who was a leader in the development of the intraoperative PTH assay and its introduction into clinical use, and his colleagues *(30)*. Briefly, the Miami criterion is a decrease in intraoperative PTH ≥ 50% from the highest of either the preincision or the preexcision level at 10 min after gland excision. Irvin's group *(96)* compared 5 criteria to the Miami QPTH criteria in 341 consecutive patients with sporadic primary hyperparathyroidism, who were followed up ≥6 months after the operation or recognized as operative failures. Results of this study are shown in Table 10-2. The Miami criterion was most accurate at 97%, although accuracy was similar at 95%, adding the requirement of a decrease at 10 min below the preincision value. All criteria were similar in false-positive percentages, whereas the Miami criteria resulted in the lowest false-negative rate, at 3% compared to 6%–24% for the other criteria ($P < 0.05$). Discussion on this article pointed out that running a 5-min sample, with the 10-min sample analyzed if needed, would speed up the operation.

A novel approach was reported by Libutti et al. *(37)* to address interindividual variability in the half-life of PTH and potential rigid timing of samples. They developed a kinetic algorithm to predict the success of parathyroid surgery according to the rate of PTH decay and found it correctly classified 45 patients with hyperparathyroidism compared to 43 patients correctly classified using a criterion of a 50% decrease at 5 min. A subsequent study *(92)* failed to validate this model, although a second model was constructed using preexcision values and 5, 10, and 15 min timed postresection samples, concluding the preoperative baseline PTH is necessary to determine cure, although insufficient for kinetic calculations, which require preexcision values.

Table 10-2 Comparison of Criteria for Use of Intraoperative PTH *(96)*

Criteria	False positives (%)	False negatives (%)	Accuracy (%)
≥50% From highest baseline at 10 min	0.9	2.6	97
≥50% From preincision baseline at 10 min	0.3	16	86
≥50% From highest baseline at 10 min and within reference range	0.4	24	79
≥50% From highest baseline at 10 min and below preincision value	0.6	6	95
≥50% From highest baseline at 5 min	0.6	11	90
≥50% From preexcision baseline at 10 min	0.6	15	87

Does performing intraoperative PTH measurements in or adjacent to the operating suite improve turnaround and operative times compared to performing intraoperative PTH measurements in the central laboratory with specimens transported via pneumatic tube or messenger? (Literature Search 74)

Guideline 150. *Evidence is lacking to recommend the location of intraoperative PTH testing either in or adjacent to the operating room or in the central laboratory. Important considerations such as interaction with the surgical team must be weighed in concert with costs and staffing issues. Studies to evaluate turnaround and operative times related to different locations have not been explicitly performed. Regardless of specific evidence, external validity may limit applicability to individual institutions.*

Strength/consensus of recommendation: I

Level of evidence: III (comparative reports and series, and opinion)

The location of intraoperative testing appears to have come full circle in the ~5 years since its inception. Initial assays were modifications of IRMA assays, thereby limiting testing to locations outside the operating suite such as the central laboratory because of radioactive tracers. The first assay specifically designed for intraoperative use was introduced and cleared by the FDA in the mid-1990s. The QuiCk-IntraOperative Intact PTH assay was designed to be performed with equipment that fit on a cart that could easily be transported outside the laboratory to the operating room or other remote location. Subsequent assays designed for rapid use have mainly focused on adaptations of assays on traditional immunoassay analyzers such as the DPC Immulite and Nichols Advantage. In a survey conducted by the College of American Pathologists in 2001 *(97)*, of 92 laboratories performing intraoperative testing, 71% of respondents performed testing in the central laboratory compared to 23% who performed testing in the operating room or surgical suite. Six percent performed testing in a satellite laboratory.

However, few data exist directly comparing testing locations. Wians et al. *(57)* performed a study in 10 patients undergoing parathyroid surgery in which samples were analyzed in the operating room by a medical technologist using the QuiCk-IntraOperative Intact PTH assay and samples were sent to the central laboratory to be analyzed on the Immulite system. Turnaround time and operative times were not directly addressed in this study, although overall surgical costs were reported to be similar (data not shown) comparing both sites. Cost per patient was calculated to be $360 for central laboratory PTH testing vs $760 for operating room testing, although the authors' preference was for intraoperative testing. In another comparison, reagent costs per test for PTH assays on 2 automated analyzers (DPC Immulite and Roche Elecsys 1010) were calculated to be 12% and 4%, respectively, of costs for a manual rapid PTH assay (Nichols QuiCk-IntraOperative Intact PTH). Despite improved costs and efficiency with automated analyzers, the authors recommended direct contact between the surgical and analytical teams to minimize transport time and improve communication *(92)*. Wenk et al. *(98)* calculated a reagent-only cost for testing 2 controls and 2 patient samples in the central laboratory with the Immulite assay of $24. They claimed that the overall cost is markedly lower than bedside tests and that assays can be done as quickly, with equal accuracy.

Although it would seem intuitive that turnaround times would be shorter with testing performed on site, studies have not been done. Times would also be institution specific, depending on the specific assay used, distance from operating suite to the laboratory, and mode of transportation to the central laboratory, including messenger or pneumatic tube. Distance from the pneumatic tube to the testing location in the central laboratory, as well as the efficiency of transfer, also contributes. Whether or not testing location affects operative times may depend on the complexity of the surgery, such as in patients with renal insufficiency, and the surgical approach. Turnaround time is an important consideration to the surgeon and laboratory; however, there are advantages and disadvantages to testing location *(97, 99)*.

The advantages to testing on site center on the ability of the technologist to interact with the surgical team, with direct involvement in preanalytic, as well as analytic, aspects of testing, increased visibility for the laboratory, and more involvement in patient care for the technologists. Disadvantages to

Table 10-3 Summary of Recommendations for Intraoperative PTH

	A Strongly recommend	B Recommend	C Recommend against	I Insufficient evidence
Disease				
Primary hyperparathyroidism	✓	✓		
Secondary hyperparathyroidism				✓
Reoperative hyperparathyroidism		✓		
MEN I				✓
Parathyroid carcinoma				✓
Venous/tumor localization				
Presurgery angiography suite		✓		
Operating suite				✓
Implementation				
Specific assay				✓
Testing location				✓

on-site testing for the laboratory include providing a dedicated technologist, as well as potentially dedicated equipment. In the central laboratory, technologists may perform other testing, and use of standard immunoassay analyzers precludes having to acquire new equipment and allows other testing, although perhaps not concurrently. Calibrations are also less frequent on the fully automated systems, and results may be more precise and accurate compared to manual methods. Reagent costs are likely to be less as a result of reagent packaging such as for individual patient use. Costs can be an important consideration for the laboratory in which, in the majority of cases, intraoperative PTH is a low-volume test. In 2002, 93% of laboratories performed testing 10 or fewer times per month, whereas 68% performed testing 5 or fewer times per month *(97)*. In centers in which testing volume is high and surgeries are performed by multiple surgeons in multiple locations, such as inpatient and outpatient surgical suites, testing in the central laboratory allows for that service, in addition to efficient use of labor and reagents *(97, 99)*.

SUMMARY

In summary, according to strong impressions from relatively few controlled studies, intraoperative PTH is recommended for routine use in patients undergoing surgery for primary hyperparathyroidism, particularly in directed surgical approaches (Table 10-3). This recommendation is based on evidence for improved patient/health, operational, and economic outcomes and applies to initial surgeries and in patients undergoing reoperative procedures. In contrast to the setting of primary hyperparathyroidism, further studies are needed to define the role of intraoperative PTH testing in patients with secondary/tertiary hyperparathyroidism, MEN I, and parathyroid cancer.

The number of commercial assays available for rapid PTH speaks to the interest in this point-of-care application. However, none of these assays was deemed superior, nor was there a recommendation for testing location. Future studies may serve to refine assay format and specificity, testing location, sampling protocols, and test interpretation, although standardization of some of these aspects of intraoperative PTH testing will be limited by institution-specific conditions. In addition to intraoperative monitoring during surgical resection, rapid PTH assays have potential applications in diagnostic localization. The assay is recommended for use in the angiography suite; however, additional studies are needed to determine whether or not the assay proves useful in the operating suite. Rapid PTH testing has spawned interest in using other rapid hormone tests intraoperatively and for tumor localization. Thus, the future is promising for rapid hormones in nonparathyroid disease applications, following in the footsteps of the rapid PTH model.

REFERENCES

1. Nussbaum SR, Thompson AR, Hutcheson KA, Gaz RD, Wang CA. Intraoperative measurement of parathyroid hormone in the surgical management of hyperparathyroidism. Surgery 1988; 104:1121–7.
2. Carter AB, Howanitz PJ. Intraoperative testing for parathyroid hormone: a comprehensive review of the use of the assay and the relevant literature. Arch Pathol Lab Med 2003;127:1424–42.
3. Sokoll LJ, Wians FH Jr, Remaley AT. Rapid intraoperative immunoassay of parathyroid hormone and other hormones: a new paradigm for point-of-care testing. Clin Chem 2004;50:1126–35.
4. Remaley AT, Woods JJ, Glickman JW. Point-of-care testing of parathyroid hormone during the surgical treatment of hyperparathyroidism. MLO Med Lab Obs 1999;31:20–4, 26–7; quiz 28–30.
5. Henry JF, Raffaelli M, Iacobone M, Volot F. Video-assisted parathyroidectomy via the lateral approach vs conventional surgery in the treatment of sporadic primary hyperparathyroidism: results of a case-control study. Surg Endosc 2001;15:1116–9.
6. Carty SE, Worsey J, Virji MA, Brown ML, Watson CG. Concise parathyroidectomy: the impact of preoperative SPECT 99mTc sestamibi scanning and intraoperative quick parathormone assay. Surgery 1997;122:1107–14; discussion 1114–6.
7. Bergenfelz A, Lindblom P, Tibblin S, Westerdahl J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a

prospective randomized controlled trial. Ann Surg 2002; 236:543–51.
8. Miccoli P, Bendinelli C, Berti P, Vignali E, Pinchera A, Marcocci C. Video-assisted versus conventional parathyroidectomy in primary hyperparathyroidism: a prospective randomized study. Surgery 1999;126:1117–21; discussion 1121–2.
9. Johnson LR, Doherty G, Lairmore T, Moley JF, Brunt LM, Koenig J, et al. Evaluation of the performance and clinical impact of a rapid intraoperative parathyroid hormone assay in conjunction with preoperative imaging and concise parathyroidectomy. Clin Chem 2001;47:919–25.
10. Chen H, Sokoll LJ, Udelsman R. Outpatient minimally invasive parathyroidectomy: a combination of sestamibi-SPECT localization, cervical block anesthesia, and intraoperative parathyroid hormone assay. Surgery 1999;126:1016–21; discussion 1021–2.
11. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. Ann Surg 2002;235:665–70; discussion 670–2.
12. Asymptomatic primary hyperparathyroidism: standards and guidelines for diagnosis and management in Canada: Consensus Development Task Force on Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism position paper. Endocr Pract 2003;9:400–5.
13. Boggs JE, Irvin GL 3rd, Carneiro DM, Molinari AS. The evolution of parathyroidectomy failures. Surgery 1999;126:998–1002; discussion 1002–3.
14. Agarwal G, Barraclough BH, Robinson BG, Reeve TS, Delbridge LW. Minimally invasive parathyroidectomy using the "focused" lateral approach, I: results of the first 100 consecutive cases. ANZ J Surg 2002;72:100–4.
15. Beck TM, Huber PR, Oertli D. Intraoperative parathormone measurement in patients with primary hyperparathyroidism: a prospective clinical study. Swiss Med Wkly 2003;133:206–9.
16. Bergenfelz A, Isaksson A, Lindblom P, Westerdahl J, Tibblin S. Measurement of parathyroid hormone in patients with primary hyperparathyroidism undergoing first and reoperative surgery. Br J Surg 1998;85:1129–32.
17. Biertho L, Chu C, Inabnet WB. Image-directed parathyroidectomy under local anaesthesia in the elderly. Br J Surg 2003; 90:738–42.
18. Boggs JE, Irvin GL 3rd, Molinari AS, Deriso GT. Intraoperative parathyroid hormone monitoring as an adjunct to parathyroidectomy. Surgery 1996;120:954–8.
19. Burkey SH, Snyder WH 3rd, Nwariaku F, Watumull L, Mathews D. Directed parathyroidectomy: feasibility and performance in 100 consecutive patients with primary hyperparathyroidism. Arch Surg 2003;138:604–8; discussion 608–9.
20. Carneiro DM, Irvin GL 3rd. New point-of-care intraoperative parathyroid hormone assay for intraoperative guidance in parathyroidectomy. World J Surg 2002;26:1074–7.
21. Catania A, Sorrenti S, Falvo L, Santulli M, Berni A, De Antoni E. Validity and limits of intraoperative rapid parathyroid hormone assay in primary hyperparathyroidism treated by traditional and mini-invasive surgery. Int Surg 2002;87:226–32.
22. Dackiw AP, Sussman JJ, Fritsche HA Jr, Delpassand ES, Stanford P, Hoff A, et al. Relative contributions of technetium Tc99m sestamibi scintigraphy, intraoperative gamma probe detection, and the rapid parathyroid hormone assay to the surgical management of hyperparathyroidism. Arch Surg 2000;135:550–5; discussion 555–7.
23. Dillavou ED, Cohn HE. Minimally invasive parathyroidectomy: 101 consecutive cases from a single surgeon. J Am Coll Surg 2003;197:1–7.
24. Flynn MB, Bumpous JM, Schill K, McMasters KM. Minimally invasive radioguided parathyroidectomy. J Am Coll Surg 2000; 191:24–31.
25. Gordon LL, Snyder WH 3rd, Wians F Jr, Nwariaku F, Kim LT. The validity of quick intraoperative parathyroid hormone assay: an evaluation in seventy-two patients based on gross morphologic criteria. Surgery 1999;126:1030–5.
26. Hallfeldt KK, Trupka A, Gallwas J, Schmidbauer S. Minimally invasive video-assisted parathyroidectomy and intraoperative parathyroid hormone monitoring: the first 36 cases and some pitfalls. Surg Endosc 2002;16:1759–63.
27. Inabnet WB, Biertho L. Targeted parathyroid surgery: a series of 100 consecutive patients. Ann Chir 2002;127:751–6.
28. Inabnet WB, Fulla Y, Richard B, Bonnichon P, Icard P, Chapuis Y. Unilateral neck exploration under local anesthesia: the approach of choice for asymptomatic primary hyperparathyroidism. Surgery 1999;126:1004–9; discussion 1009–10.
29. Irvin GL 3rd, Carneiro DM. "Limited" parathyroidectomy in geriatric patients. Ann Surg 2001;233:612–6.
30. Irvin GL 3rd, Dembrow VD, Prudhomme DL. Clinical usefulness of an intraoperative "quick parathyroid hormone" assay. Surgery 1993;114:1019–22; discussion 1022–3.
31. Irvin GL 3rd, Dembrow VD, Prudhomme DL. Operative monitoring of parathyroid gland hyperfunction. Am J Surg 1991; 162:299–302.
32. Irvin GL 3rd, Deriso GT 3rd. A new, practical intraoperative parathyroid hormone assay. Am J Surg 1994;168:466–8.
33. Irvin GL 3rd, Prudhomme DL, Deriso GT, Sfakianakis G, Chandarlapaty SK. A new approach to parathyroidectomy. Ann Surg 1994;219:574–9; discussion 579–81.
34. Irvin GL 3rd, Sfakianakis G, Yeung L, Deriso GT, Fishman LM, Molinari AS, et al. Ambulatory parathyroidectomy for primary hyperparathyroidism. Arch Surg 1996;131:1074–8.
35. Jaskowiak NT, Sugg SL, Helke J, Koka MR, Kaplan EL. Pitfalls of intraoperative quick parathyroid hormone monitoring and gamma probe localization in surgery for primary hyperparathyroidism. Arch Surg 2002;137:659–68; discussion 668–9.
36. Kao PC, van Heerden JA, Farley DR, Thompson GB, Taylor RL. Intraoperative monitoring of parathyroid hormone with a rapid automated assay that is commercially available. Ann Clin Lab Sci 2002;32:244–51.
37. Libutti SK, Alexander HR, Bartlett DL, Sampson ML, Ruddel ME, Skarulis M, et al. Kinetic analysis of the rapid intraoperative parathyroid hormone assay in patients during operation for hyperparathyroidism. Surgery 1999;126: 1145–50; discussion 1150–1.
38. Lorenz K, Miccoli P, Monchik JM, Duren M, Dralle H. Minimally invasive video-assisted parathyroidectomy: multiinstitutional study. World J Surg 2001;25:704–7.
39. Mandell DL, Genden EM, Mechanick JI, Bergman DA, Diamond EJ, Urken ML. The influence of intraoperative parathyroid hormone monitoring on the surgical management of hyperparathyroidism. Arch Otolaryngol Head Neck Surg 2001;127:821–7.
40. Mengozzi G, Baldi C, Aimo G, Mullineris B, Salvo R, Biasiol S, et al. Optimizing efficacy of quick parathyroid hormone determination in the operating theater. Int J Biol Markers 2000; 15:153–60.
41. Miccoli P, Bendinelli C, Vignali E, Mazzeo S, Cecchini GM, Pinchera A, et al. Endoscopic parathyroidectomy: report of an initial experience. Surgery 1998;124: 1077–9; discussion 1079–80.
42. Miccoli P, Berti P, Conte M, Raffaelli M, Materazzi G. Minimally invasive video-assisted parathyroidectomy: lesson learned from 137 cases. J Am Coll Surg 2000;191:613–8.

43. Miller P, Kindred A, Kosoy D, Davidson D, Lang H, Waxman K, et al. Preoperative sestamibi localization combined with intraoperative parathyroid hormone assay predicts successful focused unilateral neck exploration during surgery for primary hyperparathyroidism. Am Surg 2003;69:82–5.
44. Patel PC, Pellitteri PK, Patel NM, Fleetwood MK. Use of a rapid intraoperative parathyroid hormone assay in the surgical management of parathyroid disease. Arch Otolaryngol Head Neck Surg 1998;124:559–62.
45. Pellitteri PK. Directed parathyroid exploration: evolution and evaluation of this approach in a single-institution review of 346 patients. Laryngoscope 2003;113:1857–69.
46. Proctor MD, Sofferman RA. Intraoperative parathyroid hormone testing: what have we learned? Laryngoscope 2003;113:706–14.
47. Ryan MF, Jones SR, Barnes AD. Clinical evaluation of a rapid parathyroid hormone assay. Ann Clin Biochem 1992;29(Pt 1): 48–51.
48. Sfakianakis GN, Irvin GL 3rd, Foss J, Mallin W, Georgiou M, Deriso GT, et al. Efficient parathyroidectomy guided by SPECT-MIBI and hormonal measurements. J Nucl Med 1996; 37:798–804.
49. Sofferman RA, Standage J, Tang ME. Minimal-access parathyroid surgery using intraoperative parathyroid hormone assay. Laryngoscope 1998;108:1497–503.
50. Sokoll LJ, Drew H, Udelsman R. Intraoperative parathyroid hormone analysis: a study of 200 consecutive cases. Clin Chem 2000; 46:1662–8.
51. Starr FL, DeCresce R, Prinz RA. Use of intraoperative parathyroid hormone measurement does not improve success of bilateral neck exploration for hyperparathyroidism. Arch Surg 2001;136:536–42.
52. Starr FL, DeCresce R, Prinz RA. Normalization of intraoperative parathyroid hormone does not predict normal postoperative parathyroid hormone levels. Surgery 2000;128:930–5;discussion 935–6.
53. Stratmann SL, Kuhn JA, Bell MS, Preskitt JT, O'Brien JC, Gable DR, et al. Comparison of quick parathyroid assay for uniglandular and multiglandular parathyroid disease. Am J Surg 2002; 184:578–81; discussion 581.
54. Udelsman R, Donovan PI, Sokoll LJ. One hundred consecutive minimally invasive parathyroid explorations. Ann Surg 2000;232:331–9.
55. Vignali E, Picone A, Materazzi G, Steffe S, Berti P, Cianferotti L, et al. A quick intraoperative parathyroid hormone assay in the surgical management of patients with primary hyperparathyroidism: a study of 206 consecutive cases. Eur J Endocrinol 2002; 146:783–8.
56. Westerdahl J, Lindblom P, Bergenfelz A. Measurement of intraoperative parathyroid hormone predicts long-term operative success. Arch Surg 2002;137:186–90.
57. Wians FH Jr, Balko JA, Hsu RM, Byrd W, Snyder WH 3rd. Intraoperative vs central laboratory PTH testing during parathyroidectomy surgery. Lab Med 2000;31:616–21.
58. Yang GP, Levine S, Weigel RJ. A spike in parathyroid hormone during neck exploration may cause a false-negative intraoperative assay result. Arch Surg 2001;136:945–9.
59. Gauger PG, Agarwal G, England BG, Delbridge LW, Matz KA, Wilkinson M, et al. Intraoperative parathyroid hormone monitoring fails to detect double parathyroid adenomas: a 2-institution experience. Surgery 2001;130:1005–10.
60. Weber CJ, Ritchie JC. Retrospective analysis of sequential changes in serum intact parathyroid hormone levels during conventional parathyroid exploration. Surgery 1999;126:1139–43; discussion 1143–4.
61. Garner SC, Leight GS Jr. Initial experience with intraoperative PTH determinations in the surgical management of 130 consecutive cases of primary hyperparathyroidism. Surgery 1999;126: 1132–7; discussion 1137–8.
62. Molinari AS, Irvin GL 3rd, Deriso GT, Bott L. Incidence of multiglandular disease in primary hyperparathyroidism determined by parathyroid hormone secretion. Surgery 1996;120:934–6; discussion 936–7.
63. Genc H, Morita E, Perrier ND, Miura D, Ituarte P, Duh QY, et al. Differing histologic findings after bilateral and focused parathyroidectomy. J Am Coll Surg 2003;196:535–40.
64. Carneiro DM, Irvin GL 3rd. Late parathyroid function after successful parathyroidectomy guided by intraoperative hormone assay (QPTH) compared with the standard bilateral neck exploration. Surgery 2000;128:925–9;discussion 935–6.
65. Perrier ND, Ituarte P, Kikuchi S, Siperstein AE, Duh QY, Clark OH, et al. Intraoperative parathyroid aspiration and parathyroid hormone assay as an alternative to frozen section for tissue identification. World J Surg 2000; 24:1319–22.
66. Burkey SH, Van Heerden JA, Farley DR, Thompson GB, Grant CS, Curlee KJ. Will directed parathyroidectomy utilizing the gamma probe or intraoperative parathyroid hormone assay replace bilateral cervical exploration as the preferred operation for primary hyperparathyroidism? World J Surg 2002;26:914–20.
67. Wilkinson RH Jr, Leight GS Jr, Garner SC, Borges-Neto S. Complementary nature of radiotracer parathyroid imaging and intraoperative parathyroid hormone assays in the surgical management of primary hyperparathyroid disease: case report and review. Clin Nucl Med 2000;25:173–8.
68. Fahy BN, Bold RJ, Beckett L, Schneider PD. Modern parathyroid surgery: a cost-benefit analysis of localizing strategies. Arch Surg 2002;137:917–22; discussion 922–3.
69. Agarwal G, Barakate MS, Robinson B, Wilkinson M, Barraclough B, Reeve TS, et al. Intraoperative quick parathyroid hormone versus same-day parathyroid hormone testing for minimally invasive parathyroidectomy: a cost-effectiveness study. Surgery 2001; 130:963–70.
70. Clary BM, Garner SC, Leight GS Jr. Intraoperative parathyroid hormone monitoring during parathyroidectomy for secondary hyperparathyroidism. Surgery 1997;122:1034–8; discussion 1038–9.
71. Lokey J, Pattou F, Mondragon-Sanchez A, Minuto M, Mullineris B, Wambergue F, et al. Intraoperative decay profile of intact (1-84) parathyroid hormone in surgery for renal hyperparathyroidism: a consecutive series of 80 patients. Surgery 2000;128:1029–34.
72. Chou FF, Lee CH, Chen JB, Hsu KT, Sheen-Chen SM. Intraoperative parathyroid hormone measurement in patients with secondary hyperparathyroidism. Arch Surg 2002;137:341–4.
73. Seehofer D, Rayes N, Ulrich F, Muller C, Lang M, Neuhaus P, et al. Intraoperative measurement of intact parathyroid hormone in renal hyperparathyroidism by an inexpensive routine assay. Langenbecks Arch Surg 2001; 386:440–3.
74. Yamashita H, Noguchi S, Futata T, Mizukoshi T, Uchino S, Watanabe S, et al. Usefulness of quick intraoperative measurements of intact parathyroid hormone in the surgical management of hyperparathyroidism. Biomed Pharmacother 2000;54(Suppl 1):108s–11.
75. Irvin GL 3rd, Molinari AS, Figueroa C, Carneiro DM. Improved success rate in reoperative parathyroidectomy with intraoperative PTH assay. Ann Surg 1999;229:874–8; discussion 878–9.
76. Rossi HL, Ali A, Prinz RA. Intraoperative sestamibi scanning in reoperative parathyroidectomy. Surgery 2000;128:744–50.

77. Thompson GB, Grant CS, Perrier ND, Harman R, Hodgson SF, Ilstrup D, et al. Reoperative parathyroid surgery in the era of sestamibi scanning and intraoperative parathyroid hormone monitoring. Arch Surg 1999;134:699–704; discussion 704–5.
78. Miura D, Wada N, Arici C, Morita E, Duh QY, Clark OH. Does intraoperative quick parathyroid hormone assay improve the results of parathyroidectomy? World J Surg 2002;26:926–30.
79. Tonelli F, Spini S, Tommasi M, Gabbrielli G, Amorosi A, Brocchi A, et al. Intraoperative parathormone measurement in patients with multiple endocrine neoplasia type I syndrome and hyperparathyroidism. World J Surg 2000;24:556–62; discussion 562–3.
80. Roman S, Udelsman R. Minimally invasive parathyroid surgery. Minerva Chir 2002;57:105–10.
81. Arnalsteen LC, Alesina PF, Quiereux JL, Farrel SG, Patton FN, Carnaille BM, et al. Long-term results of less than total parathyroidectomy for hyperparathyroidism in multiple endocrine neoplasia type 1. Surgery 2002;132:1119–24; discussion 1124–5.
82. Kivlen MH, Bartlett DL, Libutti SK, Skarulis MC, Marx SJ, Simonds WF, et al. Reoperation for hyperparathyroidism in multiple endocrine neoplasia type 1. Surgery 2001;130:991–8.
83. Weigel RJ, Macdonald JS, Haller D, McDougall IR. Cancer of the endocrine system. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, Gillies McKenna W, eds. Clinical Oncology, 3rd ed. Philadelphia, PA: Elsevier Churchill Livingstone, 2004:1611–48.
84. Inabnet WB 3rd, Dakin GF, Haber RS, Rubino F, Diamond EJ, Gagner M. Targeted parathyroidectomy in the era of intraoperative parathormone monitoring. World J Surg 2002;26:921–5.
85. Alexander HR Jr, Chen CC, Shawker T, Choyke P, Chan TJ, Chang R, et al. Role of preoperative localization and intraoperative localization maneuvers including intraoperative PTH assay determination for patients with persistent or recurrent hyperparathyroidism. J Bone Miner Res 2002;17(Suppl 2):N133–40.
86. Udelsman R, Osterman F, Sokoll LJ, Drew H, Levine MA, Chan DW. Rapid parathyroid hormone measurement during venous localization. Clin Chim Acta 2000;295:193–8.
87. Udelsman R, Aruny JE, Donovan PI, Sokoll LJ, Santos F, Donabedian R, et al. Rapid parathyroid hormone analysis during venous localization. Ann Surg 2003; 237:714–9; discussion 719–21.
88. Bergenfelz A, Algotsson L, Roth B, Isaksson A, Tibblin S. Side localization of parathyroid adenomas by simplified intraoperative venous sampling for parathyroid hormone. World J Surg 1996; 20:358–60.
89. Saharay M, Farooqui A, Farrow S, Fahie-Wilson M, Brown A. Intra-operative parathyroid hormone assay for simplified localization of parathyroid adenomas. J R Soc Med 1996;89:261–4.
90. Taylor J, Fraser W, Banaszkiewicz P, Drury P, Atkins P. Lateralization of parathyroid adenomas by intra-operative parathormone estimation. J R Coll Surg Edinb 1996;41:174–7.
91. Hermsen D, Franzson L, Hoffmann JP, Isaksson A, Kaufman JM, Leary E, et al. Multicenter evaluation of a new immunoassay for intact PTH measurement on the Elecsys System 2010 and 1010. Clin Lab 2002;48:131–41.
92. Bieglmayer C, Prager G, Niederle B. Kinetic analyses of parathyroid hormone clearance as measured by three rapid immunoassays during parathyroidectomy. Clin Chem 2002;48:1731–8.
93. Yamashita H, Gao P, Noguchi S, Cantor T, Uchino S, Watanabe S, et al. Role of cyclase activating parathyroid hormone (1-84 PTH) measurements during parathyroid surgery: potential improvement of intraoperative PTH assay. Ann Surg 2002;236:105–11.
94. Bilezikian JP, Potts JT Jr, Fuleihan Gel H, Kleerekoper M, Neer R, Peacock M, et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab 2002;87:5353–61.
95. Lindblom P, Valdemarsson S, Westerdahl J, Tennvall J, Bergenfelz A. Hyperthyroidism after surgery for primary hyperparathyroidism. Langenbecks Arch Surg 1999;384:568–75.
96. Carneiro DM, Solorzano CC, Nader MC, Ramirez M, Irvin GL 3rd. Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: which criterion is the most accurate? Surgery 2003;134:973–9; discussion 979–81.
97. Hortin GL, Carter AB. Intraoperative parathyroid hormone testing: survey of testing program characteristics. Arch Pathol Lab Med 2002;126:1045–9.
98. Wenk RE, Efron G, Madamba L. Central laboratory analyses of intact PTH using intraoperative samples. Lab Med 2000;31:158–61.
99. Sokoll LJ. Intraoperative parathyroid hormone. In: Nichols JH, ed. Point-of-Care Testing Performance Improvements and Evidence-Based Outcomes. New York, NY: Marcel Dekker, Inc., 2003: 417–38.

PUBLIC COMMENTS

I was reviewing the National Academy of Clinical Biochemistry (NACB) LMPG presentations and noticed that calcium measurements for monitoring parathyroid surgery were missing. There was a recent paper describing the benefits of kinetic total calcium levels. This isn't something done at my institution (at least not yet) but may be at others. Here is the reference: Diaz-Aguirregoitia et al. J Am Coll Surg 2004;198:519–524.

Use of serum calcium as an intraoperative monitor for surgery in primary hyperparathyroidism has been proposed in only a few studies in the literature, with mixed results. Randomized controlled trials are needed to determine whether benefit exists.

Chapter **11**

pH Testing

James H. Nichols, Dawn Taylor, Heike Varnholt, and Leslie Williams

INTRODUCTION

pH testing is used in a variety of medical applications, including critical-care blood pH, renal-function urine pH, gastric fluid pH to monitor acid suppression therapy, evaluation of ruptured membranes during delivery, diagnosis of bacterial vaginosis, placement of gastrointestinal (GI) feeding tubes, and chemical burn treatment in the emergency room. pH can be determined by electrode and colorimetric litmus paper or dipstick methodologies. These guidelines will focus primarily on the use of pH paper in determining gastric pH, placement of GI feeding tubes, and treatment of chemical burns. Guidelines in other sections will focus on blood pH, urine pH, and use of pH during delivery and evaluation of infection.

Does the use of pH paper to diagnose and monitor treatment of chemical exposure in the emergency department and urgent care patient populations improve length of stay and severity of burn compared to empirical treatment (no monitoring)? (Literature Search 75)

Guideline 151. *We note that pH paper may have utility in monitoring the treatment of chemical exposure in the emergency department and urgent care patient populations, but there is insufficient evidence to make a strong recommendation for or against its routine use. pH testing poses no risk to the patient, and the minimal cost of testing has led to its common availability. However, a systematic examination should be conducted to determine whether pH testing has an incremental benefit during irrigation therapy after chemical exposure that outweighs the time and expense required to maintain test quality training and documentation.*

Strength/consensus of recommendation: I

Level of evidence: III (clinical experience, descriptive studies, case reports and opinion)

Literature Search 75 summarizes the results of our literature search of MEDLINE, OVID, and the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse databases for peer-reviewed articles that address patient outcome from using pH litmus paper in the acute management of chemical exposure. The quality of literature describing the use of pH paper in the treatment of chemical exposure is very poor and does not adequately link patient outcome to the use of or failure to use pH paper. Several studies use pH testing as a means of monitoring changes during irrigation therapy rather than as the goal or endpoint of that therapy *(1–13)*. In these studies, the change in pH was monitored to note the effects of chemical exposure and washing of the exposed eye or skin area with different irrigation fluids and lengths of time. The recommended duration of irrigation and type of fluid varied, but continuous washing of the affected area as soon as possible after chemical exposure was of utmost importance to prevent permanent tissue damage *(3*, *4*, *14–16)*. It was difficult, however, to distinguish whether pH paper had any incremental benefit over the dilutional effects of simply flushing the exposed area with adequate amounts of fluid during a sufficient amount of time after exposure because patient outcome was not directly compared with and without pH monitoring. Yano et al. *(5)* exposed rats to alkaline skin injuries and suggested that the pH at the skin surface is important and that irrigation should continue until the pH of the skin surface returns to normal. Amshel et al. *(14)* recommended irrigation of the eyes after anhydrous ammonia burns for at least 20 min or until a conjunctival sac pH < 8.5 is achieved. A review of chemical eye injuries by Burns and Paterson *(17)* further indicated, "It is generally accepted that the pH of the external eye should return to normal before discontinuing irrigation. If prolonged irrigation does not return the pH to within the normal range, particulate matter possibly remains." pH monitoring could thus have a role in determining the endpoint of irrigation therapy or provide the necessary criteria for further treatment. However, these recommendations are based on clinical experience rather than direct comparison of the effects of pH testing in different groups of patients. Additionally, much of the published research on treatment of chemical exposure has been conducted on animals, and animal-based conclusions may not be capable of being directly extrapolated to human patients *(1–5*, *8*, *10*, *11)*.

The type of chemical may also be a consideration when using pH paper for monitoring exposure and ingestions. Some chemicals may not alter pH (organic chemicals) or may be so

acidic or basic that standard pH paper cannot adequately measure the agent. Krenzelok and Clinton *(13)* recommend that "a sample of the ingested agent and its original container . . . be brought with the patient [to the emergency department]. The information obtained from [pH testing] provides objective data regarding the alkalinity of the product and strongly influences the decision to perform endoscopy on each victim." A wide-range pH paper of 1–12 and also pH paper with an extended range of 12–14 is recommended because some pH paper commonly found in emergency departments has too narrow a pH range to be useful in evaluating caustic substances. Others, however, have noted that pH paper is inaccurate in the assessment of strong acids and strong bases, and biases of 1.7 units or more may inappropriately alter treatment decisions, although patient outcomes have not been thoroughly examined *(10)*.

Of further consideration is the ability to obtain a reliable result from pH paper. pH paper is hygroscopic and susceptible to light and changes in humidity. Storage conditions and operator technique should therefore be monitored to ensure adequate response and interpretation of results. pH paper measures pH in color-coded increments. Accurate paper readings are dependent on sufficient color vision and adequate lighting to discriminate a color change in the presence of interfering paper staining by components such as blood, antacids, and bile *(18, 19)*. The burden and expense of documenting operator training, competency, and quality control of pH paper are not insignificant, yet the cost of the pH paper itself is minimal, and pH testing poses virtually no risk to the patient, provided proper technique is used to collect the sample and perform the test. The pH paper should not be placed in the eye or directly in contact with an exposed area of skin but should test the tears and irrigation fluid flushing the exposed area. Direct contact can lead to further irritation because of the chemicals in the paper, and pH paper is not a sterile medium.

Our literature search also found 2 other emergent or acute applications of pH testing: prevention of aspiration pneumonia in surgical patients and the differential diagnosis of diarrhea. Aspiration of stomach contents can lead to pulmonary damage because of its acidity, and unconscious or anesthetized patients are at higher aspiration risk. Johnston et al. *(9)* recommend monitoring the pH of gastric contents as an indicator of the risk of pulmonary aspiration during anesthesia. Administration of preoperative cimetidine can block the secretion of acid and provide protection at intubation or extubation. Wynn and Modell *(20)* noted that the critical pH below which severe lung damage occurs varies from species to species; for example, 1.7 for rats and 2.1 to 2.4 for rabbits. A critical pH of <2.5 has been suggested for humans but has not been proven. Nevertheless, gastric aspirates have commonly been termed "acidic" at pH values <2.5 *(20)*. pH testing may thus have a role in monitoring gastric acidity before surgery.

In a separate application, the American Gastroenterological Association suggests that a low fecal pH < 5.3 is characteristic of diarrhea caused solely by carbohydrate malabsorption, whereas a pH > 5.6 argues for a generalized malabsorption syndrome that involves fecal loss of amino acids and fatty acids in addition to carbohydrate *(21)*. Fecal pH testing may therefore be useful in distinguishing the causes of diarrhea. The use of pH paper is not directly recommended in either of these applications, and a pH meter may be better suited and more capable of distinguishing narrow pH differences, such as 5.3 from 5.6, in the presence of gastric or fecal substances that can affect pH color change.

Does continuous gastric pH monitoring, compared to random gastric pH determinations, improve patient symptoms and severity in the management of achlorhydria and gastric reflux in inpatient and endoscopy patients? (Literature Search 76)

Guideline 152. *We recommend against the intermittent use of pH paper on gastric aspirates in the diagnosis of gastric reflux disease in favor of continuous monitoring. The role of pH testing to manage acid suppression therapy is controversial. Although the use of pH testing is common on critical care units, there is a lack of evidence that pH monitoring to adjust drug dosage improves either morbidity or mortality in these patients.*

Strength/consensus of recommendation: C

Level of evidence: II and III (well-designed case-controlled, correlation trials and opinion)

Literature Search 76 lists the results of our search for articles that examined patient outcome from the use of pH monitoring in achlorhydria and gastric reflux disease. Continuous pH monitoring is considered the gold standard for the diagnosis of gastroesophageal reflux (GER) *(22–24)*. Ambulatory intraesophageal pH monitoring is regarded as the most accurate, clinically relevant measure of GER available *(23)* and is useful in measuring gastric pH changes, estimating esophageal acid exposure, and documenting reflux episodes *(25)*. The test involves tiny pH electrodes that are swallowed or passed transesophageally to the depth of the gastric sphincter or into the stomach to sense pH changes at those sites. Data are continuously recorded in a portable data logger that can be wirelessly or manually downloaded after the procedure. Computer software is available for statistical data reduction to determine the cumulative exposure to acid, number of episodes, average duration, number of episodes longer than 5 min, and the longest episode of pH < 4.0. Continuous pH monitoring demonstrates the highest values of sensitivity (88%) and specificity (98%) *(26)* for the diagnosis of GER compared with other methods of endoscopy, manometry, barium esophagogram, reflux scintigraphy, cinematography, or reliance on symptoms such as heartburn and regurgitation *(22, 27, 28)*.

Continuous pH monitoring has also provided insight into the various complications of GER. Esophageal damage is more likely to occur with excessive exposure to gastric juice, especially fluids with a pH < 2.0, and patients with strictures and Barrett's esophagus, a potential precursor of esophageal carcinoma, have been reported in prolonged exposure to acid of

increased concentration *(26, 29, 30)*. A comprehensive review found pH monitoring alone and in conjunction with motility monitoring to be valuable in the evaluation of patients with a variety of symptoms, ranging from noncardiac chest pain and gastric, pulmonary, laryngeal, and dental disease to the assessment of medical and surgical reflux therapies *(26, 27)*.

Inhibition of acid secretion with H2 receptor antagonists or neutralization of stomach acid with antacids is frequently used to prevent stress ulcers and bleeding, especially in acutely ill patients. pH monitoring has been used to guide antacid and H2 antagonists, with the goal of achieving and maintaining a gastric pH > 4, and this type of pH monitoring has become the standard of practice on critical care patients, but there is a general lack of supporting evidence that such monitoring improves patient morbidity and mortality *(31)*. Because sucralfate therapy does not alter pH, the monitoring of pH is not warranted with this drug *(32)*.

When clinicians do consider monitoring, pH can be tested continuously with gastric electrodes or intermittently on gastric aspirates using either a pH meter or pH paper. pH meters have better accuracy for measuring pH when compared to pH paper *(18, 33–37)*, but pH meters may not be practical to maintain at all sites where patients are being monitored. There are mixed reports on the ability of pH paper to adequately estimate gastric pH. Bias has been noted between pH paper and pH meters in the pH range of 2–6 that tends to overestimate the patient's gastric pH by litmus paper. Although some investigators find this bias to be clinically relevant *(18, 34)*, others claim the error bias is smaller than the paper color increments and the use of pH paper is reasonable *(37, 38)*. It is important to note that these studies do not recommend implementation of pH meters for routine monitoring of antacid therapy until further studies specifically evaluate the effects of the pH meter/paper bias on patient outcome *(34)*.

Other studies have compared nasogastric tubes containing a pH electrode capable of continuous monitoring and gastric aspirate pH by litmus paper for assessing antacid therapy *(33, 36, 39)*. Although general concordance between the methods was found, some discrepancies with pH paper measurement were hypothesized to be the result of aspirated antacid residue *(36)*, the presence of proteins and bile, or simply the heterogeneous nature of gastric contents *(35)*. The timing of gastric aspirates may be critical to the agreement between continuous monitoring and pH paper. Poor correlation was noted for both the median pH values and the percentage of time below pH 3 between 24-h monitoring and once-daily aspirates *(40)*, whereas better correlation was found with more frequent aspirate measurements *(36, 41)*. Intragastric pH measurements may actually be more reflective of the microenvironment surrounding mucosal cells but could also be registering only the gastric pH in contact with the electrode and differ in various parts of the stomach or gastric contents *(19, 37, 42, 43)*. pH electrodes can measure pH when it is difficult to obtain a sufficient volume of aspirate. This may be important in monitoring intestinal pH when the collection of adequate amounts of aspirate is difficult *(19, 44)*. Given the time involved in collecting an aspirate and the potential for various interferences with paper color changes, continuous pH monitoring was judged to be a simpler, safer, faster, and more reliable measure of gastric pH when compared to measurement of gastric aspirates with pH paper *(19, 33, 36)*. However, continuous pH monitoring is expensive, and litmus paper might offer a more economical alternative for those clinicians wanting to monitor acid therapies at the bedside *(45)*.

Continuous pH monitoring is not without challenges. The electrodes must be calibrated before each use and the calibration drift monitored after each patient. There is no standard method for calibration or consensus about acceptable bias and drift. Calibration is conducted with pH buffers at room temperature, so appropriate correction factors must be factored into the monitor's software to account for differences between body and room temperature *(26)*. Additional corrections may be necessary at very low pH or pH values near 7, at which certain types of electrodes may display more bias *(26)*. Internal placement of the electrode will affect the test results. If the electrode is not far enough into the esophagus, the monitor may fail to detect reflux episodes, and if the electrode is placed too far, the test may monitor gastric or duodenal pH changes *(26)*. Drift can be judged by testing of pH buffers before and after patient monitoring. Most studies have limited the examination of data from patients for whom the electrode did not drift by more than 0.2–0.4 pH units during the testing period *(25, 44, 46, 47)*. Despite these limitations, continuous pH monitoring is currently considered the gold standard in diagnosis of GER. Monitoring therapy with pH paper, although considered a standard of care in many critical care units, may have a clinical role, but there is a lack of supporting evidence that pH monitoring to guide acid suppression therapies actually lowers patient morbidity and mortality *(31)*. Clinically significant bleeding as opposed to occult bleeding has been suggested as a more appropriate therapeutic endpoint *(32)*.

Does the use of pH paper for assisting the placement of nasogastric tubes, compared to clinical judgment (air, pressure), improve the placement of tubes for inpatient, endoscopy, home care, and nursing home patients? (Literature Search 77)

Guideline 153. *We recommend the use of pH testing to assist in the placement of nasogastric tubes. Radiography is considered the gold standard means of determining tube placement, but there is fair evidence that pH testing can predict the position of nasogastric tubes while reducing the number of radiographs and exposure of the patient to additional radiation. The choice of measuring pH with an intragastric electrode or testing tube aspirates with a pH meter or pH paper will depend on consideration of the clinical limitations of each method, and there is conflicting evidence about which method is better.*

Strength/consensus of recommendation: B

Level of evidence: II and III (prospective comparative trials and expert opinion)

Fourteen articles were found in our literature search to address our clinical question and have a focus on the use of pH testing for nasogastric tube placement. (Literature Search 77) Methods to ensure correct placement of a nasogastric (NG) or nasointestinal (NI) tubes include careful insertion of an appropriate length of tube, direct visualization of the oropharynx to confirm esophageal entry, auscultation of the gastric area during insufflation of air, aspiration of gastric contents from the tube, irrigation of the tube with 10 to 50 mL of water, abdominal roentgenogram to confirm tube position, and direct palpation of the tube within the stomach during intraabdominal procedures *(48)*. Radiography is considered the gold standard means of determining tube placement in clinically ambiguous cases; however, pH testing may provide a faster, safer, and more economical means of screening tube placement before radiography is considered. Gastric contents are normally more acidic than intestinal or respiratory fluids. Neuman et al. *(49)* noted that an aspirate pH > 4 was not useful in predicting malposition of the tube (i.e., respiratory vs placement in the GI tract), but an aspirate pH of <4 can reduce the need for radiograph films and exposure of the patient to additional radiation (positive predictive value, 100%; sensitivity, 100%; specificity, 88%; for n = 46 patients and 78 tube placements).

Because acid inhibitors and antacids increase gastric pH, studies on patients under acid suppression suggest that a higher gastric cutoff of pH 6.0 may provide better discrimination of tube placement and may further be useful in distinguishing gastric from intestinal placements. More than 81% of gastric samples were found to have a pH between 1 and 4, whereas more than 88% of intestinal aspirates had a pH > 6 *(38, 50)*. Pulmonary fluid has a pH > 6.5, confounding the interpretation of aspirates with pH > 6 between intestinal and pulmonary placement. Radiography studies may be useful in equivocal cases of aspirated fluid with a pH between 4 and 6. A change of more than 4 pH units, the addition of bilirubin measurement, and the visual characteristics or volume of the aspirate have been suggested as possible ways to improve the prediction of tube placement *(51–55)*. However, the effect of these suggestions on patient outcome remains to be examined.

Although pH testing is useful in determining tube placement, there is some controversy about which method of monitoring pH is better: use of a continuous intragastric electrode or measurement of the pH of tube aspirates with a pH meter or pH paper. Intragastric monitoring with a pH probe attached to the end of a feeding tube can assist in both tube placement and monitoring of acid suppression therapy for several hours. These probes are technically simpler and faster and may be more accurate than testing gastric aspirates with pH paper *(33, 36)*. Intragastric pH monitoring is capable of continuously monitoring pH changes of the gastric contents, but this pH may not reflect the actual pH at the mucosal cell surface *(37)*. Therapy to raise the pH content of gastric contents based on gastric aspirates may vary significantly from intragastric pH, overestimating the true intragastric acidity, and guide therapy changes that may not be sufficiently protective. This hypothesis is supported by case reports of bleeding and treatment failure while patients receive acid suppression, and significant bleeding as opposed to occult bleeding may be a better endpoint of acid therapy than pH *(32)*.

Testing the pH of aspirated gastric contents with paper or a pH meter also may not provide equivalent pH results. Several studies have noted clinically relevant biases between pH paper and pH meters in the pH range of 2 to 6 that would have led to overestimation of gastric pH in 4 of 51 patients *(34)* and would have resulted in inappropriate treatment for 28% of the samples tested in another study *(18)*. These biases are believed to be related to the limitations of accurate pH paper assessment in the presence of salts (antacids) and interferences from bile, protein, and other substances found in an inhomogeneous sample such as gastric fluid *(18, 56)*. The patient outcome predicted by the pH paper bias has not been confirmed. Other studies have claimed that the magnitude of the pH bias is smaller than the error of pH paper measurement (typically read in 0.5- to 1.0-pH-unit increments) *(38)*. Clearly, pH testing of gastric aspirates has clinical utility in the determination of feeding tube placement, and pH paper can be used to judge the pH of gastric aspirates, provided that appropriate consideration is given to its limitations. pH testing in general is not a total replacement for radiography, because gastric fluid is capable of being aspirated in only ~85%–95% of cases, and fluids with pH > 6 may not be conclusive for gastric placement (because both intestinal and pulmonary placements can have pH values above 6.0). pH testing can, however, reduce the need for reliance on radiographic confirmation in every tube placement, providing efficiency and cost savings in patient management.

Is one brand of pH paper better than another brand in improving patient symptoms and time to treatment of chemical burns in emergency and urgent care patients, and in improving the accuracy of nasogastric tube placement in inpatient, endoscopy, home care, and nursing home patients? (Literature Search 78)

Guideline 154. *There is insufficient evidence to recommend one brand of pH paper over another brand of pH paper for use in the treatment of chemical burns or placement of nasogastric tubes.*

Strength/consensus of recommendation: I

Level of evidence: III (case reports and opinion)

Literature Search 78 summarizes the results of the literature search for studies comparing clinical outcomes from the use of different pH papers. Two studies were found that compared pH results between different brands of pH paper. Brands with multiple color changes were found to be more accurate when compared to pH meter results *(57, 58)*. Products providing more than 1 color change or multiple overlapping scales of colors were found to detect more subtle pH changes and were preferred by nurses and anesthetists over those papers with a single color change. The accuracy of single-color pH papers ranged from 20% to 83%, depending on the paper *(57)*. Single-color pH

papers were noted to have major deficiencies discriminating pH 4, whereas multiple-color papers had more difficulty in the low range of pH < 1 *(58)*. The effects of these inaccuracies on patient outcome were not examined. In light of the age of these studies (1983 and 1987) and variety of pH papers available on the market, there is insufficient evidence to recommend one brand of pH paper over another for monitoring antacid therapy, feeding tube placement, or irrigation of chemical burns.

In summary, continuous pH monitoring is recommended for the diagnosis of GER disease, and intermittent testing by pH meter or litmus paper does not have diagnostic utility in this disorder. pH testing seems to have a beneficial clinical role in confirming the placement of feeding tubes. However, the use of pH testing in managing acid suppression therapy and determining the efficacy of wound irrigation after chemical exposure will require further studies that directly examine the effects of pH testing on patient outcome. More important, studies are needed to determine the type of monitoring that is most effective and to define when more accurate measurement by pH meter is required or when less precise estimates by pH paper may suffice. pH paper is inexpensive and may be considered inconsequential in patient management, but inaccuracies in pH results can lead to undertreatment with acid inhibitors, inappropriate feeding tube placement, and premature discontinuation of irrigation for chemical burns, all of which have the potential for serious and costly patient consequences. Clinicians are encouraged to thoroughly examine the accuracy, applicability, and benefits of any test before implementation in patient care and verify continued outcomes periodically after any change in practice.

REFERENCES

1. Schrage NF, Kompa S, Haller W, Langefeld S. Use of an amphoteric lavage solution for emergency treatment of eye burns: first animal type experimental clinical considerations. Burns 2002; 28:782–6.
2. Beiran I, Miller B, Bentur Y. The efficacy of calcium gluconate in ocular hydrofluoric acid burns. Hum Exp Toxicol 1997;16:223–8.
3. Yano K, Hosokawa K, Kakibuchi M, Hikasa H, Hata Y. Effects of washing acid injuries to the skin with water: an experimental study using rats. Burns 1995;21:500–2.
4. Yano K, Hata Y, Matsuka K, Ito O, Matsuda H. Effects of washing with a neutralizing agent on alkaline skin injuries in an experimental model. Burns 1994;20:36–9.
5. Yano K, Hata Y, Matsuka K, Ito O, Matsuda H. Experimental study on alkaline skin injuries: periodic changes in subcutaneous tissue pH and the effects exerted by washing. Burns 1993; 19:320–3.
6. Khurana AK, Chaudhary R, Ahluwalia BK, Gupta S. Tear film profile in dry eye. Acta Ophthalmol 1991;69:79–86.
7. Herr RD, White GL Jr, Bernhisel K, Mamalis N, Swanson E. Clinical comparison of ocular irrigation fluids following chemical injury. Am J Emerg Med 1991;9:228–31.
8. Flynn WJ, Mauger TF, Hill RM. Corneal burns: a quantitative comparison of acid and base. Acta Ophthalmol 1984;62:542–8.
9. Johnston JR, McCaughey W, Moore J, Dundee JW. A field trial of cimetidine as the sole oral antacid in obstetric anaesthesia. Anaesthesia 1982;37:33–8.
10. Gruber RP, Laub DR, Vistnes LM. The effect of hydrotherapy on the clinical course and pH of experimental cutaneous chemical burns. Plast Reconstr Surg 1975;55:200–4.
11. Bertram E, Bromberg BE, Song IC, Walden RH. Hydrotherapy of chemical burns. Plast Reconstr Surg 1965;35:85–95.
12. Bautista A, Varela R, Villanueva A, Estevez E, Tojo R, Cadranel S. Motor function of the esophagus after caustic burn. Eur J Pediatr Surg 1996;6:204–7.
13. Krenzelok EP, Clinton JE. Caustic esophageal and gastric erosion without evidence of oral burns following detergent ingestion. JACEP 1979;8:194–6.
14. Amshel CE, Fealk MH, Phillips BJ, Caruso DM. Anhydrous ammonia burns case report and review of the literature [review]. Burns 2000;26:493–7.
15. Janda AM. Ocular trauma: triage and treatment. Postgrad Med 1955–1960;90:51–2.
16. Lorette JJ Jr, Wilkinson JA. Alkaline chemical burn to the face requiring full-thickness skin grafting [comment]. Ann Emerg Med 1988;17:739–41.
17. Burns FR, Paterson CA. Prompt irrigation of chemical eye injuries may avert severe damage. Occup Health Saf 1989;58:33–6.
18. Caballero GA, Ausman RK, Quebbeman EJ, Schulte WJ, Lin L. Gastric secretion pH measurement: what you see is not what you get! Crit Care Med 1990;18:396–9.
19. Durham RM, Weigelt JA. Monitoring gastric pH levels. Surg Gynecol Obstet 1989;169:14–6.
20. Wynne JW, Modell JH. Respiratory aspiration of stomach contents [review]. Ann Intern Med 1977;87:466–74.
21. Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. Gastroenterology 1999; 116:1464–86.
22. Bollschweiler E, Feussner H, Holscher AH, Siewert JR. pH monitoring: the gold standard in detection of gastrointestinal reflux disease [review]? Dysphagia 1993;8:118–21.
23. Hendrix TR. pH monitoring: is it the gold standard for the detection of gastroesophageal reflux disease [review]? Dysphagia 1993; 8:122–4.
24. Johnson LF, DeMeester TR. Development of the 24-hour intraesophageal pH monitoring composite scoring system. Clin Gastroenterol 1986;8(Suppl 1):52–8.
25. Boesby S, Madsen T, Sorensen HR. Gastro-oesophageal acid reflux: method for 12-hour continuous recording of oesophageal pH with analysis of records. Scand J Gastroenterol 1975;10:379–84.
26. Bremner RM, Bremner CG, DeMeester TR. Gastroesophageal reflux: the use of pH monitoring [review]. Curr Probl Surg 1995;32:429–558.
27. Kahrilas PJ, Quigley EM. Clinical esophageal pH recording: a technical review for practice guideline development. Gastroenterology 1996;110:1982–96.
28. Sondheimer JM. Continuous monitoring of distal esophageal pH: a diagnostic test for gastroesophageal reflux in infants. J Pediatr 1980;96:804–7.
29. Dubois A. Clinical relevance of gastroduodenal dysfunction in reflux esophagitis [review]. J Clin Gastroenterol 1986;8(Suppl 1): 17–25.
30. Bremner RM, Crookes PF, DeMeester TR, Peters JH, Stein HJ. Concentration of refluxed acid and esophageal mucosal injury. Am J Surg 1992;164:522–6; discussion 526–7.
31. Anonymous. ASHP therapeutic guidelines on stress ulcer prophylaxis: ASHP Commission on Therapeutics and approved by the ASHP board of directors on November 14, 1998. Am J Health Syst Pharm 1999;56:347–79.

32. Smythe MA, Zarowitz BJ. Changing perspectives of stress gastritis prophylaxis. Ann Pharmacother 1994;28:1073–85.
33. Neill KM, Rice KT, Ahern HL. Comparison of two methods of measuring gastric pH [comment]. Heart Lung 1993;22:349–55.
34. Bradley JS, Phillips JO, Cavanaugh JE, Metzler MH. Clinical utility of pH paper versus pH meter in the measurement of critical gastric pH in stress ulcer prophylaxis. Crit Care Med 1998; 26:1905–9.
35. Dobkin ED, Yeston NS. Use of pH paper to reflect gastric pH [comment]. Chest 1992;101:885–6.
36. Eisenberg PG, Cort D, Zuckerman GR. Prospective trial comparing a combination pH probe-nasogastric tube with aspirated gastric pH in intensive care unit patients [comment]. Crit Care Med 1990;18:1092–5.
37. Meiners D, Clift S, Kaminski D. Evaluation of various techniques to monitor intragastric pH. Arch Surg 1982;117:288–91.
38. Metheny N, Williams P, Wiersema L, Wehrle MA, Eisenberg P, McSweeney M. Effectiveness of pH measurements in predicting feeding tube placement. Nurs Res 1989;38:280–5.
39. Driscoll DM, Cioffi WG Jr, Molter NC, McManus WF, Mason AD Jr, Pruitt BA Jr. Intragastric pH monitoring. J Burn Care Rehabil 1993;14:517–24.
40. Bonten MJ, Gaillard CA, Stockbrugger RW, van Tiel FH, van der Geest S, Stobberingh EE. Assessment of gastric acidity in intensive care patients: intermittent pH registration cannot replace continuous pH monitoring [review]. Intensive Care Med 1996;22:220–5.
41. Savarino V, Mela GS, Scalabrini P, Sumberaz A, Fera G, Celle G. 24-hour comparison between pH values of continuous intraluminal recording and simultaneous gastric aspiration. Scand J Gastroenterol 1987;22:135–40.
42. Fisher RS, Sher DJ, Donahue D, Senior J, Krevsky B. A single intragastric pH electrode does not accurately measure intragastric acidity [comment]. Am J Gastroenterol 1996;91:1167–72.
43. Miller FA, Doberneck RC. Diagnosis of the acid-peptic diathesis by continuous pH analysis. Surg Clin North Am 1967;47:1325–34.
44. Benn A, Cooke WT. Intraluminal pH of duodenum and jejunum in fasting subjects with normal and abnormal gastric or pancreatic function. Scand J Gastroenterol 1971;6:313–7.
45. Levine RL, Fromm RE Jr, Mojtahedzadeh M, Baghaie AA, Opekun AR Jr. Equivalence of litmus paper and intragastric pH probes for intragastric pH monitoring in the intensive care unit. Crit Care Med 1994;22:945–8.
46. Gledhill T, Leicester RJ, Addis B, Lightfoot N, Barnard J, Viney N, et al. Epidemic hypochlorhydria. BMJ (Clin Res Ed) 1985; 290:1383–6.
47. Stein HJ, Feussner H, Kauer W, DeMeester TR, Siewert JR. Alkaline gastroesophageal reflux: assessment by ambulatory esophageal aspiration and pH monitoring. Am J Surg 1994; 167:163–8.
48. Hecker RB, Harris S, Robert J, Otchy D. Intra-abdominal palpation of a nasogastric tube in the stomach does not assure appropriate placement. South Med J 1990;83:1223–5.
49. Neumann MJ, Meyer CT, Dutton JL, Smith R. Hold that x-ray: aspirate pH and auscultation prove enteral tube placement. J Clin Gastroenterol 1995;20:293–5.
50. Metheny N, Reed L, Wiersema L, McSweeney M, Wehrle MA, Clark J. Effectiveness of pH measurements in predicting feeding tube placement: an update. Nurs Res 1993;42:324–31.
51. Metheny N, Wehrle MA, Wiersema L, Clark J. Testing feeding tube placement: auscultation vs. pH method [erratum appears in Am J Nurs 1998;98:1289] [review]. Am J Nurs 1998;98:37–42; quiz 42–3.
52. Metheny NA, Stewart BJ, Smith L, Yan H, Diebold M, Clouse RE. pH and concentration of bilirubin in feeding tube aspirates as predictors of tube placement. Nurs Res 1999;48:189–97.
53. Metheny N. Measures to test placement of nasogastric and nasointestinal feeding tubes: a review [review]. Nurs Res 1988; 37:324–9.
54. Berry S, Orr M, Schoettker P, Lacy J, Davis C, Warshawsky K, et al. Intestinal placement of pH-sensing nasointestinal feeding tubes. JPEN J Parenter Enteral Nutr 1994;18:67–70.
55. Metheny NA, Smith L, Stewart BJ. Development of a reliable and valid bedside test for bilirubin and its utility for improving prediction of feeding tube location. Nurs Res 2000;49:302–9.
56. Dobkin ED, Valcour A, McCloskey CR, Allen L, Kambe JC, Gleason E, et al. Does pH paper accurately reflect gastric pH? [comment]. Crit Care Med 1990;18:985–8.
57. Chaffe A. Which pH paper? Br J Anaesth 1987;59:1189–91.
58. More DG, Boutagy J, Shenfield GM. pH testing paper for measurement of intragastric acidity: an assessment. Anaesth Intensive Care 1983;11:147–50.

PUBLIC COMMENTS

Received during the AACC presentation: It seems that your group has left off one of the most important uses of pH testing, nitrazine paper. Have you looked at nitrazine for women's health? *In our introduction section, we specifically state, "These guidelines will focus primarily on the use of pH paper in determining gastric pH, placement of GI feeding tubes, and treatment of chemical burns. Guidelines in other sections will focus on blood pH, urine pH, and use of pH during delivery and evaluation of infection." Blood pH can be found in the critical-care section grouped with blood gases. Urine pH is addressed in the renal guidelines. Use of nitrazine paper and ruptured membranes is found in the reproduction section. Finally, nitrazine or pH testing for bacterial vaginosis can be found in the infectious disease section.*

No other comments have been received.

Chapter **12**

Renal Function Testing

William Clarke, Stephen J. Frost, Edward Kraus, Maria Ferris, Bernard Jaar, Jean Wu, Sandra Humbertson, Karen Dyer, Eric Schmith, and Katie Gallagher

INTRODUCTION

Dipstick urinalysis (DUA) is one of the cornerstones of point of care testing (POCT): relatively inexpensive, robust, easy to perform, painless to the patient, and available worldwide. Almost since the inception of the Clinistix (Ames Co, Elkhart, IN, USA) in 1956, DUA has been a staple for community health and preoperative screening and in the workup of urinary tract and systemic diseases. However, the real clinical utility of DUA is more often assumed than proven. In addition, recent advances in technology have introduced the ability to perform more advanced testing (e.g., quantification of blood urea nitrogen [BUN], creatinine) at the patient bedside. The guidelines will focus on the use of POCT for renal function or urinalysis in a variety of clinical settings and patient populations. Guidelines in other sections will address urine glucose, ketones or microalbumin (diabetes), and urine dipstick leukocyte esterase and nitrite (infectious disease).

Does measurement of BUN or creatinine at the point of care (vs the core laboratory) result in quicker time to treatment, decreased wait time, or decreased length of stay (LOS) for inpatient, emergency department (ED), dialysis, cardiovascular diagnostics laboratory (CVDL), or chemotherapy patients? (Literature Search 79)

Guideline 155. *We recommend against routinely providing POCT for creatinine or BUN in the ED; we found fair evidence that POCT is ineffective in this environment.*

Strength/consensus of recommendation: C

Level of evidence: II

Guideline 156. *However, we recommend that clinicians routinely provide POCT in the CVDL for creatinine and BUN; we found fair evidence that POCT in this environment improves important patient outcomes and that the benefits outweigh any potential harm.*

Strength/consensus of recommendation: B

Level of evidence: II

We selected 13 articles *(1–13)* for full-text review (from 77 abstracts), and from these 13 articles, 3 were accepted for grading with respect to the clinical question. The first 2 articles presented studies about the use of POCT in the ED. Tsai et al. *(13)* conducted a cost-effectiveness study to determine time and labor costs for POCT vs central laboratory testing in an ED setting. The study was conducted during a 4-week period at a teaching hospital in Philadelphia, Pennsylvania, and included a cohort of 210 patients presenting to the ED who were triaged at the urgent or emergent level and had blood drawn for a Chem-7 panel (which includes BUN and creatinine). It should be noted that the POC device was able to measure only BUN. The main outcome measures included test turnaround time (TAT) and cost per test, including labor for POCT vs central laboratory testing. This study found and average TAT of 8 min for POCT compared to 59 min for central laboratory testing. When cost was examined, depending on testing personnel, the cost for POCT ranged from $14.37 to $16.67, whereas the cost for central laboratory testing was $11.14. The authors stated that the cost per test would decrease according to increased testing volume and that the study did not take into account any cost savings due to decreased LOS and increased patient throughput for the ED. According to these statements, their opinion was that POCT in the ED could be a cost-effective solution.

However, a second study by Parvin et al. *(7)*, using a device similar to that used in the previous study, examined the relationship of LOS to implementation of POCT in the ED. This study defined LOS as the length of time between initial patient interview and discharge; the study examined patient LOS distribution during a 5-week experimental period after implementation of POCT and compared it to the distribution during a 5-week control period before implementation and a 3-week control period after POCT use was removed. During the study period, there were ~15,000 ED patient visits, of which 4985 patients had at least 1 Na, K, Cl, BUN, or glucose test ordered from the ED (2067 experimental and 2918 control). No decrease in LOS was observed during the study period; median LOS during the experimental period was 209 min compared to 201 min during the control periods. The authors further analyzed the data by stratification of patients according to presenting condition, discharge/admit status, or presence/absence of other central laboratory tests, but these results did not reveal a decrease in patient

LOS for any patient subgroup during the experimental period. According to the increase in cost per test and lack of evidence that LOS is improved or ED throughput increased, we do not see any evidence that POCT for renal function effectively improves patient outcomes.

The third graded article dealt with use of POCT in the CVDL to reduce patient wait times. Nichols et al. *(4)* conducted a study in 4 phases to establish the impact of implementation of POCT for coagulation and renal function testing on the amount of time between when a patient's procedure was schedule and when it actually occurred. Phase 1 examined overall patient management and workflow in the CVDL. In phase 2, POCT was implemented, but central laboratory results were used for patient management. In phase 3, therapeutic decisions were made according to POCT results, and in phase 4, the authors worked to optimize workflow around the availability of POCT. In phase 1, the authors demonstrated that 44% of the central laboratory results were not available before the scheduled procedure time (n = 135). Phase 2 results showed that the mean waiting time for patients who needed renal testing was 188 (54 min (n = 14). For patients needing renal function testing, phases 3 and 4 were combined, and use of POCT decreased the mean patient wait time to 141 ± 52 min (n = 18; $P = 0.02$). The evidence in this article demonstrates that implementation of POCT in the CVDL led to a statistically significant decrease in wait times for patients needing renal function testing.

Does screening for renal insufficiency by urine pH dipstick test at the point of care result in earlier diagnosis of renal insufficiency and fewer adverse events or decreased LOS for patients compared to screening by core laboratory urine pH testing? (Literature Search 80)

Guideline 157. *We are unable to recommend for or against routine use of POCT with urine pH dipstick to screen for renal insufficiency.*

Strength/consensus of recommendation: I

Although we were able to select 3 articles *(14–16)* for full-text review (from 310 abstracts), we were unable to grade any of them, because either they did not specifically address the clinical question or they did not contain an evaluation of patient outcomes.

Does screening for metabolic disorders using urine dipstick pH at the point of care result in earlier diagnosis of metabolic disorders, along with fewer adverse events and more rapid time to treatment for patients in outpatient clinics or the Neonatal Intensive Care Unit (NICU)/nursery when compared to screening by core laboratory urine pH testing? (Literature Search 81)

Guideline 158. *We are unable to recommend for or against routine use of urine dipstick pH testing for metabolic disorder screening at the point of care.*

Strength/consensus of recommendation: I

Six articles *(16–21)* were selected for full-text review (from 310 abstracts), but we were unable to grade the evidence with respect to patient outcomes because they either did not specifically address the clinical question or they did not contain evidence relating to patient outcomes.

Does measurement of urine specific gravity via dipstick testing at the point of care to evaluate renal function result in decreased patient wait time, quicker time to treatment, fewer adverse events, or decreased LOS for inpatient, ED, or outpatient clinic patients when compared to measurement of urine specific gravity in the core laboratory? (Literature Search 82)

Guideline 159. *We are unable to recommend for or against the routine use of urine dipsticks to measure urine specific gravity at the point of care for evaluation of renal function.*

Strength/consensus of recommendation: I

Of 6 articles *(22–27)* that were selected for full-text review (from 21 abstracts), none of them were graded with respect to strength of evidence, because they either did not specifically address the clinical question or they did not contain evidence relating to patient outcomes.

Does assessment of specimen integrity by measurement of urine specific gravity by dipstick testing at the point of care result in fewer repeated patient visits because of invalid urine specimens in the ED, physician 's office laboratory, or workplace drug testing setting? (Literature Search 83)

Guideline 160. *We cannot recommend for or against the routine use of urine specific gravity by dipstick testing for assessment of urine specimen integrity at the point of care.*

Strength/consensus of recommendation: I

Only 1 article *(28)* was selected from 2 abstracts for full-text review, and it was not graded, because it did not discuss evidence relating to patient outcomes.

Does determination of hydration status by measurement of plasma, serum, whole blood, or urine osmolality at the point of care result in decreased patient wait time, quicker time to treatment, decreased LOS, or fewer adverse events for inpatient, ED, or outpatient clinic patients compared to measurement of osmolality in the core laboratory? (Literature Search *84*)

Guideline 161. *We are unable to recommend for or against routine point of care measurement of osmolality—blood or urine—for determination of patient hydration status.*

Strength/consensus of recommendation: I

Although 3 articles *(22, 29, 30)* were selected for full-text review (from 6 abstracts), we were unable to grade any of the articles, because they either did not specifically address the clinical question or they did not contain evidence pertaining to patient outcomes.

Does screening for proteinuria using urine dipstick testing at the point of care to evaluate renal function result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased LOS for inpatient, ED, or outpatient clinic patients when compared to urine protein screening using a core laboratory method? (Literature Search 85)

Guideline 162. *We recommend against routinely screening for proteinuria with urine dipstick testing at the point of care; we found fair evidence that POCT screening in this environment is ineffective for improving patient outcomes.*

Strength/consensus of recommendation: C

Level of evidence: II

We selected 32 articles *(14, 20, 31–60)* for full-text review (from 260 abstracts); of these 32 articles, 6 were suitable for grading with respect to the clinical question. The first study, by Hermansen and Blodgett *(14)*, was performed to evaluate the benefits and costs of routine admission dipstick urinalyses. This study followed up 954 pediatric admissions at the authors' institution. DUA was performed on all admissions, and the results were reviewed between 12 and 36 h postadmission for the presence of glucosuria, hematuria, and proteinuria. If an abnormality was found, the chart was reviewed periodically until the abnormality was classified with respect to the clinical diagnosis. After the patient was discharged, the chart was reviewed to determine the costs incurred as a result of the screening effort; no attempt was made to evaluate the effect on LOS. The authors found that the presence of abnormalities and false-positive or -negative results were comparable to those of nonhospitalized children. Their conclusions pointed to the difficulty in justifying a routine screening DUA on every pediatric hospital admission. A separate study by Shaw et al. *(53)* compared DUA to microscopic examination for diagnosis of urine abnormalities. The results of urinalyses on 1839 patient samples were evaluated and yielded at 16% false-negative rate for dipstick 1+ proteinuria (with trace blood) that improved to 13% by lowering to trace protein and improved to 3.3% when trace protein was used and leukocyte esterase was added to the dipstick analysis. The study found the test strips to have a sensitivity of 62%–70% and specificity of 71%–79% for detection of abnormal urine sediment.

Two of the studies focused on comparison of DUA for proteinuria, with urine protein/creatinine ratio (P/Cr) analysis performed in the central laboratory. Ralston et al. *(54)* examined screening for proteinuria in a rheumatology clinic setting. In this study, measurements of P/Cr ratio in "spot" or random urine samples were compared with central laboratory testing of 24-h quantitative proteinuria and DUA in 104 samples from 90 patients presenting consecutively to a rheumatology unit. Significant proteinuria in the study was defined as >300 mg/24 h by core laboratory methods. Compared to the central laboratory method, the false-positive rate (positive dipstick results at <300 mg/24 h) was 100% for trace results (n = 15), 76% for 1+ results (n = 46), 38% for 2+ results (n = 21), 15% for 3+ results (n = 15), and 0% for 4+ results (n = 7). Setting the dipstick positive result at 1+ yielded a sensitivity of 100% but poor specificity because of the high rate of false negatives in the 1+ to 3+ range (48%). In comparison, the P/Cr ratio was able to achieve both specificity and sensitivity of 97%, according to the authors. The second study, by Abitbol et al. *(20)*, investigated the quantification of proteinuria with urinary P/Cr ratios compared to random testing with dipsticks in nephritic children. The investigation included 64 children (45 male) with nephritic syndrome that provided 145 timed, 24-h urine specimens and 150 random urine specimens that were tested by DUA, as well as central laboratory determination of urine P/Cr. Nephrotic-range proteinuria was defined as >1.0 g/m^2/day. Positive results (for nephritic proteinuria) were designated as a ratio of >1.0 for P/Cr or 3+ and 4+ for DUA. DUA for proteinuria produced a sensitivity of 70%, specificity of 68%, and positive predictive value (PPV) and negative predictive value (NPV) of 89% and 60%, respectively. Using random P/Cr ratios, a sensitivity of 95%, a specificity of 93%, and a PPV and NPV of 93% and 100%, respectively, were obtained. The authors point out the high negative predictability for urine P/Cr ratio in contrast to the low negative predictability for DUA and assert the random P/Cr ratio to be a better assessment tool for proteinuria in children with nephrosis.

Two of the more recent graded studies presented points of view that screening for dipstick proteinuria exhibits potential to contribute to improved patient outcomes. Craig et al. *(43)* conducted a feasibility study of early detection and treatment of renal disease by mass screening using systematic review and meta-analysis, as well as an evaluation of cost-effectiveness. In the study, the authors assert that if screening is implemented solely on the basis of proteinuria, raised serum creatinine, or raised blood pressure, then adverse effects of additional investigations would be trivial. However, based on their systematic review, it was concluded that the poor specificity of dipsticks would result in a high proportion of the population being recalled for more tests before being declared false positives. The authors state that if screening results in early treatment with angiotensin-converting enzyme (ACE) inhibitors, then it would be possible that 340 fewer people would develop end-stage renal disease (ESRD) for every 10,000 treated. Based on their assumptions, the study predicts that a dipstick screening program (coupled with early intervention) for men and women aged 50 years and older would prevent 205 cases of ESRD and would result in a net cost savings for the healthcare system despite increased costs incurred by widespread screening.

Agarwal et al. *(39)* pose the question as to whether DUA for proteinuria can be used to guide hypertension management. In this study, 332 patients (all male) attending the renal clinic at a VA hospital had urine protein and creatinine levels measured, as well as routine DUA. The investigators were interested in

patients with proteinuria >1 g/day or greater (corresponds to P/Cr ratio of 1 or greater), because practice guidelines called for lower blood pressure targets in these patients. The authors found that when comparing DUA with a P/Cr ratio, a dipstick result of 4 gives a 92% chance of having a P/Cr ratio of 1 or greater. Conversely, when the urine dipstick is free of protein, proteinuria with a P/Cr ratio of >1 can be ruled out. Last, the authors demonstrated that receiver operator characteristic (ROC) analysis of protein dipsticks with a cutoff value of 3 gives the best combination of sensitivity and specificity (96% and 87%, respectively) in predicting a P/Cr ratio of 1 or greater. Although the above studies demonstrate promise for the use of dipstick proteinuria analysis, they offer little direct evidence for the improvement of patient outcomes. According to the studies that were graded, we do not see any evidence that supports improved patient outcomes based on screening for proteinuria using DUA.

Does detection of glomerular dysfunction by evaluation of hematuria using dipstick testing at the point of care result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased LOS for inpatient, ED, or outpatient clinic patients when compared to evaluation of hematuria using core laboratory urinalysis? (Literature Search 86)

Guideline 163. *We are unable to recommend for or against dipstick testing for hematuria to evaluate the extent of glomerular dysfunction at the point of care.*

Strength/consensus of recommendation: I

Sixteen articles *(27, 48, 53, 61–73)* were selected for full-text analysis (from 215 abstracts), but we were unable to grade any of those articles, because they either did not specifically address the clinical question or they did not contain evidence pertaining to patient outcomes.

Does analysis of urine or serum electrolytes at the point of care result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased LOS for inpatient, ED, or outpatient clinic patients when compared to analysis of electrolytes using the core laboratory? (Literature Search 87)

Guideline 164. *We cannot recommend for or against measurement of urine or serum electrolytes at the point of care.*

Strength/consensus of recommendation: I

Although we were able to select 7 articles *(1, 2, 8, 28, 74–76)* for full-text analysis (from 20 abstracts), we were not able to grade any of those articles, because they either did not specifically address the clinical question or they did not contain evidence pertaining to patient outcomes.

Does evaluation for pregnancy-induced hypertension or preeclampsia using urine protein dipstick testing at the point of care result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased LOS for ED, outpatient clinic, or labor and delivery patients when compared to urine protein measurement using core laboratory methods? (Literature Search 88)

Guideline 165. *We recommend against routine use of urine protein dipstick testing at the point of care for antenatal evaluation of hypertension or preeclampsia; we found fair evidence that protein dipstick testing in this environment is largely ineffective.*

Strength/consensus of recommendation: C

Level of evidence: II

We selected 17 articles *(16, 44, 45, 49, 56, 59, 77–87)* for full-text review (from 260 abstracts), and from these 17 articles, 2 were accepted for grading with respect to the clinical question. In a 2001 study, Waugh et al. *(80)* examined the accuracy of urine dipsticks for protein measurement in hypertensive pregnancies. In this study, 24-h urine specimens were collected from 197 consecutive pregnant women who were at risk for hypertensive pregnancy. Hypertension was defined as a sustained systolic blood pressure of >140 mm Hg, a diastolic blood pressure of >90 mm Hg on 2 occasions, or a diastolic pressure of >110 mm Hg on a single occasion. The urine specimens were analyzed by DUA and 2 biochemical assays, the benzethonium chloride assay and the Bradford assay. A positive test result for proteinuria was defined as a result of 1+ or greater for DUA or a 24-h urinary protein of 0.3 g/24 h for both biochemical assays. A second analysis was performed for both biochemical assays with a cutoff of 0.3 mg/mL according to the fact that the trace/1+ threshold for detection of proteinuria in dipstick methodology is set at a protein concentration of 0.3 mg/mL. Using the gold standard definition (0.3 g/24 h) for biochemical assays, the prevalence of proteinuria according to DUA (1+) was 16.2%, compared to a prevalence of 70.1% detected with the benzethonium chloride method and 24.9% with the Bradford assay. In comparison to the benzethonium method, the dipstick analysis yielded a PPV of 96.9% and an NPV of 22.5%; using the Bradford assay as the reference method, DUA gave a PPV of 87.5% and an NPV of 87.3%. Changing the gold standard definition to 0.3 mg/mL for the biochemical assays did not significantly affect the PPV but did show some improvement for the NPV (increased to 53.9% and 92.1 for the benzethonium and Bradford assays, respectively). It should be noted that both the Bradford assay and urine dipstick methodology are particularly sensitive to albumin and transferrin, whereas the benzethonium chloride assay is sensitive to these proteins and many others (the authors demonstrate this using qualitative gel electrophoresis). According to this information, the authors assert that benzethonium chloride is the preferred gold standard for biochemical assays and that, in comparison to this standard, urine dipsticks produce far too many false-negative results in hypertensive pregnant women to be

useful, even when a similar concentration cutoff is used rather than the traditional proteinuria definition of 0.3 g/24 h.

A more recent study by Murray et al. *(85)* examines whether routine urinalysis in the antenatal period facilitates a diagnosis of preeclampsia. This study was conducted as a prospective observational study, in which 1000 women were enrolled at their first antenatal visit; 913 completed the study. At the first antenatal visit, a urine sample was collected for DUA and central laboratory testing (urine dipsticks were read using a Bayer Clinitek 50; Bayer HealthCare, Diagnostics Division, UK). Of the 913 enrollees, 11 did not have dipstick testing performed at their first visit, 35 women demonstrated dipstick proteinuria (1+), and 867 did not exhibit dipstick proteinuria on the first visit. Of the 867 patients without dipstick proteinuria, only 338 women developed proteinuria at some time during their pregnancy. Statistically, there were no significant differences in the proportion of women with and without dipstick proteinuria on their first visit who developed hypertension during pregnancy. The authors conclude that, although "at-risk" women may benefit from routine DUA for proteinuria, low-risk women do not benefit from routine dipstick proteinuria screening. According to the above studies, we do not see any evidence that routine screening for proteinuria by DUA leads to improved patient outcomes.

Does the use of urine dipstick pH testing at the point of care to predict renal stone recurrence result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased LOS for inpatient, ED, or outpatient clinic patients compared to core laboratory urine pH testing? (Literature Search 89)

Guideline 166. *We are not able to recommend for or against routine use of urine dipstick pH testing at the point of care to predict renal stone recurrence.*

Strength/consensus of recommendation: I

Of the 4 articles *(25, 57, 88, 89)* that were selected for full-text review (from 310 abstracts), none were able to be graded, because they either did not specifically address the clinical question or they did not contain evidence pertaining to patient outcomes.

Does dipstick hematuria testing at the point of care to detect intraabdominal trauma result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased LOS for ED patients compared to evaluation of hematuria using core laboratory urinalysis? (Literature Search 90)

Guideline 167. *We are unable to recommend for or against dipstick hematuria testing at the point of care to detect intraabdominal trauma.*

Strength/consensus of recommendation: I

We were able to select 17 articles *(63–65, 67, 90–102)* for full-text review, but of these articles none were graded, because they either did not specifically address the clinical question or they did not contain evidence pertaining to patient outcomes.

Does measurement of lactate at the point of care to assess or correct lactate buffer replacement in hemodialysis patients result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased LOS? (Literature Search 91)

Guideline 168. *We cannot recommend for or against measurement of lactate at the point of care to assess or correct lactate buffer replacement in hemodialysis patients.*

Strength/consensus of recommendation: I

We pulled 3 articles *(100–102)* for full-text review, but none of the articles were graded, because they either did not specifically address the clinical question or they did not contain evidence pertaining to patient outcomes.

Does detection of myoglobinuria using urine dipstick testing at the point of care as an indicator for possible renal complications of muscle injury result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased LOS for inpatient, ED, and outpatient clinic patients when compared to evaluation of myoglobinuria using core laboratory urinalysis? (Literature Search 92)

Guideline 169. *There is not sufficient evidence to recommend for or against urine dipstick testing for myoglobinuria at the point of care as an indicator for possible renal complications of muscle injury.*

Strength/consensus of recommendation: I

Four articles *(103–106)* were selected for full-text review (from 7 abstracts); however, none of these articles were graded, because they either did not specifically address the clinical question or they did not contain evidence pertaining to patient outcomes.

Does measurement of microalbuminuria using dipstick testing at the point of care to assess nondiabetic nephropathy result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased LOS for inpatient, ED, and outpatient clinic patients when compared to evaluation of microalbuminuria using core laboratory methods? (Literature Search 93)

Guideline 170. *We are unable to recommend dipstick testing for microalbuminuria at the point of care to assess nondiabetic nephropathy.*

Strength/consensus of recommendation: I

We selected 11 articles *(35, 36, 42, 107–114)* for full-text review (from 38 abstracts), but we were not able to grade any of the articles, because they either did not specifically address the clinical question or they did not contain evidence pertaining to patient outcomes.

In summary, with respect to most of the clinical questions, there is insufficient evidence to recommend for or against POCT for renal function evaluation or urinalysis. In the few cases in which there is evidence, it does not support the routine use of POCT. We recommend against DUA for proteinuria both for screening and also for evaluation of pregnancy-induced hypertension or preeclampsia. We were also unable to recommend POCT for BUN or creatinine, with 1 exception, the CVDL setting. We were able to find evidence that, in a CVDL setting, implementation of renal function testing at the point of care was able to reduce patient wait times for a scheduled procedure *(4)*. Studies are needed that not only address comparison of POCT methods to core laboratory methods but also measure the impact of POCT on specific patient outcomes. These studies are needed to address the variety of settings in which renal POCT is performed, and they should be controlled to address specific patient populations (e.g., ED, outpatient). Ideally, studies will be performed in a randomized-control format, with groups treated according to either POCT or core laboratory methods.

REFERENCES

1. Gault MH, Harding CE. Evaluation of i-STAT portable clinical analyzer in a hemodialysis unit. Clin Biochem 1996;29:117–24.
2. Gault MH, Harding CE, Duffett S, Longerich L. i-STAT hand-held point-of-care analyzer for dialysis units. Nephron 1998;80:344–8.
3. Hernandez-Herrera G, Martin-Malo A, Rodriguez M, Aljama P. Assessment of the length of each hemodialysis session by on-line dialysate urea monitoring. Nephron 2001;89:37–42.
4. Nichols JH, Kickler TS, Dyer KL, Humbertson SK, Cooper PC, Maughan WL, et al. Clinical outcomes of point-of-care testing in the interventional radiology and invasive cardiology setting. Clin Chem 2000;46:543–50.
5. Nosanchuk JS, Keefner R. Cost analysis of point-of-care laboratory testing in a community hospital. Am J Clin Pathol 1995; 103:240–3.
6. Papadea C, Foster J, Grant S, Ballard SA, Cate JC 4th, Southgate WM, et al. Evaluation of the i-STAT Portable Clinical Analyzer for point-of-care blood testing in the intensive care units of a university children's hospital. Ann Clin Lab Sci 2002;32:231–43.
7. Parvin CA, Lo SF, Deuser SM, Weaver LG, Lewis LM, Scott MG. Impact of point-of-care testing on patients' length of stay in a large emergency department. Clin Chem 1996;42:711–7.
8. Kost GJ, Vu HT, Inn M, DuPlantier R, Fleisher M, Kroll MH, et al. Multicenter study of whole-blood creatinine, total carbon dioxide content, and chemistry profiling for laboratory and point-of-care testing in critical care in the United States. Crit Care Med 2000;28:2379–89.
9. Baier KA, Markham LE, Flaigle SP, Nelson PW, Shield CF, Muruve NA, et al. Point-of-care testing in an organ procurement organization donor management setting. Clin Transplant 2003;17(Suppl 9):48–51.
10. Asimos AW, Gibbs MA, Marx JA, Jacobs DG, Erwin RJ, Norton HJ, et al. Value of point-of-care blood testing in emergent trauma management. J Trauma 2000; 48:1101–8.
11. Canaud B, Bosc JY, Cabrol L, Leray-Moragues H, Navino C, Verzetti G, et al. Urea as a marker of adequacy in hemodialysis: lesson from in vivo urea dynamics monitoring. Kidney Int Suppl 2000;76:S28–40.
12. Croal BL, Mutch WJ, Clark BM, Dickie A, Church J, Noble D, et al. The clinical application of a urine albumin:creatinine ratio point-of-care device. Clin Chim Acta 2001;307:15–21.
13. Tsai WW, Nash DB, Seamonds B, Weir GJ. Point-of-care versus central laboratory testing: an economic analysis in an academic medical center. Clin Ther 1994;16:898–910; discussion 854.
14. Hermansen MC, Blodgett FM. Prospective evaluation of routine admission urinalyses. Am J Dis Child 1981;135:126–30.
15. Muntner P, He J, Hamm L, Loria C, Whelton PK. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol 2002;13:745–53.
16. Ruttimann S, Clemencon D. Usefulness of routine urine analysis in medical outpatients. J Med Screen 1994;1:84–7.
17. Belford EM, McKenna MJ, Whitehouse FW, Tomlanovich MC, Nowak RM. Evaluation of a new chemical dip strip for detecting ketonemia in the emergency setting. Am J Emerg Med 1987; 5:393–4.
18. Ojwang PJ, Manickum T, Deppe WM. Galactosaemia in black South African children. East Afr Med J 1999;76:247–50.
19. Abbasi IA, Hess LW, Johnson TR, McFadden E, Chernow B. Leukocyte esterase activity in the rapid detection of urinary tract and lower genital tract infections in obstetric patients. Am J Perinatol 1985;2:311–3.
20. Abitbol C, Zilleruelo G, Freundlich M, Strauss J. Quantitation of proteinuria with urinary protein/creatinine ratios and random testing with dipsticks in nephrotic children. J Pediatr 1990;116:243–7.
21. US Preventive Services Task Force. Screening for asymptomatic bacteriuria, hematuria and proteinuria: the U.S. Preventive Services Task Force. Am Fam Physician 1990;42:389–95.
22. de Buys Roessingh AS, Drukker A, Guignard JP. Dipstick measurements of urine specific gravity are unreliable. Arch Dis Child 2001;85:155–7.
23. Karp WB, Kanto WP Jr, Robertson AF. Quality control of laboratory tests run in a neonatal intensive care unit. Am J Dis Child 1986;140:114–6.
24. Knottenbelt JD. Traumatic rhabdomyolysis from severe beating: experience of volume diuresis in 200 patients. J Trauma 1994; 37:214–9.
25. McCormack M, Dessureault J, Guitard M. The urine specific gravity dipstick: a useful tool to increase fluid intake in stone forming patients. J Urol 1991;146:1475–7.
26. Parikh CR, Gyamlani GG, Carvounis CP. Screening for microalbuminuria simplified by urine specific gravity. Am J Nephrol 2002; 22:315–9.
27. Tighe P. Laboratory-based quality assurance programme for near-patient urine dipstick testing, 1990-1997: development, management and results. Br J Biomed Sci 1999;56:6–15.
28. Birch NC, Stickle DF, Young A, Medina P, Hinrichs SH. Evaluation of urine specimen integrity in a public health STD screening program. Am J Clin Pathol 2003;119:516–21.
29. Coritsidis GN, Guru K, Ward L, Bashir R, Feinfeld DA, Carvounis CP. Prediction of acute renal failure by "bedside formula" in medical and surgical intensive care patients. Ren Fail 2000;22:235–44.
30. Kost GJ. New whole blood analyzers and their impact on cardiac and critical care. Crit Rev Clin Lab Sci 1993;30:153–202.

31. Edworthy SM, Bloch DA, McShane DJ, Segal MR, Fries JF. A "state model" of renal function in systemic lupus erythematosus: its value in the prediction of outcome in 292 patients. J Rheumatol 1989;16:29–35.
32. Koseki Y, Terai C, Moriguchi M, Uesato M, Kamatani N. A prospective study of renal disease in patients with early rheumatoid arthritis. Ann Rheum Dis 2001;60:327–31.
33. Johnson H Jr, Knee-Ioli S, Butler TA, Munoz E, Wise L. Are routine preoperative laboratory screening tests necessary to evaluate ambulatory surgical patients? Surgery 1988;104:639–45.
34. Pugia MJ, Wallace JF, Lott JA, Sommer R, Luke KE, Shihabi ZK, et al. Albuminuria and proteinuria in hospitalized patients as measured by quantitative and dipstick methods. J Clin Lab Anal 2001;15:295–300.
35. Pugia MJ, Lott JA, Luke KE, Shihabi ZK, Wians FH Jr, Phillips L. Comparison of instrument-read dipsticks for albumin and creatinine in urine with visual results and quantitative methods. J Clin Lab Anal 1998;12:280–4.
36. Pugia MJ, Lott JA, Clark LW, Parker DR, Wallace JF, Willis TW. Comparison of urine dipsticks with quantitative methods for microalbuminuria. Eur J Clin Chem Clin Biochem 1997; 35:693–700.
37. Olivarius ND, Mogensen CE. Danish general practitioners' estimation of urinary albumin concentration in the detection of proteinuria and microalbuminuria. Br J Gen Pract 1995;45:71–3.
38. Hall DJ, Diasio R, Goplerud DR. cis-Platinum in gynecologic cancer, III: toxicity. Am J Obstet Gynecol 1981;141:309–12.
39. Agarwal R, Panesar A, Lewis RR. Dipstick proteinuria: can it guide hypertension management? Am J Kidney Dis 2002; 39:1190–5.
40. Poulsen PL, Hansen B, Amby T, Terkelsen T, Mogensen CE. Evaluation of a dipstick test for microalbuminuria in three different clinical settings, including the correlation with urinary albumin excretion rate. Diabete Metab 1992;18:395–400.
41. Sewell DL, Burt SP, Gabbert NJ, Bumgardner RV. Evaluation of the Chemstrip 9 as a screening test for urinalysis and urine culture in men. Am J Clin Pathol 1985;83:740–3.
42. Lum G. How effective are screening tests for microalbuminuria in random urine specimens? Ann Clin Lab Sci 2000;30:406–11.
43. Craig JC, Barratt A, Cumming R, Irwig L, Salkeld G. Feasibility study of the early detection and treatment of renal disease by mass screening. Intern Med J 2002;32:6–14.
44. Barton JR, O'Brien J M, Bergauer NK, Jacques DL, Sibai BM. Mild gestational hypertension remote from term: progression and outcome. Am J Obstet Gynecol 2001;184:979–83.
45. Saudan PJ, Brown MA, Farrell T, Shaw L. Improved methods of assessing proteinuria in hypertensive pregnancy. Br J Obstet Gynaecol 1997;104:1159–64.
46. Marx AM, Kropf J, Gressner AM. On the performance and reliability of mechanized urine teststrip measurement in comparison with visual reading. J Clin Chem Clin Biochem 1989;27:433–43.
47. Crowley ST, Cantwell B, Abu-Alfa A, Rigsby MO. Prevalence of persistent asymptomatic proteinuria in HIV-infected outpatients and lack of correlation with viral load. Clin Nephrol 2001;55:1–6.
48. Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, et al. Prevalence of kidney damage in Australian adults: the AusDiab Kidney Study. J Am Soc Nephrol 2003;14:S131–8.
49. Kuo VS, Koumantakis G, Gallery ED. Proteinuria and its assessment in normal and hypertensive pregnancy. Am J Obstet Gynecol 1992;167:723–8.
50. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int 2003; 63: 1468–74.
51. Grimm RH Jr, Svendsen KH, Kasiske B, Keane WF, Wahi MM. Proteinuria is a risk factor for mortality over 10 years of follow-up: MRFIT Research Group: Multiple Risk Factor Intervention Trial. Kidney Int Suppl 1997;63:S10–4.
52. Culleton BF, Larson MG, Parfrey PS, Kannel WB, Levy D. Proteinuria as a risk factor for cardiovascular disease and mortality in older people: a prospective study. Am J Med 2000;109:1–8.
53. Shaw ST Jr, Poon SY, Wong ET. "Routine urinalysis." Is the dipstick enough? JAMA 1985;253:1596–600.
54. Ralston SH, Caine N, Richards I, O'Reilly D, Sturrock RD, Capell HA. Screening for proteinuria in a rheumatology clinic: comparison of dipstick testing, 24 hour urine quantitative protein, and protein/creatinine ratio in random urine samples. Ann Rheum Dis 1988;47:759–63.
55. Guthrie RM, Lott JA. Screening for proteinuria in patients with hypertension or diabetes mellitus. J Fam Pract 1993;37:253–6.
56. Gribble RK, Fee SC, Berg RL. The value of routine urine dipstick screening for protein at each prenatal visit. Am J Obstet Gynecol 1995;173:214–7.
57. Kawamura T, Ohta T, Ohno Y, Wakai K, Aoki R, Tamakoshi A, et al. Significance of urinalysis for subsequent kidney and urinary tract disorders in mass screening of adults. Intern Med 1995;34:475–80.
58. Karras DJ, Heilpern KL, Riley LJ, Hughes L, Gaughan JP. Urine dipstick as a screening test for serum creatinine elevation in emergency department patients with severe hypertension. Acad Emerg Med 2002;9:27–34.
59. Meyer NL, Mercer BM, Friedman SA, Sibai BM. Urinary dipstick protein: a poor predictor of absent or severe proteinuria. Am J Obstet Gynecol 1994;170:137–41.
60. Newman DJ, Pugia MJ, Lott JA, Wallace JF, Hiar AM. Urinary protein and albumin excretion corrected by creatinine and specific gravity. Clin Chim Acta 2000;294:139–55.
61. Kore RN, Dow CS, Desai KM. A new automated system for urine analysis: a simple, cost-effective and reliable method for distinguishing between glomerular and nonglomerular sources of haematuria. BJU Int 1999;84:454–60.
62. White AV, Hoy WE, McCredie DA. Childhood post-streptococcal glomerulonephritis as a risk factor for chronic renal disease in later life. Med J Aust 2001;174:492–6.
63. Woolhandler S, Pels RJ, Bor DH, Himmelstein DU, Lawrence RS. Dipstick urinalysis screening of asymptomatic adults for urinary tract disorders, I: hematuria and proteinuria. JAMA 1989;262:1214–9.
64. Moore GP, Robinson M. Do urine dipsticks reliably predict microhematuria? the bloody truth! Ann Emerg Med 1988;17:257–60.
65. Kerr S, Marshall C, Sinclair D. Emergency physicians versus laboratory technicians: are the urinalysis and microscopy results comparable? a pilot study. J Emerg Med 1999;17:399–404.
66. Dimech W, Roney K. Evaluation of an automated urinalysis system for testing urine chemistry, microscopy and culture. Pathology 2002;34:170–7.
67. Lee-Lewandrowski E, Corboy D, Lewandrowski K, Sinclair J, McDermot S, Benzer TI. Implementation of a point-of-care satellite laboratory in the emergency department of an academic medical center: impact on test turnaround time and patient emergency department length of stay. Arch Pathol Lab Med 2003;127:456–60.
68. Lun A, Ivandic M, Priem F, Filler G, Kirschstein M, Ehrich JH, et al. Evaluation of pediatric nephropathies by a computerized Urine Protein Expert System (UPES). Pediatr Nephrol 1999;13:900–6.

69. Khan MA, Shaw G, Paris AM. Is microscopic haematuria a urological emergency? BJU Int 2002;90:355–7.
70. Hogg RJ, Harris S, Lawrence DM, Henning PH, Wigg N, Jureidini KF. Renal tract abnormalities detected in Australian preschool children. J Paediatr Child Health 1998;34:420–4.
71. Tentori F, Stidley CA, Scavini M, Shah VO, Narva AS, Paine S, et al. Prevalence of hematuria among Zuni Indians with and without diabetes: the Zuni Kidney Project. Am J Kidney Dis 2003;41:1195–204.
72. Jou WW, Powers RD. Utility of dipstick urinalysis as a guide to management of adults with suspected infection or hematuria. South Med J 1998;91:266–9.
73. Arm JP, Peile EB, Rainford DJ, Strike PW, Tettmar RE. Significance of dipstick haematuria, 1: correlation with microscopy of the urine. Br J Urol 1986;58:211–7.
74. Morimatsu H, Rocktaschel J, Bellomo R, Uchino S, Goldsmith D, Gutteridge G. Comparison of point-of-care versus central laboratory measurement of electrolyte concentrations on calculations of the anion gap and the strong ion difference. Anesthesiology 2003;98:1077–84.
75. Murthy JN, Hicks JM, Soldin SJ. Evaluation of i-STAT portable clinical analyzer in a neonatal and pediatric intensive care unit. Clin Biochem 1997;30:385–9.
76. Free AH, Free HM. Urinalysis: its proper role in the physician's office. Clin Lab Med 1986;6:253–66.
77. Goh JT, Krause H. A prospective observational study on the accuracy of patient self-testing of urine at an antenatal clinic. Aust N Z J Obstet Gynaecol 2002;42:67–8.
78. Millar JG, Campbell SK, Albano JD, Higgins BR, Clark AD. Early prediction of pre-eclampsia by measurement of kallikrein and creatinine on a random urine sample. Br J Obstet Gynaecol 1996;103:421–6.
79. Martin JN Jr, May WL, Magann EF, Terrone DA, Rinehart BK, Blake PG. Early risk assessment of severe preeclampsia: admission battery of symptoms and laboratory tests to predict likelihood of subsequent significant maternal morbidity. Am J Obstet Gynecol 1999;180:1407–14.
80. Waugh J, Bell SC, Kilby M, Lambert P, Shennan A, Halligan A. Effect of concentration and biochemical assay on the accuracy of urine dipsticks in hypertensive pregnancies. Hypertens Pregnancy 2001;20:205–17.
81. North RA, Taylor RS, Schellenberg JC. Evaluation of a definition of pre-eclampsia. Br J Obstet Gynaecol 1999;106:767–73.
82. Wallace JF, Pugia MJ, Lott JA, Luke KE, Shihabi ZK, Sheehan M, et al. Multisite evaluation of a new dipstick for albumin, protein, and creatinine. J Clin Lab Anal 2001;15:231–5.
83. Uttendorfsky OT, Veersema D, Mooij PN, Stolte LA. Protein/creatinine ratio in the assessment of proteinuria during pregnancy. Eur J Obstet Gynecol Reprod Biol 1988;27:221–6.
84. Sibai BM, Ewell M, Levine RJ, Klebanoff MA, Esterlitz J, Catalano PM, et al. Risk factors associated with preeclampsia in healthy nulliparous women: the Calcium for Preeclampsia Prevention (CPEP) Study Group. Am J Obstet Gynecol 1997; 177:1003–10.
85. Murray N, Homer CS, Davis GK, Curtis J, Mangos G, Brown MA. The clinical utility of routine urinalysis in pregnancy: a prospective study. Med J Aust 2002;177:477–80.
86. Bell SC, Halligan AW, Martin A, Ashmore J, Shennan AH, Lambert PC, et al. The role of observer error in antenatal dipstick proteinuria analysis. Br J Obstet Gynaecol 1999; 106:1177–80.
87. Jazayeri A, Chez RA, Porter KB, Jazayeri M, Spellacy WN. Urine protein dipstick measurements: a screen for a standard, 24-hour urine collection. J Reprod Med 1998;43:687–90.
88. Bove P, Kaplan D, Dalrymple N, Rosenfield At, Verga M, Anderson K, et al. Reexamining the value of hematuria testing in patients with acute flank pain. J Urol 1999;162:685–7.
89. Trainor LD, Steinberg JP, Austin GW, Solomon HM. Indinavir crystalluria: identification of patients at increased risk of developing nephrotoxicity. Arch Pathol Lab Med 1998;122:256–9.
90. Jacobs IA, Kelly K, Valenziano C, Chevinsky AH, Pawar J, Jones C. Cost savings associated with changes in routine laboratory tests ordered for victims of trauma. Am Surg 2000; 66:579–84.
91. Chandhoke PS, McAninch JW. Detection and significance of microscopic hematuria in patients with blunt renal trauma. J Urol 1988;140:16–8.
92. Mariani AJ, Luangphinith S, Loo S, Scottolini A, Hodges CV. Dipstick chemical urinalysis: an accurate cost-effective screening test. J Urol 1984;132:64–6.
93. Daum GS, Krolikowski FJ, Reuter KL, Colby JM, Silva WM. Dipstick evaluation of hematuria in abdominal trauma. Am J Clin Pathol 1988;89:538–42.
94. Ford EG, Karamanoukian HL, McGrath N, Mahour GH. Emergency center laboratory evaluation of pediatric trauma victims. Am Surg 1990;56:752–7.
95. Muckart DJ, McDonald MA. Evaluation of diagnostic peritoneal lavage in suspected penetrating abdominal stab wounds using a dipstick technique. Br J Surg 1991;78:696–8.
96. Sinert R, Kohl L, Rainone T, Scalea T. Exercise-induced rhabdomyolysis. Ann Emerg Med 1994;23:1301–6.
97. Press SM, Smith AD. Incidence of negative hematuria in patients with acute urinary lithiasis presenting to the emergency room with flank pain. Urology 1995;45:753–7.
98. Kennedy TJ, McConnell JD, Thal ER. Urine dipstick vs. microscopic urinalysis in the evaluation of abdominal trauma. J Trauma 1988;28:615–7.
99. Propp DA, Weber D, Ciesla ML. Reliability of a urine dipstick in emergency department patients. Ann Emerg Med 1989; 18:560–3.
100. Shirey TL. Critical care profiling for informed treatment of severely ill patients. Am J Clin Pathol 1995;104:S79–87.
101. Slomovitz BM, Lavery RF, Tortella BJ, Siegel JH, Bachl BL, Ciccone A. Validation of a hand-held lactate device in determination of blood lactate in critically injured patients. Crit Care Med 1998;26:1523–8.
102. Boldt J, Kumle B, Suttner S, Haisch G. Point-of-care (POC) testing of lactate in the intensive care patient: accuracy, reliability, and costs of different measurement systems. Acta Anaesthesiol Scand 2001;45:194–9.
103. Ahsan SK, Washington RJ, Ahsan N. Myoglobinuria: evaluation of methods in the clinical diagnosis acute renal failure. Indian J Med Sci 2001;55:443–52.
104. Kasik JW, Leuschen MP, Bolam DL, Nelson RM. Rhabdomyolysis and myoglobinemia in neonates. Pediatrics 1985;76:255–8.
105. Line RL, Rust GS. Acute exertional rhabdomyolysis. Am Fam Physician 1995;52:502–6.
106. Loun B, Copeland KR, Sedor FA. Ultrafiltration discrepancies in recovery of myoglobin from urine. Clin Chem 1996; 42:965–9.
107. Gerber LM, Johnston K, Alderman MH. Assessment of a new dipstick test in screening for microalbuminuria in patients with hypertension. Am J Hypertens 1998;11:1321–7.

108. Gerber LM, Schwartz JE, Cedeno-Mero C, Warren K, Pickering TG. Association of urinary albumin concentration with casual and ambulatory blood pressure: a similar relationship in normotensive and hypertensive subjects. Blood Press Monit 2001; 6:245–51.
109. Bakris GL. Microalbuminuria: prognostic implications. Curr Opin Nephrol Hypertens 1996;5:219–23.
110. Bakris GL. Microalbuminuria: what is it? why is it important? what should be done about it? J Clin Hypertens (Greenwich) 2001;3:99–102.
111. Berry J. Microalbuminuria testing in diabetes: is a dipstick as effective as laboratory tests? Br J Community Nurs 2003; 8:267–73.
112. Davidson MB, Smiley JF. Relationship between dipstick positive proteinuria and albumin:creatinine ratios. J Diabetes Complications 1999;13:52–5.
113. Hoy W, Jim S, Warrington W, Light A, Megill D. Urinary findings and renal function in adult Navajo Indians and associations with type 2 diabetes. Am J Kidney Dis 1996;28:339–49.
114. Lindeman RD, Romero L, Liang HC, Hundley R, Baumgartner R, Koehler K, et al. Prevalence of proteinuria/microalbuminuria in an elderly urban, biethnic community. Geriatr Nephrol Urol 1998;8:123–30.

PUBLIC COMMENTS

No public comments were received on the guidelines.

Chapter **13**

Reproductive Testing

Ann M. Gronowski, David G. Grenache, Glenn Markenson, Robin Weiner, Laurence M. Demers,* and Patrick St. Louis**

INTRODUCTION

The use of point-of-care testing (POCT) for fertility or reproduction-related markers is limited to only a few types of tests. These include urine/serum-based testing as an aid in the early diagnosis of pregnancy, urine-based biochemical tests and bioelectric measurements for predicting ovulation, ferning and pH testing for detection of premature rupture of membranes, and detection of cervicovaginal fetal fibronectin (fFN) for the prediction of preterm delivery. This chapter will examine the clinical utility of these tests and the effect they have on patient outcomes. There are a number of publications that have examined the ability of the urine-based tests human chorionic gonadotropin hormone (hCG) and luteinizing hormone (LH) to measure a given amount of antigen (analytical sensitivity). These guidelines do not address studies such as these and focus only on studies that have examined measurable clinical outcomes.

URINE/SERUM HCG TESTING

Does the use of urine hCG POCT as an aid in the diagnosis of pregnancy improve outcomes (i.e., reduce clinic visits or reduce length of stay [LOS] in the emergency department or reduce number of contraindicated drugs or therapies) compared to serum core laboratory hCG? (Literature Search 94)

Guideline 171. *We note that the use of rapid urine/serum hCG devices may have utility in settings such as the emergency department or urgent care centers, but remarkably, no studies have been published that examine outcomes such as LOH, number of clinic visits, or the number of contraindicated drugs or procedures. Therefore, there is not sufficient evidence to make any recommendation for or against the use of rapid urine/serum hCG tests. We note that the use of home urine hCG devices may have utility and reduce adverse social behaviors, but no studies have been published that examine outcomes in this setting either. Therefore, there is not sufficient evidence to make any recommendation for or against the use of home urine hCG tests.*

Strength/consensus of recommendation: I

Level of evidence: III (no studies, clinical experience)

Literature Search 94 summarizes the results of our literature search.

Is the diagnostic accuracy of urine hCG POCT equivalent to serum core laboratory hCG? (Literature Search 95)

Guideline 172. Early s*tudies have indicated much brand-by-brand variation in point-of-care (POC) laboratory hCG devices. Recent studies (after 1990) have not been conducted, making a recommendation difficult. According to the published data available, caution should be used with POC hCG devices. Since new novel technologies have significantly enhanced these earlier tests, further studies are needed to determine which devices are most accurate and consistent in performance. POC hCG devices may have utility as an aid in the diagnosis of ectopic pregnancy, although this utility has not been adequately compared to the use of in-lab testing. Therefore, there is not sufficient evidence to make any recommendation for or against the use of POC urine hCG devices for the diagnosis of ectopic pregnancy. Studies also indicate brand-by-brand variation in rapid home hCG devices. However, recent studies (after 1989) have not been conducted, making a recommendation difficult. According to*

Continued on next page

*Robin Weiner, Quidel Corporation, San Diego, CA, U.S.A, Laurence M. Demers, Ph.D., FACB, Milton S. Hershey Medical Center, Hershey, PA, U.S.A, and Patrick St. Louis, Ph.D., Sainte-Justine Hospital, Montreal, Quebec, Canada served as consultants on this chapter.

Continued from previous page

the published data available, caution should be used with home hCG devices. Further studies are needed to determine which devices are most accurate.

Strength/consensus of recommendation: I

Level of evidence: II (observational and retrospective cohort studies)

Literature Search 95 summarizes the results for our literature search. There are 3 settings in which urine/serum POC testing has been examined: hospital laboratory for the diagnosis of pregnancy, hospital laboratory for the diagnosis of ectopic pregnancy, and home for the early diagnosis of pregnancy.

Four studies (1979, 1985, 1986 and 1990) have examined the accuracy of POC urine/serum hCG devices in a hospital setting *(1–4)*. All of these studies are more than 10 years old. Two of the 4 reports tested samples that were submitted to the laboratory for hCG testing *(2, 3)*. Of the other 2 reports, one used urine from known pregnant and nonpregnant women *(1)*. The other used urine and serum from women pre- and postelective abortion *(4)*. A summary of these studies is shown in Table 13-1. These data demonstrate that even in a hospital setting, there are significant differences in accuracy for detecting pregnancy between different manufacturer's devices. These findings were consistent for urine and serum samples. Because these studies are all more than 14 years old and there have been numerous changes in method technology for these devices since that time, conclusions cannot be drawn to its application today.

Seven studies have been published that examine the accuracy of POC hCG devices to diagnose ectopic pregnancies *(2, 5–10)*. Six of the 7 articles were published before 1989 *(2, 6–10)*. As indicated previously, none of these studies examined whether patients were treated differently according to the availability of a POC test. These studies examined the ability to accurately detect ectopic pregnancy with a POC hCG device. A summary of the findings is shown in Table 13-2. These studies show that, with the exception of the first study from 1985 *(2)*, POC hCG devices were able to detect ectopic pregnancies with a sensitivity of >90%. In fact, only 1 device had a sensitivity of 90%; the remainder were >93% *(9)*. The majority of these studies were conducted during a period when STAT quantitative hCG testing was not readily available from the laboratory. Studies need to be performed that compare the sensitivity of POC urine hCG tests to laboratory quantitative hCG tests. The Wong and Suat *(5)* study from 2000 did compare the sensitivity of the POC device to quantification using the Abbott IMx (Abbott Laboratories, Abbott Park, IL, USA). This study reported sensitivities of 96.9% and 97.4%, respectively, suggesting that the POC devices may perform much like the laboratory quantitative assays. Further studies are needed to confirm these findings. Furthermore, studies need to be performed that compare treatment differences for those diagnosed with a contemporary POC hCG device vs a contemporary quantitative serum hCG.

Only 1 article (in 1989) has been published on the accuracy of home devices *(11)*. This article compared the accuracy of 9 pregnancy devices intended for home use. The urine used was from nonpregnant women and women who were 3 months pregnant. No urine was examined from women around the time of the missed menses. The authors noted a big variation in the accuracy between devices (range, 69.6% to 97.1%). The

Table 13-1 Published Studies Examining the Accuracy of POC hCG Devices for Detecting Pregnancy in a Hospital Setting

Ref	Year	Population	Sample	Sensitivity (%)	Specificity (%)	Accuracy for detecting pregnancy (%)	No. of devices
(1)	1979	Known preg/nonpreg	Urine	89–100	95–100		7
(2)	1985	Evaluated in emergency department	Urine	82	97	95	1
(3)	1986	Submitted for hCG	Urine	86.1–98.4	94.6–100	89–99	8
(4)	1990	Pre- and postabortion	Urine	70.6–90.6	92.9–100	73.7–91.9	3
(4)	1990	Pre- and postabortion	Serum	67.1–94.1	78.6–100	71.7–91.9	3

Table 13-2 Published Studies Examining the Sensitivity of POC Urine hCG Devices for Detecting Ectopic Pregnancies

Ref	Year	Population	n	No. of ectopic	Sensitivity (%)	No. of devices
(2)	1985	Patients evaluated for pregnancy in emergency department	607	N/R	60	1
(10)	1986	Patients evaluated for pregnancy (68% emergency department)	884	27	96	1
(9)	1986	Patients with gynecologic emergencies	46	30	90–100	7
(8)	1987	Suspected ectopic	909	71	100	1
(7)	1987	Suspected ectopic	107	17	94	1
(6)	1989	Suspected ectopic	51	6	100	1
(5)	2000	Known ectopic pregnancies	207	207	96.9	1

N/R, not reported.

accuracy that was measured was lower than the manufacturers' claimed accuracy in all cases (range of claimed accuracies, 96%–99.5%). Many of the devices (6/9) gave uncertain results. The uncertain results, as a percentage of total results for that brand of device, ranged from 0%–21%. The authors found similar discrepancies in the sensitivity and specificity for detecting pregnancy, as well (measured sensitivity, 51.7%–100%; claimed sensitivity, 97.8%–99%; measured specificity, 60.5% to 100%, claimed specificity, 94%–100%). These data indicate that there were significant differences in accuracy for detecting pregnancy between home devices. In addition, there were significant differences between manufacturer claims of accuracy and measured accuracy in this one study with early over-the-counter devices. Although this study indicates that these types of analyses are quite valuable, it is the only one that has been done. Because this study is 15 years old, its application to today's tests is unclear. A recent study by Cole et al. *(12)* and in *Consumer Reports (13)* has tried to address such concerns, but these studies use artificially spiked, not real, urine samples. Clearly, further studies are required to assess the accuracy of the newer rapid home hCG devices.

How early in gestation does urine hCG POCT diagnose pregnancy accurately and how does this compare to serum core laboratory hCG? (Literature Search 96)

Guideline 173. *We note that it is unclear how early all home urine hCG devices can detect pregnancy. It is clear that there are brand-by-brand differences. Recent studies (after 1989) have not been conducted, making a recommendation difficult. According to the published data available, caution should be used in interpreting home hCG devices early after missed menses. Further studies are needed to determine which newer over-the-counter devices are best able to detect early pregnancy.*

Strength/consensus of recommendation: I

Level of evidence: III (single retrospective cohort studies)

Literature Search 96 summarizes the results for our literature search. Only 1 article has examined how early in gestation POCT hCG devices aid in the diagnosis of pregnancy using patient urine. Asch et al. *(14)* collected urine on days 7–16 after ovulation from women trying to get pregnant. They used samples from 35 women who eventually had increasing hCG concentrations and visualization of an intrauterine gestational sac by ultrasound. Three rapid home hCG devices were compared. Testing was performed by laypersons (junior high school students). The results are shown in Table 13-3. The results demonstrate significant brand-by-brand variation in the ability to detect pregnancy at various times after ovulation. At the expected day of menses, the 3 devices were able to detect hCG 70%, 88%, and 95% of the time. By 2 days after missed menses, one device detected hCG 100% of the time, but the other 2 devices detected hCG 75% and 95% of the time. This study was performed in 1988, and clearly the brands and assay formulation have changed since that time. Studies need to be conducted with modern home hCG devices. Recently, Cole et al. *(12)* have tried to address this question. However, their study was not included in this analysis, because real urine was not used to test the devices. Their group determined the concentration of urine in women at various times after missed menses. Then they tested various home hCG devices for the ability to detect urine with hCG added at those concentrations. Cole's group found that, in theory, an analytical sensitivity of 12.5 mIU/mL was needed to detect 95% of pregnancy at the time of the missed menses. They found that only 1 home pregnancy device had this sensitivity. This research raises questions about the ability of even modern home pregnancy devices to detect early pregnancy. Clearly, more studies using real urine samples (similar to the Asch et al. *(14)* study) and modern home pregnancy devices are needed.

What is the diagnostic accuracy of urine hCG POCT when performed by a layperson compared to the diagnostic accuracy of serum or urine core laboratory hCG? (Literature Search 97)

Guideline 174. *No studies have been published that compare the accuracy of hCG POC devices when performed by a layperson vs the accuracy of a core laboratory. Therefore, there is not sufficient evidence to make any recommendation about laypersons and the use of home urine hCG tests.*

Strength/consensus of recommendation: I

Level of evidence: III (no studies, clinical experience)

Table 13-3 Percentage of Positive hCG Results[a]

	Days After Ovulation or Follicular Aspiration									
Device	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14[b]**	**15**	**16**
1	0	0	0	10	36	60	75	88	100	100
2	0	0	25	35	65	80	95	95	95	95
3	0	0	5	15	20	30	60	70	75	75

[a] Reference (14).

[b] Day 14 is the day of expected menses.

Literature Search 97 summarizes the results for our literature search.

What is the diagnostic accuracy of urine hCG POCT when performed by a layperson compared to the diagnostic accuracy of urine POCT in a core laboratory? (Literature Search 98)

Guideline 175. *Studies have clearly shown decreased accuracy of urine POCT devices when performed by laypersons. We recommend that manufacturers provide clear concise instructions for use and adequate (easy to interpret) quality-control measures to maximize the proper use and interpretation of these devices. We recommend that physicians confirm results with quantitative serum hCG.*

Strength/consensus of recommendation: I

Level of evidence: III (observational cohorts and blind randomized cohort)

Literature Search 98 summarizes the results for our literature search. Three studies have examined the accuracy of POC hCG devices in trained vs untrained individuals *(15–17)*. All 3 studies were 1993 and earlier. The first study, published in 1977, compared inexperienced individuals, medical technicians with general chemistry knowledge, and medical technicians with extensive rapid hCG device experience *(17)*. The researchers found that the inexperienced persons had significantly more false-positive and false-negative results than both medical technicians with general chemistry knowledge and medical technicians with extensive experience. This study used a very old hemagglutination assay, so the application of its conclusions to today's devices is inappropriate. The second study was performed in 1986 and compared 3 brands of home hCG devices *(16)*. Urine samples were obtained from women shortly after missed menses and split in half. One half was tested on 3 devices by the investigator and one half was returned to the layperson for testing on the same 3 devices. Unfortunately, the study did not report the accuracy of the layperson specifically. They did examine accuracy in the context of psychological and socioeconomic variables. They found that accuracy in laypersons increased with age and in persons with more education. Income had no effect. Anxiety level (based on whether the patient was trying to get pregnant or was unmarried) also had little effect. The final study, from 1993, examined all 27 home-use hCG devices that were currently sold in France *(15)*. First, testing was performed by experienced clinical chemistry technologists. The authors selected 11 devices that had 100% sensitivity and 100% specificity for detecting hCG in samples with no hCG, a low positive adjusted to the claimed detection limit of the kit and a high positive adjusted to twice the claimed detection limit. These devices and urine samples were then give to 631 women ages 14–49 years. When performed by laypersons, the specificity ranged from 76.9% to 100% (6/11 were <94%; mean, 93.4%), the sensitivity range for the low positive hCG sample was 0%–100% (mean, 42.1%), and high positive was 20%–100% (mean, 59.7%). It is clear from this study that results using POC hCG devices vary between trained and untrained personnel. The authors stress the need for rigorous validation of home pregnancy kits and adequate quality-control measures. These data also demonstrate the need for clear concise instructions for laypersons.

URINE LH OVULATION TESTS

Is the diagnostic accuracy of urine LH tests sufficient for detecting ovulation using progesterone or ultrasound as a gold standard for confirming ovulation? (Literature Search 99)

Guideline 176. *We note that POC tests have excellent diagnostic sensitivity for the detection of ovulation. We can strongly recommend the use of these devices when the purpose of using them is to detect ovulation.*

Strength/consensus of recommendation: A

Level of evidence: II (cohort studies)

Literature Search 99 summarizes the results for our literature search. There is clear and compelling evidence that urine LH POCT devices detect the LH surge. As ovulation frequently occurs between 32 and 38 h after the LH surge is detected in the plasma, detection of LH in the urine should be an indication that ovulation is approaching and identifies the beginning of peak fertility *(18)*. Table 13-4 summarizes studies that have investigated the ability of urine LH tests to detect ovulation in normal and clomiphene citrate–stimulated cycles. These studies have reported sensitivities of 85%–100% (median, 100%). Two studies reported rare instances in which urine LH tests failed to identify an LH surge despite evidence of ovulation by gold-standard methods *(19, 20)*. The specificity of urine LH POCT for detecting ovulation is difficult to evaluate because only a few studies have included anovulatory women *(21–23)*. When the data allowed the calculation of diagnostic specificity, the luteinizing unruptured follicle syndrome was often used to explain false-positive results *(20, 24, 25)*. Although this finding is technically a false-positive result, the test devices still performed as they were designed: to detect an increased concentration of urinary LH.

Is the diagnostic accuracy of urine LH tests sufficient for *predicting* ovulation using progesterone or ultrasound as a gold standard for confirming ovulation? (Literature Search 100)

Guideline 177. *We recommend the use of urine LH tests to predict ovulation within 48 h of a positive test.*

Strength/consensus of recommendation: B

Level of evidence: II (cohort studies)

Table 13-4 Studies That Have Investigated the Detection and Prediction of Ovulation Using Urine LH POCT

Ref	Year	Population	n Patients/cycles	Sensitivity[a] (%)	Specificity[b] (%)	Predictive value[c] (%)	Comments
(21)	2001	Infertile but ovulatory women	101/101	100	25	85	
(41)	1996	Normal women	26/26	100	ND[d]	92	
(42)	1994	Infertility patients	145/269	100	0	100	9 false positives in nonovulatory patients attributed to LUF[e]
(24)	1990	Infertile but normally cycling women	50/50	100	0	85	3 false positives attributed to LUF
(43)	1989	Normally cycling women	33/33	100	ND	91	
(44)	1987	Spontaneous and stimulated cycles	27/30	100	ND	93 and 100	2 different devices evaluated
(22)	1986	Spontaneous and stimulated cycles	55/75	100	100	NA[f]	
(19)	1990	Normally cycling women	20/20	85	ND	87	
(23)	2000	Normally cycling women	11/11	100	100	100	
(20)	1991	Infertility patients	115/303	99	80	NA	2 false positives attributed to LUF
(45)	1990	Normally cycling women	55/55	100	ND	100	Predictive value for 36 h before ovulation
(25)	1988	Infertility patients	15/25	100	0	100	3 false positives attributed to LUF; predictive value for 36 h before ovulation
(46)	1989	Infertility patients	29/29	96	ND	93	

[a] Sensitivity to detect ovulation = number of patients who were LH positive/number of patients with confirmed ovulation.
[b] Specificity to detect absence of ovulation = number of patients who were LH negative/number of patients without confirmed ovulation.
[c] Predictive value identifies the percentage of ovulations accurately predicted to occur within 48 h of a positive urine LH POCT.
[d] Not done.
[e] Luteinizing unruptured follicle syndrome.
[f] Not applicable. Study investigated only ovulation detection, not prediction.

Literature Search 100 summarizes the results for our literature search. The most likely use of urine LH POCT is to predict a time when ovulation is likely to occur to potentially increase likelihood of pregnancy. Although the studies examined for this report defined this time interval from anywhere between 36 and 72 h, most considered the 48-h period before ovulation as the optimal time for detection. This is an appropriate time frame because the window for fertilization is brief, and introduction of sperm into the female genital tract within 2 days before ovulation has the highest probability of conception *(26)*. In this regard, the sensitivity of urine LH POCT to predict ovulation (defined as the detection of the LH surge within 48 h before ovulation, determined by the gold standard), although not as robust as their ability to detect ovulation, ranged from 85%–100% (median, 93%) (Table 13-4).

Does the use of urine LH tests for predicting ovulation in women not treated in a fertility clinic improve outcomes (i.e., increase conception rates, decrease number of clinic visits, or number of unwanted pregnancies) compared to no use of prediction tests? (Literature Search 101)

Guideline 178. *There is insufficient evidence to make any recommendation for or against the use of home urine LH testing to improve conception rates in women not seeking fertility treatments.*

Strength/consensus of recommendation: I

Level of evidence: III

Literature Search 101 summarizes the results for our literature search. No articles have examined the clinical utility of urine LH tests as ovulation predictors in a home setting with women who were not being treated in a fertility clinic. This is precisely the population to which these devices are marketed, and such studies would be very useful. Although it is logical to assume that the use of these devices would increase conception rates, it is also possible that the devices are not needed by this population for whom infertility may not be a problem. Until such data are available, these statements are purely speculative.

Does the use of urine LH tests for predicting ovulation in women undergoing fertility treatment improve outcomes (i.e., increase conception rates, decrease number of clinic visits, number of fertility treatment cycles) compared to no use of prediction tests? (Literature Search 102)

Guideline 179. *We can make no recommendation for or against routinely providing urine LH tests to improve outcomes. There are limited data available to adequately assess the utility of the test to improve conception rates, clinic visit frequency, or fertility treatment cycles. Although these questions are certainly of considerable interest, clear-cut answers remain elusive and additional studies need to be performed.*

Strength/consensus of recommendation: I

Level of evidence: I (at least 1 randomized controlled trial)

Literature Search 102 summarizes the results for our literature search. Of the studies that have examined specific outcomes, most have reported on the ability of urine LH tests to increase conception rates in women undergoing artificial insemination. The data from these studies suggest that the availability of urine LH tests does not have a positive effect on conception rates; however, the data are from small studies and are relatively limited. Two studies investigating the ability of urine LH tests to improve pregnancy rates reported that they were worse in the POCT group compared to controls. One reported a 13.7% pregnancy rate in the POCT group (n = 346 cycles), which was significantly lower than the 18% rate achieved by patients whose inseminations were timed by a laboratory-performed serum LH test (n = 1119 cycles) ($P < 0.05$) *(27)*. The second reported that a pregnancy rate of 3.4% was significantly lower in the POCT group (n = 174 cycles) compared to the 12.7% rate achieved by a quantitative urine LH group (n = 110 cycles) ($P < 0.005$) *(28)*.

Five studies reported that POCT offered no benefit over other methods of timing inseminations *(29–33)*. Kossoy et al. *(29)* reported that pregnancy rates were unaffected by use of POCT, with a 13% rate achieved with POCT (n = 67 cycles) and 12% without (n = 43 cycles). Leader and colleagues *(30)* reported that pregnancy rates were unaffected by use of POCT in patients with either unexplained infertility (n = 110) or for those with partners with male factor infertility (n = 50). In women with unexplained infertility, pregnancy rates were 20.4% for those who used POCT LH tests and 16% for those who did not ($P > 0.05$). Likewise, fecundity in women whose partners were infertile was 8% in the POCT group and 11.1% for those who did not use POCT (P not given) *(30)*. Robinson et al. *(31)* also reported that pregnancy rates were unaffected by the use of POCT (8.1%; n = 123 cycles) compared to those who used basal body temperature (BBT) monitoring and cervical mucus scoring methods of detection (6.5%; n = 111 cycles) ($P > 0.05$). Another study by Kossoy et al. *(32)* reported no significant differences in pregnancy rates when POCT was used along with BBT and cervical mucus scoring (13%; n = 26) compared to just BBT and mucus scoring (11%; n = 94) (P not given). Last, Brook et al. *(33)* reported no significant differences in pregnancy rates when POCT was compared against serum LH, BBT, or cervical mucus scoring for timing of inseminations. Cumulative pregnancy rates in each group were 34% (n = 545 cycles), 34% (n = 236 cycles), 31% (n = 405 cycles), and 37% (n = 209 cycles), respectively ($P > 0.05$).

In addition to fecundity, other outcomes addressed in various studies include the use of urine LH tests to time inseminations, to limit number of clinic visits per treatment cycle, and to investigate the number of inseminations required to achieve pregnancy. Unfortunately, the numbers of studies investigating these other outcomes are also limited. Only 1 study investigated the timing of insemination using urine LH tests, and it reported that timing was correctly predicted in 25 patients when POCT urine LH was combined with ultrasound monitoring of follicle size. Insemination was considered to have been correctly timed only if follicle size measured ≥18 mm and an LH surge was detected in the urine. This approach predicted all those women who ovulated (n = 20) and detected unfavorable conditions for insemination in the remaining 5 *(34)*. Lack of a control group, however, seriously limits the conclusions of this study.

In a study to investigate the effect of urine LH POCT on the number of clinic visits per treatment cycle, Robinson et al. *(31)* found that, at 1.5 visits/cycle, there were significantly fewer visits to the fertility clinic per cycle for POCT patients (n = 123 cycles) compared to the 2.4 visits/cycle observed with a control group that did not use POCT (n = 111 cycles) ($P < 0.001$).

Kossoy et al. *(32)* reported no differences in the number of insemination cycles required to achieve conception when comparing POC LH testing in addition to BBT and cervical scoring (n = 26) to controls using only BBT and cervical scoring (n = 94) ($P = 0.79$).

What is the diagnostic accuracy of urine LH POCT ovulation tests when performed/interpreted by a layperson as compared to the diagnostic accuracy of urine LH in a core laboratory (performed by Clinical Laboratories Improvement Act [CLIA]-approved laboratory staff)? (Literature Search 103)

Continued on next page

Continued from previous page

Guideline 180. *There is insufficient evidence to evaluate the diagnostic accuracy of results obtained from layperson- or laboratory-performed "urine" LH testing.*

Strength/consensus of recommendation: I

Level of evidence: III (descriptive studies)

Literature Search 103 summarizes the results for our literature search. Only 1 study was identified, and it reported an 89% agreement between layperson-tested and gynecologist-tested (not laboratory-tested) POCT results ($P = 0.5$) *(20)*. Although this outcome was not specifically addressed in other studies, there are studies that comment on large numbers of laypersons that report the performing and reading of POCT urine LH tests confusing. However, this was more frequently associated with older studies that used older POCT technology and may not be relevant with devices available today.

What is the diagnostic accuracy of urine LH POCT ovulation tests when performed/interpreted by a layperson as compared to the diagnostic accuracy of serum LH in a core laboratory (performed by CLIA-approved laboratory staff)? (Literature Search 104)

Guideline 181. *There is insufficient evidence to evaluate the diagnostic accuracy of results obtained from layperson-performed urine LH tests compared to laboratory-performed "serum" LH testing.*

Strength/consensus of recommendation: I

Level of evidence: III (expert opinion)

Literature Search 104 summarizes the results of our literature search. No studies were identified that examined the performance of layperson-performed POCT against serum LH performed by laboratory personnel.

NONURINE OVULATION TESTS

Nonurine tests for predicting ovulation include devices that measure electrical admittance (1/impedence) or electrical resistance in saliva, vaginal mucus, or both and the fern test. Although few, these devices offer unique methods of ovulation detection and may have broad appeal, particularly because they are reusable rather than disposable.

Is the diagnostic accuracy of nonurine POCT ovulation tests sufficient to predict ovulation using progesterone or ultrasound as a gold standard for confirming ovulation? (Literature Search 105)

Guideline 182. *We note that there is limited useful evidence to support the use of nonurine POCT for predicting ovulation, and the available evidence is generally of poor quality. We therefore can make no recommendation for or against the use of nonurine POCT for ovulation prediction*

Strength/consensus of recommendation: I

Level of evidence: III (descriptive studies)

Literature Search 105 summarizes the results for our literature search. Studies from only 2 devices that measure electrical admittance or electrical resistance have been reported in the literature: the Ovulon fertility monitor (Conception Technology, Inc., Fort Collins, CO, USA) and the Cue Ovulation Monitor (Zetek, Inc., Aurora, CO, USA). Although 10 studies were identified that investigated the use and performance of these types of devices, only 4 provided sufficient data to determine their ability to predict ovulation within 48 h of its occurrence *(35–38)*. Of these 4, only 1 *(38)* used ultrasound of follicular size as the gold standard for detecting ovulation, whereas the other studies used urine LH measurements (qualitative or quantitative) or serum LH measurements to confirm ovulation. A study by Moreno et al. *(38)* compared readings from the Cue Ovulation Monitor to follicle size determined by ultrasound in 29 cycles from 11 normally cycling women. They reported that the monitor produced the expected vaginal nadir signal 2 days before ovulation in 93% of cycles. However, because the signal is a nadir, it can be correctly identified only retrospectively, making daily interpretation of signals for predicting ovulation challenging, if not impossible. The predictive abilities reported by the other 3 studies were 74% *(37)*, 52% *(35)*, and 55% *(36)*. However, the lack of a gold standard method for confirming ovulation seriously limits interpretation of these results.

Four studies examined the utility of fern testing performed on saliva or cervical mucus as a predictor of ovulation. Theoretically, a pattern of "ferning" is observed on examination of dried saliva or cervical mucus that coincides with the fertile period in the female. The ferning or crystallization is caused by alterations in the fluid concentrations of sodium and chloride that cyclically increases under the influence of estrogen. Only 2 of the 4 studies used ultrasound of follicular size as the gold standard for confirming ovulation, and one of these did not report the predictive ability of the fern test. A study by Guida et al. *(39)* evaluated the efficacy of salivary ferning to detect ovulation (determined by ultrasound) in 125 cycles from 40 normal cycling women. They reported that the fern test predicted ovulation 1 day before the event in 21% of cycles and the day after in another 21%. However, 59% of the tests were excluded because they were uninterpretable. According to this, they concluded that the salivary fern test was a poor method for predicting ovulation. Although the other studies did not include an appropriate gold standard method for confirming ovulation, one report identified ferning patterns throughout the entire menstrual cycle and in salivary specimens collected from men *(40)*.

pH/NITRAZINE TESTS FOR PREMATURE RUPTURE OF MEMBRANES

Premature rupture of the membranes (PROM), a common obstetrical problem, refers to amniotic membrane rupture before the start of labor or regular uterine contractions. If it occurs before term, it is designated as preterm premature rupture of the membranes (PPROM). Because the pH range of amniotic fluid (pH 7.0–7.7) is higher than the normally acidic vagina (pH 3.8–4.2), an often-used test in the assessment of a patient with suspected membrane rupture is the analysis of vaginal pH with nitrazine article *(47)*.

Does the pH/nitrazine test accurately predict preterm premature rupture of membranes? (Literature Search 106)

Guideline 183. *We note that the evidence is insufficient to recommend for or against providing pH/nitrazine tests for the prediction of preterm premature rupture of membranes.*

Strength/consensus of recommendation: I

Level of evidence: III (descriptive studies)

Literature Search 106 summarizes our literature search. Only 1 study for predicting PPROM was identified. This study of 115 patients at high risk for a low-birth-weight infant used an indirect method of serially measuring vaginal pH from 23 weeks' gestation to delivery and a pH cutoff of > 4.5 *(48)*. Sixteen percent of the patients studied developed PPROM, although the method of diagnosing PROM was not reported. The use of a mean pH > 4.5 produced a 32% positive predictive value (PPV) and a 90% negative predictive value (NPV) for PPROM. However, to be clinically useful, pH must be evaluated prospectively, and in that regard the study found that any single pH result > 4.5 produced positive and NPVs of 19% and 89%, respectively. Because the objective of this study was to use vaginal pH to predict PPROM, it could be argued that the predictive values may offer an advantage over no prediction method. Considering the limited availability of data, however, no recommendation for using pH to predict preterm PROM can be made at this time.

Does the pH/nitrazine test accurately identify women with ruptured membranes and/or women whose membranes have not ruptured? (Literature Search 107)

Guideline 184. *We note that the pH/nitrazine test is sensitive only when used in women for whom membrane status is known. When applied to patients suspected of having PROM, the test does not appear to be sufficiently sensitive or specific enough for diagnostic determination of premature rupture of membranes. Accordingly, we do not recommend the use of pH/nitrazine testing alone for the detection of premature rupture of membranes.*

Strength/consensus of recommendation: C

Level of evidence: II (case-controlled studies)

Literature Search 107 summarizes our literature search. The evidence indicates that the pH/nitrazine test has high sensitivity when used in populations of women who were definitively known to have either PROM or intact membranes *(49–60)*. Because of a lack of a gold standard method of determining PROM, most studies used clinical observation and interpretation as the definitive test. However, the diagnostic utility of the test deteriorates when it is applied to populations for whom the test would be used, namely, women in whom PROM is suspected but not known. Table 13-5 summarizes the data from some of these studies.

The study by Watanabe et al. *(53)* was well designed and reported excellent sensitivity (100%) and marginal specificity (79%) when pH was used in a population of patients known to have PROM because of amniotomy or obvious leakage of amniotic fluid (n = 32) compared to those who did not (n = 19). However, when the pH test was used in a group of women in whom PROM was suspected but not obvious, the test did not perform well, producing a sensitivity of 72% and a specificity of 64% (n = 40).

Similarly, Garite and Gocke *(54)* reported 91% sensitivity and 73% specificity when 23 women with PROM identified by gross pooling of amniotic fluid and 22 with intact membranes were evaluated with vaginal pH. Unfortunately, this study did not evaluate women in whom PROM was uncertain.

A study by Kishida et al. *(56)* used vaginal or cervical fluid pH to evaluate PROM in women with obvious leakage of

Table 13-5 Studies That Have Investigated the Use of pH/Nitrazine Tests for the Detection of Ruptured Membranes

Reference	Year	Population	n	pH Cutoff	Sensitivity (%)	Specificity (%)
(53)	1995	Membrane status known	51	≥7.0	100	79
		Membrane status unknown	40		72	64
(54)	1990	Membrane status known	45	>6.0	91	73
(56)	1995	Membrane status known	103	>6.5	92	53
(58)	1977	Membrane status known	39	Not given	100	92
(59)	1987	Membrane status known	79	≥7.0	77	81
(60)	1995	Membrane status known	30	Not given	100	41

amniotic fluid, as well as in those with intact membranes and in whom PROM was uncertain (patients with only slight leakage of fluid suspected to be amniotic fluid). However, all the data were combined for analysis to produce an overall sensitivity of 92% and a specificity of 53% (n = 103).

Unlike other investigations that noted only marginal specificity, a study of 39 women with intact membranes for whom membrane status was known at the time of testing reported that vaginal pH had excellent specificity (92%) *(58)*. After amniotomy, the use of vaginal pH was 100% sensitive. As has been noted, though, this is not a population that would likely benefit from a test for PROM.

Rochelson et al. *(59)* reported a sensitivity of 77% and a specificity of 81% in 48 women with PROM identified by clinically evident rupture and 31 with intact membranes when measuring pH from specimens collected from the posterior fornix. The lower sensitivity was attributed to the prolonged time period (>12 h) between rupture and specimen collection in 21% of the patients.

According to these data, it is difficult to recommend the use of pH/nitrazine testing alone in evaluating a patient for PROM. The test may better be used as a supportive test in conjunction with other clinical findings.

Does the pH/nitrazine test improve outcomes (number of admissions, use of antibiotics, neonatal morbidity/mortality) compared to the fern test in women suspected of having PROM? (Literature Search 108)

Guideline 185. *We note that the evidence is insufficient to recommend for or against providing pH/nitrazine tests for the prediction of preterm premature rupture of membranes.*

Strength/consensus of recommendation: I

Level of evidence: III (descriptive studies)

Literature Search 108 summarizes our literature search.

FERN TESTS FOR PREMATURE RUPTURE OF MEMBRANES

Another test used frequently to assess a patient with suspected membrane rupture is the fern test. When fluid from the vagina is smeared onto a glass slide and allowed to dry, amniotic fluid will produce a fern pattern.

Does the fern test accurately identify women with ruptured membranes and/or women whose membranes have not ruptured? (Literature Search 109)

Guideline 186. *We note that the fern test is neither sensitive nor specific enough for diagnostic determination of premature rupture of membranes. We recommend against routinely providing fern testing alone for the detection of ruptured membranes*

Strength/consensus of recommendation: C

Level of evidence: III (case-controlled studies)

Literature Search 109 summarizes our literature search. There is limited evidence that suggests the fern test has high specificity and sensitivity when used in populations of women who were definitively known to have either PROM or intact membranes. Garite and Gocke *(54)* reported a sensitivity of 97% and specificity of 100% when they evaluated 23 women with gross pooling of amniotic fluid and 22 with intact membranes. Another study also reported a sensitivity of 62%, with 100% specificity in 48 women with obvious amniotic fluid leakage and 31 with intact membranes *(59)*. The lower sensitivity was attributed to the prolonged time period (>12 h) between rupture and specimen collection in 21% of the patients. When investigating the use of the fern test in 51 women whose membrane status was definitively known, Watanabe et al. *(53)* reported the test to be 84% sensitive and 95% specific.

Similar to the pH/nitrazine test, the performance of the fern test deteriorates when applied to a population of women in whom membrane integrity status is uncertain (the very population in whom the test would be used). de Haan et al. *(61)* reported a sensitivity of 51% and specificity of 71% in 100 patients with suspected PROM, although the method used to eventually categorize these patients into those with or without PROM was never described. The low sensitivity is particularly concerning because false-negative results might delay appropriate treatments. The study by Watanabe et al. *(53)* discussed previously also included 40 women with unknown membrane status, and in this population the fern test was only 50% sensitive and 86% specific.

Similar to the pH/nitrazine test, the data for the fern test suggest it may better be used as a supportive test in conjunction with other clinical findings.

fFN TESTING FOR PREMATURE DELIVERY

Does performing a single rapid fFN assay improve outcomes (such as number of patient admissions, LOS, use of tocolytic medications, cost, neonatal morbidity/mortality, maternal morbidity because of adverse effects of intervention therapy) compared to cervical dilation, Bishop score, contraction number, or cervical length by ultrasound in women with symptoms of preterm labor, intact membranes, and cervical dilation <3 cm? (Literature Search 110)

Continued on next page

Continued from previous page

Guideline 187. *There are no studies that directly compared rapid fFN to any other method to predict preterm birth. There are several noncomparison studies, but none are available that investigated the role of rapid fFN in decreasing neonatal morbidity or mortality. There are 3 outcome studies available that investigated length of maternal stay, maternal transfers to a tertiary-care facility, and need for tocolysis. Two of 3 studies demonstrated that rapid fFN decreases the need for tocolysis and the need for maternal transfer to a tertiary-care facility. It is important to note that these studies used historical controls for comparison. The third study, the only investigation that used a randomized study design, was not powered to detect a difference in the number of maternal transfers to a tertiary-care facility (primary outcome measure) and did not demonstrate an overall difference in length of maternal hospitalization in patients with symptoms of preterm labor (secondary outcome measure). Therefore, additional well-designed studies are needed to determine the true efficacy of fFN testing.*

Strength/consensus of recommendation: I

Level of evidence: II (cohort studies)

Literature Search 110 summarizes our literature search. There is only 1 study that used a randomized control design *(62)*. In this study, all patients enrolled had a rapid fFN performed. They were then randomized into 2 groups, one that allowed providers to know the test results and one group that was blinded to the test results. The primary objective of this study was to look at the number of maternal transports between the 2 groups. A power analysis with this endpoint suggested that 500 patients needed to be enrolled. The study was terminated because of low enrollment, with only 114 patients enrolled. Because of the low numbers, the primary outcome comparison could not be performed. The following secondary outcomes comparisons were noted: The overall LOH was no different between the 2 groups: fFN unknown 8.1 h vs fFN known 6.8 h ($P = 0.35$).

1. Looking at the group that had a least a 6-h stay (17% of all patients): The mean hospital stay in the fFN unknown group was 37.8 h vs 22.7 h in the fFN known group ($P = 0.04$).

Therefore, in this study, rapid fFN was noted to improve care only in those patients with a LOH $>$ 6 h, and only by a hospital stay decrease of 2 h. The clinical and financial impact of a decrease in LOH of 2 h may not support the cost of testing. This study, however, had low enrollment and the possibility of not finding a difference, because of a type II error for the other characteristics of improved care such as maternal transport, and use of tocolysis is highly possible.

There is another study that explored the utility of rapid fFN in prevention of unnecessary maternal transports to a tertiary-care center because of symptoms of preterm labor *(63)*. This investigation looked at the number of maternal transports to a tertiary-center before and after rapid fFN was available at the same facility. This investigation noted a 51% decrease in the number of maternal transports after rapid fFN was available. This study used historical cohorts for comparison; thus, a change in physician practice patterns over time may also have influenced the decrease in maternal transports.

Only one study examined the value of rapid fFN in the prevention of maternal tocolysis for suspected preterm labor *(64)*. These investigators used historical controls from the same institution, with symptoms of preterm labor before the use of rapid fFN, and then compared them to a group that used a rapid fFN to determine whether tocolysis should be used. There was a significant difference, with 100% of the control group (n = 30) receiving tocolysis compared to 20% (n = 3) of the group that was screened with a rapid fFN ($P = 0.0001$). However, the use of historical controls is a major study design flaw and may have resulted in selection bias.

Does performing a single rapid fFN assay improve outcomes (such as number of patient admissions, LOS, use of tocolytic medications, cost, neonatal morbidity/mortality, maternal morbidity because of adverse effects of intervention therapy) compared to fFN enzyme-linked immunosorbent assay (ELISA) in women with symptoms of preterm labor, intact membranes, and cervical dilation $<$3 cm? (Literature Search 111)

Guideline 188. *No studies performed a direct comparison of rfFN to the ELISA fFN and reported any of the outcomes of interest. Validation of this test appears to be limited to studies that looked at the sensitivity, specificity, and negative and PPV for predicting preterm birth and then compared these results to previous published results of fFN determined by an ELISA microtiter plate. No study used the same sample that was measured using the 2 different methods. Therefore, there is insufficient evidence to compare clinical outcomes between the rfFN and the ELISA fFN.*

Strength/consensus of recommendation: I

Level of evidence: III (no studies)

Literature Search 111 summarizes our literature search.

Do repeated rapid fFN tests decrease costs and improve clinical outcomes? At what testing interval? (Literature Search 112)

Guideline 189. *There were no studies available that addressed the issue of the utility of repeated rapid fFN*

Continued on next page

Continued from previous page

testing. In addition, there were no studies available to determine the appropriate interval between samplings. Therefore, there is insufficient evidence to make recommendations about repeated sampling or the appropriate interval between sampling.

Strength/consensus of recommendation: I

Level of evidence: III (no studies)

Literature Search 112 summarizes our literature search.

What are rapid fFN PPV and NPV values for preterm delivery? Does rapid fFN reliably identify women at risk of preterm delivery and/or women at no risk of preterm delivery? (Literature Search 113)

Guideline 190. *The major strength of this test is the strong NPV. Studies have clearly demonstrated the high NPV of rapid fFN, with NPVs > 95% to predict preterm birth within 7 days of testing. A negative rapid fFN result in symptomatic patients is a reliable test to place women at low risk of preterm birth within 7 days of testing. However, the PPV of rapid fFN is a poor predictor of preterm birth. Therefore, a positive rapid fFN should not be used as the primary guide for therapeutic decisions related to the imminent prevention of preterm birth.*

Strength/consensus of recommendation: I

Level of evidence: II (cohort studies)

Literature Search 113 summarizes our literature search. Since 1998, 4 studies have examined the PPVs and NPVs of rapid fFN for preterm delivery in symptomatic patients. The data from these 4 studies are summarized in Tables 13-6 and 13-7. These studies are difficult to compare directly because they used different endpoints for the definition of preterm birth. These endpoints included delivery within 7 days of testing, 14 days of testing, and 21 days of testing and delivery at <34 weeks or <37 weeks.

An investigation performed in 1998 was retrospective in design *(65)*. The goal of this study was to determine whether the results of rfFN as used in clinical practice in patients with symptoms of preterm labor were comparable to results from previous blinded research investigations. This study noted that when used in actual clinical practice, the NPV for birth before 34 weeks was 98% compared to a PPV of 45% for birth <34 weeks.

Another retrospective study used multiple endpoints for determining preterm birth, including delivery within 7 days of testing and 14 days of testing and delivery at <34 weeks or <37 weeks *(66)*. The purpose of this study was also to determine whether the utility of rapid fFN in actual clinic practice was comparable to that seen in previous investigational studies that kept clinicians blinded to the fFN results. These investigators noted that when delivery within 7 days was used as an endpoint, the PPV was actually greater than reported in previous blinded studies that used the ELISA fFN. The ELISA fFN studies reported a sensitivity between 44% and 90%, specificity 45% and 90%, PPV 43% and 83%, and NPV of 63% and 93% when using preterm birth before 37 weeks as a cutoff *(67–72)*. Those ELISA fFN-based studies that used delivery within 7 days found a sensitivity between 90% and 100%, specificity 83% and 71%, PPV 6% and 29%, and NPV of 99% and 100% *(67–69)*.

The largest study, involving 501 samples, was also retrospective in design and used delivery at <7 days, <14 days, and <21

Table 13-6 Published Studies Examining the Positive Predictive Value of rfFN for Preterm Birth in Patients With Symptoms of Preterm Labor

		Positive predictive value (%)			
Author	**n**	**PPV within 7 days**	**PPV within 14 days**	**PPV < 34 weeks**	**PPV < 37 weeks**
Luzzi (73)	133	4	6		
Plaut (62)	108		10		
Lopez (66)	85	40	40	55	85
Chuileannain (65)	70			45	

Table 13-7 Published Studies Examining the Negative Predictive Value of rfFN for Preterm Birth in Patients With Symptoms of Preterm Labor

		Negative predictive value (%)			
Author	**n**	**NPV within 7 days**	**NPV within 14 days**	**NPV < 34 weeks**	**NPV < 37 weeks**
Luzzi (73)	133	96.8	93.7		
Plaut (62)	108		98		
Lopez (66)	85	98	95	94	52
Chuileannain (65)	70			98	

days as endpoints for determining the PPV and NPV *(11)*. The NPVs obtained for patients that delivered within 7, 14, and 21 days of testing were 96.8%, 93.7%, and 93.7%, respectively. The authors concluded that this compared well to previous reports that used ELISA-based testing systems (as discussed above).

There was only 1 study that used a prospective study design *(62)*. In this study, all patients that had symptoms of preterm labor had a rapid fFN performed. They were then randomized into a group in which the providers knew the results of testing and another group in which the providers were blinded to the results of the rapid fFN tests. The primary purpose of this study was to compare treatment decisions in patients with known rapid fFN tests result to a group in which the rapid fFN results were unknown. They then looked at the data to determine the PPV and NPV, using delivery within 14 days of testing as an endpoint. The PPV was 10% and the NPV was 98%.

In summary, despite that fact that POC reproductive-related testing represents a huge portion of the over-the-counter testing market and a huge portion of the decentralized hospital testing, very little outcomes-based research has been done on these devices. For rapid urine/serum hCG testing, we found no data that indicate that these devices alter outcomes for patients. The devices do seem to be able to accurately detect hCG in normal and ectopic pregnancies, but we noted great brand-to-brand variability. We also found decreased accuracy when these devices are used by laypersons. For urine LH testing, we found that these devices detect and predict ovulation well. However, there are few data to suggest that these devices increase pregnancy rates for any women. We also found decreased accuracy when these devices are used by laypersons. There is limited useful evidence for the use of nonurine ovulation tests, and none of these devices are recommended. Despite their common use within hospitals, we found limited evidence to support the use of pH/nitrazine or fern testing to predict or detect PROM. Finally, studies indicate that rapid fFN testing does appear to have a high NPV, but no studies have been done to compare outcomes using the rapid vs ELISA formats. In conclusion, many outcomes-based studies are still needed on POC reproductive-related testing devices to support their use.

REFERENCES

1. Sullivan TF, Barg WF, Stiles GE. Evaluation of a new rapid slide test for pregnancy. Am J Obstet Gynecol 1979;133:411–14.
2. Naryshkin S, Aw TC, Filstein M, Strauss JF, Kiechle FL, Jacobson S. Comparison of the performance of serum and urine hCG immunoassays in the evaluation of gynecologic patients. Ann Emerg Med 1985;14:1074–6.
3. Gelletlie R, Nielsen JB. Evaluation and comparison of commercially available pregnancy tests based on monoclonal antibodies to human choriogonadotropin. Clin Chem 1986;32:2166–70.
4. Christensen H, Thyssen HH, Schebye O, Berget A. Three highly sensitive "bedside" serum and urine tests for pregnancy compared. Clin Chem 1990;36:1686–8.
5. Wong E, Suat SOB. Ectopic pregnancy: a diagnostic challenge in the emergency department. Eur J Emerg Med 2000;7:189–94.
6. Hofmeyr GJ, Rodrigues FA, Koll PC. A sensitive bedside urine test for human chorionic gonadotropin in suspected ectopic pregnancy. S Afr Med J 1989;75:49–50.
7. Buck RH, Pather N, Moodley J, Joubert SM, Norman RJ. Bedside application of an ultrasensitive urine test for hCG in patients with suspected ectopic pregnancy. Ann Clin Biochem 1987;24:268–72.
8. Buck RH, Gihwala N, Rom L, Joubert SM, Norman RJ. Detection of urinary human chorionic gonadotropin by rapid immunoconcentration method is the first-line test for suspected ectopic pregnancy. Fertil Steril 1987;48:761–5.
9. Buck RH, Norman RJ, Reddi K, Moodley J, Joubert SM. Various methods for determining urinary choriogonadotropin evaluated for the early diagnosis of ectopic pregnancy. Clin Chem 1986;32:879–82.
10. Cartwight PS, Victory DF, Moore RA, Anderson JR, Brown DH. Performance of a new enzyme-linked immunoassay urine pregnancy test for the detection of ectopic gestation. Ann Emerg Med 1986;15:1198–9.
11. Latman NS, Bruot BC. Evaluation of home pregnancy test kits. Biomed Instrum Technol 1989;23:144–149.
12. Cole LA, Khanlian SA, Sutton JM, Davies S, Rayburn WF. Accuracy of home pregnancy tests at the time of missed menses. Am J Obstet Gynecol 2004;190:100–5.
13. Anonymous. When the test really counts. Consumer Rep 2003; 2:45–50.
14. Asch RH, Asch B, Asch G, Asch M, Bray R, Rojas FJ. Performance and sensitivity of modern home pregnancy tests. Int J Fertil 1988;33:154–61.
15. Daviaud J, Fournet D, Ballongue C, Guillem GP, Leblanc A, Casellas C, et al. Reliability and feasibility of pregnancy home-use tests: laboratory validation and diagnostic evaluation by 638 volunteers. Clin Chem 1993;39:53–9.
16. Doshi ML. Accuracy of consumer performed in-home tests for early pregnancy detection. Am J Public Health 1986;76:512–4.
17. Arends J, Uldall A. The reliability of pregnancy tests performed by trained and untrained persons. Dan Med Bull 1977;24:115–6.
18. Corsan GH, Ghazi D, Kemmann E. Home urinary luteinizing hormone immunoassays: clinical applications. Fertil Steril 1990;53: 591–601.
19. Rodriquez MH, Mishell DR Jr, Grozinger C, Cao JN, Lacarra M. Comparison of TestPack and Ovustick for predicting ovulation. J Reprod Med 1990;35:133–5.
20. Martinez AR, Bernardus RE, Kucharska D, Schoemaker J. Urinary luteinizing hormone testing and prediction of ovulation in spontaneous, clomiphene citrate and human menopausal gonadotropin-stimulated cycles: a clinical evaluation. Acta Endocrinol (Copenh) 1991;124:357–63.
21. Guermandi E, Vegetti W, Bianchi MM, Uglietti A, Ragni G, Crosignani P. Reliability of ovulation tests in infertile women. Obstet Gynecol 2001;97:92–6.
22. Elkind-Hirsch K, Goldzieher JW, Gibbons WE, Besch PK. Evaluation of the OvuSTICK urinary luteinizing hormone kit in normal and stimulated menstrual cycles. Obstet Gynecol 1986;67: 450–3.
23. Ghazeeri GS, Vongprachanh P, Kutteh WH. The predictive value of five different urinary LH kits in detecting the LH surge in regularly menstruating women. Int J Fertil Womens Med 2000;45:321–6.
24. Luciano AA, Peluso J, Koch EI, Maier D, Kuslis S, Davison E. Temporal relationship and reliability of the clinical, hormonal, and ultrasonographic indices of ovulation in infertile women. Obstet Gynecol 1990;75:412–6.

25. Fedele L, Brioschi D, Dorta M, Marchini M, Parazzini F. Prediction and self-prediction of ovulation in clomiphene citrate-treated patients. Eur J Obstet Gynecol Reprod Biol 1988;28: 297–303.
26. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation: effects on the probability of conception, survival of the pregnancy, and sex of the baby. N Engl J Med 1995;333:1517–21.
27. Horne G, Jamaludin A, Critchlow JD, Falconer DA, Newman MC, Oghoetuoma J, et al. A 3 year retrospective review of intrauterine insemination, using cryopreserved donor spermatozoa and cycle monitoring by urinary or serum luteinizing hormone measurements. Hum Reprod 1998;13:3045–8.
28. Anderson RA, Eccles SM, Irvine DS. Home ovulation testing in a donor insemination service. Hum Reprod 1996;11:1674–7.
29. Kossoy LR, Hill GA, Parker RA, Rogers BJ, Dalglish CS, Herbert GM 3rd, et al. Luteinizing hormone and ovulation timing in a therapeutic donor insemination program using frozen semen. Am J Obstet Gynecol 1989;160:1169–72.
30. Leader LR, Russell T, Stenning B. The use of Clearplan home ovulation detection kits in unexplained and male factor infertility. Aust N Z J Obstet Gynaecol 1992;32:158–60.
31. Robinson JN, Lockwood GM, Dalton JD, Franklin PA, Farr MM, Barlow DH. A randomized prospective study to assess the effect of the use of home urinary luteinizing hormone detection on the efficiency of donor insemination. Hum Reprod 1992;7:63–5.
32. Kossoy LR, Hill GA, Herbert CM, Brodie BL, Dalglish CS, Dupont WD, et al. Therapeutic donor insemination: the impact of insemination timing with the aid of a urinary luteinizing hormone immunoassay. Fertil Steril 1988;49:1026–9.
33. Brook PF, Barratt CL, Cooke ID. The more accurate timing of insemination with regard to ovulation does not create a significant improvement in pregnancy rates in a donor insemination program. Fertil Steril 1994;61:308–13.
34. Irons DW, Singh M. Evaluation of transvaginal sonography combined with a urinary luteinizing hormone monitor in timing donor insemination. Hum Reprod 1994;9:1859–62.
35. Fehring RJ. A comparison of the ovulation method with the CUE ovulation predictor in determining the fertile period. J Am Acad Nurse Pract 1996;8:461–6.
36. Fernando RS, Regas J, Betz G. Ovulation prediction and detection with the CUE Ovulation Predictor. Hum Reprod 1988;3:419–24.
37. Fehring RJ, Schlaff WD. Accuracy of the Ovulon fertility monitor to predict and detect ovulation. J Nurse Midwifery 1998;43: 117–20.
38. Moreno JE, Weitzman GA, Doody MC, Gibbons WE, Besch P, Goldzieher JW. Temporal relation of ovulation to salivary and vaginal electrical resistance patterns: implications for natural family planning. Contraception 1988;38:407–18.
39. Guida M, Tommaselli GA, Palomba S, Pellicano M, Moccia G, Di Carlo C, et al. Efficacy of methods for determining ovulation in a natural family planning program. Fertil Steril 1999;72:900–4.
40. Fehring RJ, Gaska N. Evaluation of the Lady Free Biotester in determining the fertile period. Contraception 1998;57:325–8.
41. Miller PB, Soules MR. The usefulness of a urinary LH kit for ovulation prediction during menstrual cycles of normal women. Obstet Gynecol 1996;87:13–7.
42. Pearlstone AC, Surrey ES. The temporal relation between the urine LH surge and sonographic evidence of ovulation: determinants and clinical significance. Obstet Gynecol 1994;83:184–8.
43. Lloyd R, Coulam CB. The accuracy of urinary luteinizing hormone testing in predicting ovulation. Am J Obstet Gynecol 1989; 160:1370–2.
44. Vermesh M, Kletzky OA, Davajan V, Israel R. Monitoring techniques to predict and detect ovulation. Fertil Steril 1987;47: 259–64.
45. Gregoriou O, Kassanos D, Vitoratos N, Papadias C, Zourlas PA. Clinical efficacy of LH-color: a new home ovulation test. Int J Gynaecol Obstet 1990;32:141–3.
46. Yong EL, Wong PC, Kumar A, Wong YC, Goh HH, Hagglund L, et al. Simple office methods to predict ovulation: the clinical usefulness of a new urine luteinizing hormone kit compared to basal body temperature, cervical mucus and ultrasound. Aust N Z J Obstet Gynaecol 1989;29:155–60.
47. Seeds AE, Hellegers AE. Acid-base determinations in human amniotic fluid throughout pregnancy. Am J Obstet Gynecol 1968; 101:257–60.
48. Ernest JM, Meis PJ, Moore ML, Swain M. Vaginal pH: a marker of preterm premature rupture of the membranes. Obstet Gynecol 1989;74:734–8.
49. Gaucherand P, Salle B, Sergeant P, Guibaud S, Brun J, Bizollon CA, et al. Comparative study of three vaginal markers of the premature rupture of membranes: insulin like growth factor binding protein 1 diamine-oxidase pH. Acta Obstet Gynecol Scand 1997;76:536–40.
50. Gorodeski IG, Haimovitz L, Bahari CM. Reevaluation of the pH, ferning and Nile blue sulphate staining methods in pregnant women with premature rupture of the fetal membranes. J Perinat Med 1982;10:286–92.
51. Hjertberg R, Belfrage P, Eneroth P. Latex agglutination test for α-fetoprotein in the diagnosis of premature rupture of the amniotic membranes (PROM). Acta Obstet Gynecol Scand 1987;66:437–9.
52. Riedewald S, Kreutzmann IM, Heinze T, Saling E. Vaginal and cervical pH in normal pregnancy and pregnancy complicated by preterm labor. J Perinat Med 1990;18:181–6.
53. Watanabe T, Minakami H, Itoi H, Sato I, Sakata Y, Tamada T. Evaluation of latex agglutination test for α-fetoprotein in diagnosing rupture of fetal membranes. Gynecol Obstet Invest 1995;39:15–8.
54. Garite TJ, Gocke SE. Diagnosis of preterm rupture of membranes: is testing for α-fetoprotein better than ferning or nitrazine? Am J Perinatol 1990;7:276–8.
55. Kishida T, Hirao A, Matsuura T, Katamine T, Yamada H, Sagawa T, et al. Diagnosis of premature rupture of membranes with an improved α-fetoprotein monoclonal antibody kit. Clin Chem 1995;41:1500–3.
56. Kishida T, Yamada H, Negishi H, Sagawa T, Makinoda S, Fujimoto S. Diagnosis of preterm premature rupture of the membranes using a newly developed AFP monoclonal antibody test kit. Eur J Obstet Gynecol Reprod Biol 1995;58:67–72.
57. Kishida T, Yamada H, Negishi H, Sagawa T, Makinoda S, Fujimoto S. Diagnosis of premature rupture of the membranes in preterm patients, using an improved AFP kit: comparison with ROM-check and/or nitrazine test. Eur J Obstet Gynecol Reprod Biol 1996; 69:77–82.
58. Mills AM, Garrioch DB. Use of the nitrazine yellow swab test in the diagnosis of ruptured membranes. Br J Obstet Gynaecol 1977;84:138–40.
59. Rochelson BL, Rodke G, White R, Bracero L, Baker DA. A rapid colorimetric AFP monoclonal antibody test for the diagnosis of preterm rupture of the membranes. Obstet Gynecol 1987; 69:163–6.
60. Yamada H, Fujimoto S. Rapid diagnosis of premature rupture of membranes using a new kit employing anti-AFP monoclonal antibody. Arch Gynecol Obstet 1995;256:57–61.
61. de Haan HH, Offermans PM, Smits F, Schouten HJ, Peeters LL. Value of the fern test to confirm or reject the diagnosis of ruptured

membranes is modest in nonlaboring women presenting with nonspecific vaginal fluid loss. Am J Perinatol 1994;11:46–50.
62. Plaut MM, Smith W, Kennedy K, Fetal fibronectin: the impact of a rapid test on the treatment of women with preterm labor symptoms. Am J Obstet Gynecol 2003;188:1588–93; discussion 1593–5.
63. Giles W, Bisits A, Knox M, Madsen G, Smith R. The effect of fetal fibronectin testing on admissions to a tertiary maternal-fetal medicine unit and cost savings. Am J Obstet Gynecol 2000; 182:439–42.
64. Watson D, Kim SJ, Humphrey MD. Study of cervicovaginal fetal fibronectin status to guide treatment of threatened preterm labour. Aust N Z J Obstet Gynaecol 1998;38:185–7.
65. Chuileannain FN, Bell R, Brennecke S. Cervicovaginal fetal fibronectin testing in threatened preterm labour: translating research findings into clinical practice. Aust N Z J Obstet Gynaecol 1998;38:399–402.
66. Lopez RL, Francis JA, Garite TJ, Dubyak JM. Fetal fibronectin detection as a predictor of preterm birth in actual clinical practice. Am J Obstet Gynecol 2000;182:1103–6.
67. Bartnicki J, Casal D, Kreaden US, Saling E, Vetter K. Fetal fibronectin in vaginal specimens predicts preterm delivery and very-low-birth-weight infants. Am J Obstet Gynecol 1996;174:971–4.
68. Iams JD, Casal D, McGregor JA, Goodwin TM, Kreaden US, Lowensohn R, et al. Fetal fibronectin improves the accuracy of diagnosis of preterm labor. Am J Obstet Gynecol 1995;173:141–5.
69. Peaceman AM, Andrews WW, Thorp JM, Cliver SP, Lukes A, Iams JD, et al. Fetal fibronectin as a predictor of preterm birth in patients with symptoms: a multicenter trial. Am J Obstet Gynecol 1997;177:13–8.
70. Burrus DR, Ernest JM, Veille JC. Fetal fibronectin, interleukin-6, and C-reactive protein are useful in establishing prognostic subcategories of idiopathic preterm labor. Am J Obstet Gynecol 1995;173:1258–62.
71. Lockwood CJ, Senyei AE, Dische MR, Casal D, Shah KD, Thung SN, et al. Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. N Engl J Med 1991;325:669–74.
72. Morrison JC, Allbert JR, McLaughlin BN, Whitworth NS, Roberts WE, Martin RW. Oncofetal fibronectin in patients with false labor as a predictor of preterm delivery. Am J Obstet Gynecol 1993;168:538–42.
73. Luzzi V, Hankins K, Gronowski AM. Accuracy of the rapid fetal fibronectin TLi system in predicting preterm delivery. Clin Chem 2003;49:501–2.

PUBLIC COMMENTS

No public comments were received on the guidelines.

Form 1

NACB LMPG Data Abstraction Form
Reference List

Clinical Question:

Databases Searched:

Search Terms/Hits:

Group abbreviation—Use first letter of each word (ID = Infectious Disease) or first two letters of single-word groups (i.e., Cardiac = CA), followed by the chronological number of citation search hits.

Citation format—Use standard citation format [Authors Last name First initial. Title. Journal Year;Volume:Page range.].

		Abstract Review				Full Text Review				
		Include?				Include?				
Group/No.	Citation	1	2	3	Reviewers	1	2	3	Reviewers	Comments
CA 5	*Smith JA, Miller K. Outcomes of X. Clin Chem 1999;45:2005–2010.*	*Y*	*N*	*Y*	*JN, CR, MD*	*Y*	*Y*		*FM, KL*	*CR felt outcomes not quantitative*

Form 2

NACB LMPG Data Abstraction Form
Systematic Review

Clinical Question:

Citation	Design	Application	Outcome	Outcome Measure	Weight of Individual Study			Reviewers	Comments
					Research Grade	Internal Validity	External Validity		
CA 5 Smith JA et al	*RCT*	*Screening pts (ambulant) in ED*	*Length of Stay*	*Time from admit to discharge*	*I*	*Fair*	*Poor*	*RB*	
	RCT	*Screening pts (ambulant) in ED*	*Length of Stay*	*Time from admit to discharge*	*I*	*Poor*	*Poor*	*JN*	
	RCT	*Screening pts (ambulant) in ED*	*Length of Stay*	*Time from admit to discharge*	*I*	*Fair*	*Poor*	*FM*	

Clinical Question:

Citation	Design	Application	Outcome	Outcome Measure	Weight of Individual Study			Reviewers	Comments
					Research Grade	Internal Validity	External Validity		

RCT, randomized controlled trial.

Form 3

NACB LMPG Data Abstraction Form
Systematic Review (Data Abstraction Form 1)

Clinical Question: *(e.g., Is Test X useful in screening for Y disorder?)*

Citation	Design	Application/Population	N Study/Control	N Evaluated Study/Control	Outcome	Outcome Measurement	P value
CA 5 Smith JA et al	*RCT*	*Screening pts (ambulant) in ED*	*N = 23 walk-in ED Control = 25 outpatient clinic pts*	N = 20 ED pts Control N = 25	*Length of Stay*	*Time from admit to discharge*	P = 0.03

Form 4

NACB LMPG Data Abstraction Form
Systematic Review (Data Abstraction Form 2)

Clinical Question: *(e.g., Is Test X useful in screening for Y disorder?)*

Citation	Design	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance Test on Subjects vs Controls?	Comparable Measurement of Outcomes?	Appropriate Analysis?	Comments
CA 5 Smith JA et al	*RCT*	*Both outpts, but ED may be more acute*	*Same groups maintained*	*RN and LPN tested in both groups*	*Time from admit to discharge measured both*	*Different N in study vs control*	*Use of control pts outside ED not comparable*

Form 5

NACB LMPG Data Abstraction Form
Systematic Review Summary

Clinical Question:

Volume of Literature			Overall Link POCT to Outcome	Net Patient Benefit?	FINAL Recommendation	Reviewers	Comments
Aggregate Internal Validity	Aggregate External Validity	Coherence Consistency					
Fair	*Poor*	*Good*	*Fair*	*Small*	*B*	*JN, RB, FM*	

Clinical Question:

Volume of Literature			Overall Link POCT to Outcome	Net Patient Benefit?	FINAL Recommendation	Reviewers	Comments
Aggregate Internal Validity	Aggregate External Validity	Coherence Consistency					

Clinical Question:

Volume of Literature			Overall Link POCT to Outcome	Net Patient Benefit?	FINAL Recommendation	Reviewers	Comments
Aggregate Internal Validity	Aggregate External Validity	Coherence Consistency					

Appendix **B**

Literature Searches

Literature Search 1

Guideline 1. QA for POCT and Medical Errors Literature Search	
Databases Searched:	
Medline OVID (1966–October Week 5, 2003)	
Search Criteria:	
1 point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized	= 2524
2 regulations OR standards OR quality assurance OR quality assessment OR EQA OR accreditation	= 74824
3 error OR errors OR mistakes	= 80109
4 1 AND 2 AND 3	= 7
Abstracts = 4 papers	
Systematic Review = 1 paper	
1 citation in final recommendations	

Literature Search 2

Guidelines 2–5. POCT Management and Quality Literature Search	
Databases Searched:	
Pubmed	
Search Criteria:	
Point of Care Testing AND (management OR organization)	= 92
Abstracts = 52 papers	
Systematic Review = 10 papers	
7 citations in final recommendations	

Literature Search 3

Guideline 6. Transcutaneous Bilirubin Literature Search	
Databases Searched:	
Medline OVID (1966–January 2004)	
Search Criteria:	
1 bilirubin AND transcutaneous	= 163
2 bilirubin AND non-invasive	= 102
3 bilirubin AND point of care	= 15
4 bilirubin AND length of stay	= 129
5 bilirubin AND clinical outcome	= 61
Abstracts = 407	
Systematic Review = 24	
3 citations in final recommendation	

Literature Search 4

Guideline 7. Transcutaneous Bilirubin Frequency Literature Search

Databases Searched:
Medline OVID (1966–January 2004)
Search Criteria:
1 bilirubin AND transcutaneous = 163
2 bilirubin AND non-invasive = 102
3 bilirubin AND point of care = 15
4 bilirubin AND dermal = 15
Abstracts = 244
Systematic Review = 55
29 citations in final recommendation

Literature Search 5

Guideline 8. Transcutaneous Bilirubin Limitations Literature Search

Databases Searched:
Medline OVID (1966–January 2004)
Search Criteria:
1 bilirubin AND transcutaneous AND phototherapy = 59
2 bilirubin AND non-invasive AND phototherapy = 9
3 bilirubin AND transcutaneous AND ill = 1
4 bilirubin AND transcutaneous AND gestational age = 26
5 bilirubin AND non-invasive AND gestational age = 5
6 bilirubin AND transcutaneous AND premature = 15
7 bilirubin AND non-invasive AND premature = 6
Abstracts = 74
Systematic Review = 43
18 citations in final recommendation

Literature Search 6

Guideline 9. Transcutaneous Bilirubin and Blood Sampling Literature Search

Databases Searched:
Medline OVID (1966–January 2004)
Search Criteria:
1 bilirubin and transcutaneous AND infection = 2
2 bilirubin AND non-invasive AND infection = 7
3 bilirubin AND transcutaneous AND osteomyelitis = 0
4 bilirubin and transcutaneous AND bleeding = 1
Abstracts = 8
Systematic Review = 8
8 citations in final recommendation

Literature Search 7

Guideline 10. Transcutaneous Bilirubin Accuracy Literature Search

Databases Searched:
Medline OVID (1966–January 2004)
Search Criteria:
(bilirubin AND transcutaneous AND serum) 163 results; OR
(bilirubin AND transcutaneous AND method) 33 results; OR
(bilirubin AND non-invasive AND method) 27 results
Abstracts = 181
Systematic Review = 77
36 citations in final recommendation

Literature Search 8

Guideline 11. Transcutaneous Bilirubin Cost Effectiveness Literature Search

Databases Searched:
Medline OVID (1966–January 2004)
Search Criteria:
1 bilirubin AND transcutaneous AND cost = 9
2 bilirubin AND non-invasive AND cost = 4
Abstracts = 10
Systematic Review = 7
4 citations in final recommendation

Literature Search 9

Guideline 12–22. Cardiac Marker Literature Search

Databases Searched:
Medline (1966–August 27, 2005)
CINHL (1982–August Week 3, 2005); no additional relevant literature
EMBASE (1988–Week 35, 2005); no additional relevant literature
Search Criteria:

1	Explode Point-of-Care Systems	=	2277
2	Explode Biological Markers	=	314530
3	Explode Troponin	=	5842
4	2 OR 3	=	318789
5	1 AND 4	=	96
6	Review Articles (not examined)	=	19
7	Case Reports (not examined)	=	3
8	Comments and Letters (not examined)	=	9
9	Language other than English (not examined)	=	6
10	Biomarkers other than Cardiac Injury (not examined)	=	26
11	Metaanalysis (not examined)	=	0

Abstracts = 33
Systematic Review = 33
18 citations in final recommendation

Literature Search 10

Guidelines 23–24. aPTT Literature Search

Abstract = 114
Systematic Review = 35
16 citations in final recommendation

Literature Search 11

Guidelines 25–28. PT Literature Search

Abstract = 132
Systematic Review = 40
19 citations in final recommendation

Literature Search 12

Guidelines 29–36. ACT Literature Search

Abstract = 370
Systematic Review = 57
46 citations in final recommendation

Literature Search 13

Guideline 37. ABG TTAT Literature Search

Search Criteria:

1	rapid laboratory results OR rapid test OR turnaround time	= 29953
2	intensive care OR critical care	= 73293
3	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
4	blood gases OR arterial gas OR ABG	= 45575
5	1 AND 2 AND 3 AND 4	

7 citations in final recommendation

Literature Search 14

Guideline 38. ABG in ICU Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	= 6135
2	rapid laboratory results OR rapid test OR turnaround time	= 29953
3	intensive care OR critical care	= 73293
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
5	blood gases OR arterial gas OR ABG	= 45575
6	1 AND 2 AND 3 AND 4 AND 5	

9 citations in final recommendation

Literature Search 15

Guideline 39. ABG in ICU and Cost Effectiveness Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	= 6135
2	rapid laboratory results OR rapid test OR turnaround time	= 29953
3	intensive care OR critical care	= 73293
4	(blood gases OR arterial gas OR ABG) AND (expense OR cost)	= 311310
5	1 AND 2 AND 3 AND 4	

2 citations in final recommendation

Literature Search 16

Guideline 40. ABG and ED TTAT Literature Search

Search Criteria:

1	rapid laboratory results OR rapid test OR turnaround time	= 29953
2	emergency department OR ED	= 211997
3	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
4	blood gases OR arterial gas OR ABG	= 45575
5	1 AND 2 AND 3 AND 4	

1 citation in final recommendation

Literature Search 17

Guideline 41. ABG ED Outcomes Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	= 6135
2	rapid laboratory results OR rapid test OR turnaround time	= 29953
3	emergency department OR ED	= 211997
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
5	blood gases OR arterial gas OR ABG	= 45575
6	1 AND 2 AND 3 AND 4 AND 5	

5 citations in final recommendation

Literature Search 18

Guideline 42. ABG TTAT Cardiac Surgery Literature Search

Search Criteria:

1	rapid laboratory results OR rapid test OR turnaround time	= 29953
2	cardiac surgery OR congenital heart surgery	= 23242
3	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
4	blood gases OR arterial gas OR ABG	= 45575
5	1 AND 2 AND 3 AND 4	

5 citations in final recommendation

Literature Search 19

Guideline 43. ABG Cardiac Surgery Outcomes Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	= 6135
2	rapid laboratory results OR rapid test OR turnaround time	= 29953
3	cardiac surgery OR congenital heart surgery	= 23242
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
5	blood gases OR arterial gas OR ABG	= 45575
6	1 AND 2 AND 3 AND 4 AND 5	

2 citations in final recommendation

Literature Search 20

Guideline 44. Glucose TTAT Literature Search

Search Criteria:

1	rapid laboratory results OR rapid test OR turnaround time	= 29953
2	intensive care OR critical care	= 73293
3	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
4	glucose	= 274635
5	1 AND 2 AND 3 AND 4	

31 citations in final recommendation

Literature Search 21

Guideline 45. Glucose Outcomes Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	= 6135
2	rapid laboratory results OR rapid test OR turnaround time	= 29953
3	intensive care OR critical care	= 73293
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
5	glucose	= 274635
6	1 AND 2 AND 3 AND 4 AND 5	

1 citation in final recommendation

Literature Search 22

Guideline 46. Lactate TTAT Literature Search

Search Criteria:

1	rapid laboratory results OR rapid test OR turnaround time	= 29953
2	intensive care OR critical care	= 73293
3	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
4	lactate	= 91783
5	1 AND 2 AND 3 AND 4	

34 citations in final recommendation

Literature Search 23

Guideline 47. Lactate Outcomes Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	= 6135
2	rapid laboratory results OR rapid test OR turnaround time	= 29953
3	intensive care OR critical care	= 73293
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
5	lactate	= 91783
6	1 AND 2 AND 3 AND 4 AND 5	

1 citation in final recommendation

Literature Search 24

Guideline 48. Mg TTAT Literature Search

Search Criteria:

1	rapid laboratory results OR rapid test OR turnaround time	= 29953
2	intensive care OR critical care	= 73293
3	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
4	magnesium	= 71753
5	1 AND 2 AND 3 AND 4	

60 citations in final recommendation

Literature Search 25

Guideline 49. Mg Outcomes Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	=	6135
2	rapid laboratory results OR rapid test OR turnaround time	=	29953
3	intensive care OR critical care	=	73293
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	=	2495257
5	magnesium	=	71753
6	1 AND 2 AND 3 AND 4 AND 5		

0 citations in final recommendation

Literature Search 26

Guideline 50. Oxygen Saturation TTAT Literature Search

Search Criteria:

1	rapid laboratory results OR rapid test OR turnaround time	= 29953
2	intensive care OR critical care	= 73293
3	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	= 2495257
4	oxygen saturation	= 15461
5	1 AND 2 AND 3 AND 4	

4 citations in final recommendation

Literature Search 27

Guideline 51. Oxygen Saturation Outcomes Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	=	6135
2	rapid laboratory results OR rapid test OR turnaround time	=	29953
3	intensive care OR critical care	=	73293
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	=	2495257
5	oxygen saturation	=	15461
6	1 AND 2 AND 3 AND 4 AND 5		

0 citations in final recommendation

Literature Search 28

Guideline 52. Carboxyhemoglobin Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	=	6135
2	rapid laboratory results OR rapid test OR turnaround time	=	29953
3	intensive care OR critical care	=	73293
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	=	2495257
5	carboxyhemoglobin	=	2991
6	1 AND 2 AND 3 AND 4 AND 5		

3 citations in final recommendation

Literature Search 29

Guideline 53. Methemoglobin Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	=	6135
2	rapid laboratory results OR rapid test OR turnaround time	=	29953
3	intensive care OR critical care	=	73293
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	=	2495257
5	methemoglobin	=	4750
6	1 AND 2 AND 3 AND 4 AND 5		

3 citations in final recommendation

Literature Search 30

Guideline 54. Electrolyte ED Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	=	6135
2	rapid laboratory results OR rapid test OR turnaround time	=	29953
3	emergency department OR ED	=	211997
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	=	2495257
5	electrolytes	=	306136
6	1 AND 2 AND 3 AND 4 AND 5		

8 citations in final recommendation

Literature Search 31

Guideline 55. Electrolyte ICU Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	=	6135
2	rapid laboratory results OR rapid test OR turnaround time	=	29953
3	intensive care OR critical care	=	73293
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	=	2495257
5	electrolytes	=	306136
6	1 AND 2 AND 3 AND 4 AND 5		

2 citations in final recommendation

Literature Search 32

Guideline 56. iCA ED Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	=	6135
2	rapid laboratory results OR rapid test OR turnaround time	=	29953
3	emergency department OR ED	=	211997
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	=	2495257
5	ionized calcium	=	3928
6	1 AND 2 AND 3 AND 4 AND 5		

2 citations in final recommendation

Literature Search 33

Guideline 57. iCa OR Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	=	6135
2	rapid laboratory results OR rapid test OR turnaround time	=	29953
3	surgery OR operating room	=	475135
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	=	2495257
5	ionized calcium	=	3928
6	1 AND 2 AND 3 AND 4 AND 5		

1 citation in final recommendation

Literature Search 34

Guideline 58. iCa ICU Literature Search

Search Criteria:

1	rapid laboratory results OR rapid test OR turnaround time	=	29953
2	intensive care OR critical care	=	73293
3	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	=	2495257
4	ionized calcium	=	3928
5	1 AND 2 AND 3 AND 4		

3 citations in final recommendation

Literature Search 35

Guideline 59. iCa ICU Outcomes Literature Search

Search Criteria:

1	point of care testing OR bedside testing OR ancillary testing OR near patient testing OR NPT OR POCT OR decentralized testing OR STAT laboratory OR satellite laboratory	=	6135
2	rapid laboratory results OR rapid test OR turnaround time	=	29953
3	intensive care OR critical care	=	73293
4	improvement OR reduction OR benefit OR morbidity OR mortality OR adverse	=	2495257
5	ionized calcium	=	3928

5 citations in final recommendation

Literature Search 36

Guideline 60–63. Glucose Self-Testing Outcomes Literature Search

Databases Searched:

PubMed (1966–December 2003)

Search Criteria:

1	primary NEXT health NEXT care	=	646
2	general NEXT practice	=	473
3	family NEXTpractice	=	579
4	health NEXT centre	=	303
5	health NEXT center	=	896
6	community NEXT care	=	780
7	primary health care	=	40852
8	primary health care[mh]	=	35717
9	primary health care[tiab]	=	7841
10	1 OR 2 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	=	43333
11	diabetes NEXT mellitus	=	639
12	diabetes mellitus[mh]	=	164269
13	diabetes mellitus	=	188463
14	11 OR 12 OR 13	=	188463
15	((blood NEXT glucose) AND self-monitoring)	=	17
16	((blood glucose) AND self-monitoring)	=	1958
17	15 OR 16	=	1958
18	10 AND 17	=	33
19	10 AND 14 AND 17	=	33

Literature Search 37

Guidelines 60–63. Glucose Self-Testing Outcomes Literature Search

Databases Searched:
The Cochrane Library (December 2003)
Search Criteria:

1	(primary NEXT health NEXT care)	= 1459
2	(general NEXT practice)	= 2661
3	(family NEXT practice)	= 2194
4	(health NEXT centre)	= 465
5	(health NEXT center)	= 474
6	(community NEXT care)	= 308
7	(1 OR 2 OR 3 OR 4 OR 5 OR 6)	= 6075
8	(diabetes NEXT mellitus)	= 7259
9	((blood NEXT glucose) AND self-monitoring)	= 196
10	(7 AND 8 AND 9)	= 10
11	(7 AND 9)	= 12

Literature Search 38

Guideline 64–65. Glucose Testing Hospital Outcomes Literature Search

Databases Searched:
PubMed (1966–December 2003)
Search Criteria:

1	point-of-care	= 2344
2	point-of-care NEXT testing	= 13
3	point NEXT care NEXT testing	= 26
4	point NEXT care	= 225
5	near-patient AND testing	= 148
6	near-patient NEXT testing	= 3
7	blood NEXT glucose	= 654
8	blood glucose	= 85581
9	7 OR 8	= 85770
10	1 OR 2 OR 3 OR 4 OR 5 OR 6	= 2618
11	9 AND 10	= 118

Literature Search 39

Guideline 64–65. Glucose Testing Hospital Outcomes Literature Search

Databases Searched:
The Cochrane Library (December 2003)
Search Criteria:

1	point-of-care	= 106
2	(point-of-care NEXT testing)	= 9
3	(point NEXT care NEXT testing)	= 18
4	(point NEXT care)	= 116
5	(near-patient AND testing)	= 11
6	(near-patient NEXT testing)	= 8
7	(blood NEXT glucose)	= 6646
8	(1 OR 2 OR 3 OR 4 OR 5 OR 6)	= 126
9	(7 AND 8)	= 8

Literature Search 40

Guideline 66–67. Gestational Glucose Testing Outcomes Literature Search

Databases Searched:

PubMed (1966–December 2003)

Search Criteria:

1	primary NEXT health NEXT care	=	646
2	general NEXT practice	=	473
3	general NEXT practicefamily NEXT practice	=	473
4	family NEXT practice	=	579
5	health NEXT centre	=	303
6	health NEXT center	=	896
7	community NEXT care	=	780
8	primary health care	=	40852
9	primary health care[mh]	=	35717
10	primary health care[tiab]	=	7841
11	primary health care[tiab]	=	7841
12	1 OR 2 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10	=	43333
13	diabetes NEXT mellitus	=	639
15	diabetes mellitus[mh]	=	164269
16	diabetes mellitus	=	188463
18	13 OR 15 OR 16	=	188463
19	((blood NEXT glucose) AND self-monitoring)	=	17
20	((blood glucose) AND self-monitoring)	=	1958
21	19 OR 20	=	1958
22	12 OR 21	=	45258
23	12 AND 21	=	33
24	point-of-care	=	2344
25	point-of-care NEXT testing	=	13
26	point NEXT care NEXT testing	=	26
27	point NEXT care	=	225
28	near-patient AND testing	=	148
29	near-patient NEXT testing	=	3
30	blood NEXT glucose	=	654
31	blood glucose	=	85581
32	30 OR 31	=	85770
33	24 OR 25 OR 26 OR 27 OR 28 OR 29	=	2618
34	32 AND 33	=	118
35	pregnan*	=	545714
36	pregnancy	=	529786
37	35 OR 36	=	547242
41	gestational diabetes	=	3606
42	gestational NEXT diabetes	=	29
43	41 OR 42	=	3614
45	43 AND 37	=	3404
48	34 AND 37 AND 43	=	1

Literature Search 41

Guideline 66–67. Gestational Glucose Testing Outcomes Literature Search

Databases Searched:
The Cochrane Library (December 2003)
Search Criteria:

1	point-of-care	=	106
2	(point-of-care NEXT testing)	=	9
3	(point NEXT care NEXT testing)	=	18
4	(point NEXT care)	=	116
5	(near-patient AND testing)	=	11
6	(near-patient NEXT testing)	=	8
7	(blood NEXT glucose)	=	6646
8	(1 OR 2 OR 3 OR 4 OR 5 OR 6)	=	126
9	(7 AND 8)	=	8
10	pregnan*	=	13866
11	(gestational NEXT diabetes)	=	153
12	(9 AND 11)	=	1
13	(9 AND 10)	=	2
14	(12 OR 13)	=	2

Literature Search 42

Guideline 68–71. HgbA1c Outcomes Literature Search

Databases Searched:
Medline (1990–May 2004)
Search Criteria:

1	Blood Chemical Analysis/ or Clinical Laboratory Information Systems/ OR Laboratories, Hospital/ OR Patients' Rooms/ OR Point-of-Care Systems/ OR point-of-care testing.mp. OR "Laboratory Techniques and Procedures"/	=	25100
2	point of care testing.mp.	=	324
3	MONITORING, PHYSIOLOGIC/	=	32365
4	(point adj3 care).mp. [mp = title, original title, abstract, name of substance, mesh subject heading]	=	1668
5	test$.mp. [mp = title, original title, abstract, name of substance, mesh subject heading]	=	1086908
6	4 AND 5	=	659
7	1 OR 2 OR 3 OR 6	=	57270
8	((glycated OR glycosylated) adj5 (haemoglobin OR hemoglobin)).mp. [mp = title, original title, abstract, name of substance, mesh subject heading]	=	11378
9	Hemoglobin A, Glycosylated/ OR haemoglobin a.mp.	=	9725
10	(Hb A1c OR Hb A OR A1c).mp. [mp = title, original title, abstract, name of substance, mesh subject heading]	=	2638
11	8 OR 9 OR 10	=	13386
12	7 AND 11	=	250
13	limit 12 to yr = 1990–2004	=	160
14	from 13 keep 1–160	=	160
15	(quality control OR quality assurance).mp. [mp = title, original title, abstract, name of substance, mesh subject heading]	=	38565
16	13 AND 15	=	14
17	(13 AND 15) NOT 14	=	0
18	Pathology, Clinical/ OR Diagnostic Tests, Routine/OR Family Practice/ OR near patient testing.mp.	=	48063
19	(near adj patient).mp. [mp = title, original title, abstract, name of substance, mesh subject heading]	=	251
20	(near adj patient adj5 test$).mp	=	183
21	18 OR 20	=	48117
22	21 AND 11	=	135
23	22 NOT 12	=	131
24	limit 23 to yr = 1990–2004	=	123
25	from 24 keep 1–123	=	123

Literature Search 43

Guideline 72–75. Fructosaming Literature Search

Databases Searched:
Highwire (January 1948–April 2003)
Pubmed (January 1963–April 2003)
Search Criteria:
1 Fructosamine = 1344
2 Home monitoring AND fructosamine = 20
Abstract = 20 papers
Systematic Review = 5 papers
4 citations in final recommendations

Literature Search 44

Guideline 76–78. Blood Ketones Literature Search

Databases Searched:
Pubmed (1966–March 2004)
Search Criteria:
1 Ketones [MESH] OR ketone bodies [MESH] or 3-hydroxybutyric acid [MESH] = 55855
2 Diabetes [FTXT] OR diabetic [FTXT] = 235591
3 1 AND 2 = 2019
4 Ketone [TITIE WORD] AND 2 = 226
5 3 AND 4 = 2057
6 5 AND English language = 1712
7 First review of 1712 citations = 200
8 Relevant citations of 200 citations = 19→18

Literature Search 45

Guideline 79–82. Urine Albumin in Diabetics Literature Search

Databases Searched:
Pubmed (January 1968–January 2004)
Search Criteria:
Terms from set 1 were individually crossed with terms from set 2.
Set 1: microalbumin, microalbuminuria, albumin:creatinine ratio, diabetic nephropathy, and albumin excretion; and
Set 2: poc, poct, point of care, point of care testing, clinic, office, physician office laboratory, and pol.
When more than 40 references were identified in any initial cross of a set 1 and set 2 term, the additional search term 'outcome' was added to the set 1 and set 2 terms to focus the search.
Systematic Review = 141
In addition four recent review articles concerning POCT and microalbuminuria were examined (186–188,197).

Literature Search 46

Guideline 83–108. Drugs of Abuse in Urine Literature Search

Databases Searched:
Medline (1966–November 2003)
EMBASE
Cochrane Database
Search Criteria:
(Point of Care Testing OR Near Patient Testing OR)
AND (Drugs OR Opiate* OR Cocaine OR Cannabis OR Ethanol OR Alcohol OR Benzodiazepine* OR Amphetamine* OR MDA OR MDMA OR Ecstasy OR Drugs of Abuse OR Substance Abuse)
Abstracts = 151 papers
Systematic Review = 100 papers
81 citations in final recommendations

Literature Search 47

Guideline 109. Bioterrorism Agent Literature Search

Databases Searched:
Medline Ovid (1966–June Week 3, 2004)
Search Criteria:

1	Bioterrorism AND testing	= 38
2	Tularemia AND rapid testing	= 0
3	Tularemia (microbiology, classification; pathology diagnosis; epidemiology)	= 257
4	Brucella AND rapid testing	= 0
5	Anthrax AND point of care testing	= 0
6	Point of care AND bioterrorism	= 0
7	Anthrax	= 1118
8	Plague (microbiology, diagnosis, pathology, etiology; transmission)	= 313
9	brucella (classification; isolation AND purification)	= 170
10	Brucellosis (classification; pathology; diagnosis; microbiology)	= 597
11	Smallpox (diagnosis; transmission; microbiology)	= 184
12	Coccidioides AND bioterrorism	= 5

Literature Search 48

Guideline 109. Bioterrorism Agent Literature Search

Databases Searched:
Pub Med (1966–June Week 3, 2004)
Search Criteria:

1	Bioterrorism AND diagnosis	= 449
2	Bioterrorism AND rapid testing	= 10
3	Anthrax AND rapid testing	= 5
4	Plague AND rapid testing	= 8
5	Botulinum toxin AND rapid testing	= 8
6	Tularemia AND rapid testing	= 1
7	Brucella AND rapid testing	= 8

Literature Search 49

Guideline 110. *Clostridium difficile* Literature Search

Databases Searched:
Medline OVID (1996–April Week 3, 2004)
Search Criteria:

1	Clostridium difficile	= 951
2	POCT	= 779472
3	Diagnostic laboratory tests	= 287172
4	1 AND 3	= 119
5	1 AND 2	= 74

Literature Search 50

Guideline 111–112. Infectious Mononucleosis Literature Search

Databases Searched:
Medline OVID (1996–June Week 3, 2004)
Search Criteria:

1	Infectious mononucleosis, EBV	= 3617
2	Rapid tests	= 148433
3	1 AND 2	= 166
4	POCT	= 694621
5	1 AND 2 AND 4 (none of the tests are related to IM POCT)	= 17

Literature Search 51

Guideline 113. *C. trachomatis* and *N. gonorrhoeae* Literature Search

Databases Searched:
Pub Med (1979–2004)
Search Criteria:

1	Chlamydia trachomatis AND medical errors	=	38
2	Chlamydia point of care tests	=	8
3	Chlamydia trachomatis point of care	=	14
4	Chlamydia trachomatis AND office practice	=	16
5	Testpack chlamydia test	=	12
6	Biostar chlamydia test	=	3
7	Clearview chlamydia test	=	23
8	Surecell chlamydia	=	12
9	Leukocyte esterase AND chlamydia trachomatis	=	44
10	Neisseria gonorrhea point of care AND medical errors	=	1
11	Neisseria gonorrhea AND office practice	=	3
12	Neisseria gonorrhea point of care tests	=	3
13	Neisseria gonorrhea diagnostic tests	=	26
14	Gram stain gonorrhea diagnosis	=	82
15	Point of care gonorrhea diagnosis	=	8
16	Physician office gonorrhea diagnosis	=	57
17	Gonorrhea diagnosis	=	4060

Literature Search 52

Guideline 114. Group A Streptococci Literature Search

Databases Searched:
Pub Med (1983–2004)
Search Criteria:

1	Group A Streptococcus	=	1015
2	Streptococcus pyogenes	=	9423
3	point of care	=	2538
4	rapid antigen	=	181
5	1 AND 3	=	1
6	1 AND 4	=	10
7	2 AND 3	=	3
8	2 AND 4	=	62

Abstracts = 62
Systematic Review = 32
31 citations in final recommendations

Literature Search 53

Guideline 115. Group B Streptococci Literature Search

Databases Searched:
PubMed (1986–2004)
Search Criteria:

1	Group B Streptococcus AND Point of Care	=	0
2	Group B Streptococcus AND rapid test	=	22
3	Group B Streptococcus AND neonate sepsis	=	63
4	Group B Streptoccus AND maternal colonization	=	2
5	Group B Streptococcus	=	81
6	Streptococcus agalactiae AND rapid test	=	108
7	Group B Streptococcus AND rapid test	=	451

Abstracts = 62
Systematic Review = 62
14 citations in final recommendations

Literature Search 54

Guideline 116. *H. pylori* Literature Search

Databases Searched:
PubMed (1990–2004)
Search Criteria:

1	H. pylori	= 1476
2	urease	= 1866
3	physician office testing	= 108
4	point of care tests	= 1414

Abstracts = 15
Systematic Review = 15
15 citations in final recommendations

Literature Search 55

Guideline 117. Diagnosis of Influenza Virus Infection Literature Search

Databases Searched:
Medline OVID (1999–July Week 1, 2005)
Search Criteria:

1	Human influenza	= 2924
2	POCT	= 10230
3	Diagnostic Laboratory Tests	= 285806
4	1 AND 2	= 8
5	1 AND 3	= 185

5 citations in final recommendations

Literature Search 56

Guideline 118. Diagnosis of RSV Infection Literature Search

Databases Searched:
Medline OVID (1999–July Week 1, 2005)
Search Criteria:

1	Human RSV	= 1386
2	POCT	= 10230
3	Diagnostic Laboratory Tests	= 285806
4	1 AND 2	= 3
5	1 AND 3	= 28

6 citations in final recommendations

Literature Search 57

Guidelines 119–128. HIV Literature Search

Databases Searched:
Medline OVID (1996–April Week 2, 2005)
Search Criteria:

1	HIV Seropositivity	=	5737
2	AIDS Serodiagnosis	=	1617
3	HIV Antibodies	=	2415
4	1 OR 2 OR 3	=	9813
5	rapid	=	109813
6	point of care	=	2559
7	5 OR 6	=	112058
8	4 AND 7	=	429
9	limit 8 to English language	=	409
10	from 9 keep 1–8, 13, 15–16, 18, 20–28, 30–32. . . .	=	109
11	from 9 keep 203–205, 209	=	4
12	from 9 keep 212, 217, 221–222, 225, 232–235. . .	=	51
13	from 9 keep 407, 409	=	2
14	10 OR 11 OR 12 OR 13	=	160

48 citations in final recommendations

Literature Search 58

Guideline 129. *Trichomonas vaginalis* Vaginitis Literature Search

Databases Searched:
Pubmed (1996–2004)
Search Criteria:

1	*Trichomonas vaginalis*	= 862
2	*Trichomonas vaginalis* AND POC	= 0
3	*Trichomonas vaginalis* AND rapid testing	= 3
4	*Trichomonas* AND POCT	= 0
5	*Trichomonas* AND point of care testing	= 0
6	Trichomonas AND lab detection	= 22
7	Trichomonas AND Affirm	= 3
8	Trichomonas AND preterm labor	= 29
9	*Trichomonas vaginalis* & preterm delivery	= 13
10	*Trichomonas vaginalis* & office testing	= 0
11	*Trichomonas vaginalis* & probes	= 9
12	*Trichomonas vaginalis* and point of care testing	= 1
13	Trichomonas AND urine	= 69
14	Trichomonas AND HIV	= 178

Abstracts = 33
Systematic Review = 33
31 citations in final recommendations

Literature Search 59

Guideline 130. *Trichomonas vaginalis* Vaginitis Literature Search

Databases Searched:
Pubmed (1996–2004)
Search Criteria:

1	Yeast AND wet preparations	= 13
2	Yeast vaginitis AND rapid diagnosis	= 29

Abstracts = 13
Systematic Review = 13
4 citations in final recommendations

Literature Search 60

Guidelines 131–133. Bacterial Vaginitis Literature Search

Databases Searched:
Pubmed (1996–2004)
Search Criteria:
1 Bacterial vaginosis AND wet preparations = 12
2 Bacterial vaginosis AND rapid diagnosis = 33
3 Bacterial vaginosis AND preterm birth = 168
12 citations in final recommendations

Literature Search 61

Guidelines 134–140. Occult Blood Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–May 28, 2004)
Search Criteria:
1 occult blood = 3676
2 occult blood AND colorectal cancer = 2049
3 fecal occult blood = 1122
4 gastric occult blood = 230
Abstracts = 171
Systematic Review = 102
75 citations in final recommendations

Literature Search 62

Guideline 141. Intraoperative PTH Primary Hyperparathyroidism Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
1 intraoperative (parathyroid hormone OR PTH = 200
2 intraoperative (parathyroid hormone OR PTH) AND primary hyperparathyroidism = 143
Abstracts = 123
Systematic Review = 110
68 citations in final recommendations

Literature Search 63

Guideline 141. Intraoperative PTH Primary Hyperparathyroidism Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
intraoperative (parathyroid hormone OR PTH) AND morbidity OR complications = 200
Abstracts = 34
Systematic Review = 32
5 citations in final recommendations

Literature Search 64

Guideline 141. Intraoperative PTH Primary Hyperparathyroidism Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
1 intraoperative (parathyroid hormone OR PTH) AND anesthesia = 33
2 intraoperative (parathyroid hormone OR PTH) AND neck exploration = 79
Abstracts = 40
Systematic Review = 32
3 citations in final recommendations

Literature Search 65

Guideline 141. Intraoperative PTH Primary Hyperparathyroidism Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
intraoperative (parathyroid hormone OR PTH) AND frozen section = 20
Abstracts = 9
Systematic Review = 8
2 citations in final recommendations

Literature Search 66

Guideline 141. Intraoperative PTH Primary Hyperparathyroidism Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
1 intraoperative (parathyroid hormone OR PTH) AND operating room time OR operative time OR surgery time = 77
2 intraoperative (parathyroid hormone OR PTH) AND operating room fee OR cost OR cost savings OR cost benefit OR hospital charges = 27
3 intraoperative (parathyroid hormone OR PTH) AND length of stay OR hospitalization = 13
Abstracts = 20
Systematic Review = 20
14 citations in final recommendations

Literature Search 67

Guideline 141. Intraoperative PTH Primary Hyperparathyroidism Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
1 intraoperative (parathyroid hormone OR PTH) AND incision = 32
2 intraoperative (parathyroid hormone OR PTH) AND cosmetic = 10
3 intraoperative (parathyroid hormone OR PTH) AND patient satisfaction OR pain = 10
Abstracts = 14
Systematic Review = 12
3 citations in final recommendations

Literature Search 68

Guideline 142. Intraoperative PTH Other Parathyroidism Diseases Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
1 intraoperative (parathyroid hormone OR PTH) AND secondary hyperparathyroidism = 19
2 intraoperative (parathyroid hormone OR PTH) AND tertiary hyperparathyroidism = 16
Abstracts = 23
Systematic Review = 22
13 citations in final recommendations

Literature Search 69

Guideline 143. Intraoperative PTH Other Parathyroidism Diseases Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
intraoperative (parathyroid hormone OR PTH) AND reoperation OR reoperative OR repeat surgery = 36
Abstracts = 21
Systematic Review = 21
8 citations in final recommendations

Literature Search 70

Guideline 144. Intraoperative PTH Other Parathyroidism Diseases Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
intraoperative (parathyroid hormone OR PTH) AND multiple endocrine neoplasia = 15
Abstracts = 11
Systematic Review = 9
6 citations in final recommendations

Literature Search 71

Guideline 145. Intraoperative PTH Other Parathyroidism Diseases Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
intraoperative (parathyroid hormone OR PTH) AND parathyroid carcinoma = 20
Abstracts = 13
Systematic Review = 8
8 citations in final recommendations

Literature Search 72

Guidelines 146–147. Intraoperative PTH Localization Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
intraoperative (parathyroid hormone OR PTH) AND angiography OR intraoperative localization) = 64
Abstracts = 10
Systematic Review = 8
6 citations in final recommendations

Literature Search 73

Guideline 148. Intraoperative PTH Secondary Questions Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
intraoperative (parathyroid hormone OR PTH) AND assay comparison OR instrumentation = 8
Abstracts = 12
Systematic Review = 10
6 citations in final recommendations

Literature Search 74

Guideline 149. Intraoperative PTH Secondary Questions Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
1 intraoperative (parathyroid hormone OR PTH)) AND protocol OR procedure OR timing OR time factors OR samples OR sampling = 99
2 intraoperative (parathyroid hormone OR PTH) AND guidelines OR standards OR criteria = 13
Abstracts = 51
Systematic Review = 36
21 citations in final recommendations

Literature Search 75

Guideline 150. Intraoperative PTH Secondary Questions Literature Search

Databases Searched:
National Library of Medicine; Pub Med (1966–November Week 2, 2003)
Search Criteria:
intraoperative (parathyroid hormone OR PTH) AND specimen transport OR pneumatic tube OR turnaround time OR location OR laboratory OR testing site = 30
Abstracts = 7
Systematic Review = 5
3 citations in final recommendations

Literature Search 76

Guideline 151. pH Testing Literature Search

Databases Searched:
Medline OVID (1966–April Week 3, 2003)
AHRQ National Guideline Clearinghouse
Search Criteria:
1 pH AND chemical burns OR Burns, Chemical = 54
2 pH AND eye OR EYE BURNS OR EYE AND lavage OR wash OR tears = 56
3 pH AND chemical burns OR Burns, Chemical AND eye OR EYE BURNS OR EYE AND ocular = 11
4 pH AND chemical burns OR Burns, Chemical/ AND ocular = 12
5 pH AND chemical burns OR Burns, Chemical AND eye OR EYE BURNS OR EYE = 23
6 pH AND emergency OR EMERGENCIES AND Reagent Strips OR pH paper OR Gastric Acidity determination = 21
7 pH AND eye OR EYE BURNS OR EYE AND emergency OR EMERGENCIES = 4
Abstracts = 129
Systematic Review = 19
21 citations in final recommendations

Literature Search 77

Guideline 152. pH Testing Literature Search

Databases Searched:
Medline OVID (1966–April Week 3, 2003)
AHRQ National Guideline Clearinghouse

Search Criteria:

1	pH AND Gastric Juice OR gastric fluid AND achlorhydria OR ACHLORHYDRIA	= 20
2	pH AND Gastric Juice/ OR gastric fluid AND gastroesophageal Reflux OR gastric reflux	= 70
3	pH AND Gastric Juice OR gastric fluid AND Gastric Acidity Determination OR continuous pH monitoring AND achlorhydria OR ACHLORHYDRIA	= 7
4	pH AND Gastric Juice OR gastric fluid AND Gastric Acidity Determination OR continuous pH monitoring AND gastroesophageal Reflux OR gastric reflux	= 15
5	pH AND Gastric Juice OR gastric fluid AND achlorhydria OR ACHLORHYDRIA AND Gastric Acidity Determination OR ambulatory pH monitoring	= 7
6	pH AND Gastric Juice OR gastric fluid AND gastroesophageal Reflux OR gastric reflux AND Gastric Acidity Determination OR ambulatory pH monitoring	= 15
7	Reagent Strips OR pH paper AND GASTRIC JUICE OR gastric OR GASTRIC ACID	= 31

Abstracts = 136
Systematic Review = 51
27 citations in final recommendations

Literature Search 78

Guideline 153. pH Testing Literature Search

Databases Searched:
Medline OVID (1966–April Week 3, 2003)
AHRQ National Guideline Clearinghouse

Search Criteria:

1	NG tube placement	= 6
2	pH AND nasogastric tube	= 134
3	Gastroccult	= 6
4	pH paper	= 45
5	Nitrazine	= 37
6	Gastric Occult Blood	= 2
7	pH AND Gastrointestinal Hemorrhage/OR Occult Blood/ AND Enteral Nutrition OR Intubation, Gastrointestinal OR Nasogastric tube	= 10
8	pH paper AND nasogastric tube	= 3
9	pH paper AND Enteral Nutrition OR Intubation, gastrointestinal/ OR Nasogastric tube	= 5
10	pH AND nasogastric tube AND Gastric Acid or Gastric Juice or gastric fluid	= 47

Abstracts = 233
Systematic Review = 19
14 citations in final recommendations

Literature Search 79

Guideline 154. pH Testing Literature Search

Databases Searched:
Medline OVID (1966–April Week 3, 2003)
AHRQ National Guideline Clearinghouse

Search Criteria:

1	Nitrazine	= 37
2	pH paper	= 45
3	pH Nitrazine	= 1
4	pH AND Nitrazine	= 12

Abstracts = 81
Systematic Review = 14
2 citations in final recommendations

Literature Search 80

Guidelines 155–156. Creatinine and BUN Testing Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	point-of-care testing	= 465
2	point of care testing	= 1343
3	ancillary testing	= 318
4	satellite testing	= 213
5	bedside testing	= 1119
6	near-patient testing	= 107
7	near patient testing	= 542
8	remote testing	= 545
9	Physician's Office Laboratories	= 91
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	= 3722
11	BUN	= 5196
12	blood urea nitrogen	= 5820
13	urea	= 57069
14	creatinine	= 38113
15	10 AND (11 OR 12 OR 13 OR 14)	= 77

Abstracts = 77
Systematic Review = 10
3 citations in final recommendations

Literature Search 81

Guideline 157. Urine pH Dipstick Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	urine	= 113844
2	pH	= 3675477
3	dipstick	= 783
4	1 AND 2 AND 3	= 310

Abstracts = 310
Systematic Review = 3
0 citations in final recommendations

Literature Search 82

Guideline 158. Urine pH Dipstick Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	urine	= 113844
2	pH	= 3675477
3	dipstick	= 783
4	1 AND 2 AND 3	= 310

Abstracts = 310
Systematic Review = 6
0 citations in final recommendations

Literature Search 83

Guideline 159. Urine Specific Gravity Dipstick Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	urine	=	113844
2	dipstick	=	783
3	specific gravity	=	1663
4	1 AND 2 AND 3	=	21

Abstracts = 21
Systematic Review = 6
0 citations in final recommendations

Literature Search 84

Guideline 160. Urine Specific Gravity Dipstick Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	urine	=	113844
2	dipstick	=	783
3	specific gravity	=	1663
4	1 AND 2 AND 3	=	2

Abstracts = 2
Systematic Review = 2
0 citations in final recommendations

Literature Search 85

Guideline 161. Osmolality Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	point-of-care testing	=	465
2	point of care testing	=	1343
3	ancillary testing	=	318
4	satellite testing	=	213
5	bedside testing	=	1119
6	near-patient testing	=	107
7	near patient testing	=	542
8	remote testing	=	545
9	Physician's Office Laboratories	=	91
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	=	3722
11	plasma	=	359288
12	serum	=	382119
13	whole blood	=	46595
14	urine	=	113844
15	11 OR 12 OR 13 OR 14	=	796369
16	osmolality	=	30001
17	10 AND 15 AND 16	=	6

Abstracts = 6
Systematic Review = 3
0 citations in final recommendations

Literature Search 86

Guideline 162. Proteinuria Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	proteinuria	= 16953
2	urine protein	= 32098
3	dipstick	= 783
4	3 AND (1 OR 2)	= 260

Abstracts = 260
Systematic Review = 32
6 citations in final recommendations

Literature Search 87

Guideline 163. Hematuria Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	urine	= 113844
2	hematuria	= 60279
3	blood	= 1319048
4	dipstick	= 783
5	1 AND 4 AND (2 OR 3)	= 215

Abstracts = 215
Systematic Review = 16
0 citations in final recommendations

Literature Search 88

Guideline 164. Electrolyte Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	point-of-care testing	= 465
2	point of care testing	= 1343
3	ancillary testing	= 318
4	satellite testing	= 213
5	bedside testing	= 1119
6	near-patient testing	= 107
7	near patient testing	= 542
8	remote testing	= 545
9	Physician's Office Laboratories	= 91
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	= 3722
11	plasma	= 359288
12	serum	= 382119
13	whole blood	= 46595
14	urine	= 113844
15	11 OR 12 OR 13 OR 14	= 796369
16	electrolytes	= 164523
17	10 AND 15 AND 16	= 20

Abstracts = 20
Systematic Review = 7
0 citations in final recommendations

Literature Search 89

Guideline 165. Proteinuria for Pre-Eclampsia Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	proteinuria	= 16953
2	urine protein	= 32098
3	dipstick	= 783
4	3 AND (1 OR 2)	= 260

Abstracts = 260
Systematic Review = 17
2 citations in final recommendations

Literature Search 90

Guideline 166. Urine pH Dipstick for Renal Stone Recurrence Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	urine	= 113844
2	pH	= 3675477
3	dipstick	= 783
4	1 AND 2 AND 3	= 310

Abstracts = 310
Systematic Review = 4
0 citations in final recommendations

Literature Search 91

Guideline 167. Hematuria for Intra-abdominal Trauma Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	urine	= 113844
2	hematuria	= 60279
3	blood	= 1319048
4	dipstick	= 783
5	1 AND 4 AND (2 OR 3)	= 215

Abstracts = 215
Systematic Review = 17
0 citations in final recommendations

Literature Search 92

Guideline 168. Lactate in Hemodialysis Patients Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	point-of-care testing	=	465
2	point of care testing	=	1343
3	ancillary testing	=	318
4	satellite testing	=	213
5	bedside testing	=	1119
6	near-patient testing	=	107
7	near patient testing	=	542
8	remote testing	=	545
9	Physician's Office Laboratories	=	91
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	=	3722
11	plasma	=	359288
12	serum	=	382119
13	whole blood	=	46595
14	11 OR 12 OR 13	=	727605
15	lactate	=	52114
16	10 AND 14 AND 15	=	9

Abstracts = 9
Systematic Review = 3
0 citations in final recommendations

Literature Search 93

Guideline 169. Myoglobin for Muscle Injury Renal Complications Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	urine	=	113844
2	dipsticks	=	783
3	myoglobin	=	5515
4	1 AND 2 AND 3	=	7

Abstracts = 7
Systematic Review = 4
0 citations in final recommendations

Literature Search 94

Guideline 170. Microalbumin for Non-diabetic Nephropathy Literature Search

Databases Searched:
Medline OVID (1966–October Week 4, 2003)
Search Criteria:

1	urine	=	113844
2	dipstick	=	783
3	microalbumin	=	160
4	microalbuminuria	=	2436
5	1 AND 2 AND (3 or 4)	=	38

Abstracts = 38
Systematic Review = 11
0 citations in final recommendations

Literature Search 95

Guideline 171. hCG Literature Search

Databases Searched:
Medline OVID (1975–September Week 2, 2003)
Search Criteria:
1 hCG AND urine AND emergency = 17
2 hCG AND pregnancy AND home AND limited to human and English language = 2
Abstracts = 19
Systematic Review = 5
0 citations in final recommendations

Literature Search 96

Guideline 172. hCG Literature Search

Databases Searched:
Medline OVID (1975–September Week 2, 2003)
Search Criteria:
1 hCG AND pregnancy AND home AND limited to human and English language = 23
2 urine AND pregnancy AND bedside AND limited to human and English language = 7
3 urine AND hCG AND pregnancy AND test AND rapid AND limited to human and English language = 12
4 home pregnancy AND limited to human and English language = 39
Abstracts = 78
Systematic Review = 12
12 citations in final recommendations

Literature Search 97

Guideline 173. hCG Literature Search

Databases Searched:
Medline OVID (1975–September Week 2, 2003)
Search Criteria:
1 hCG AND pregnancy AND home AND limited to human and English language = 23
2 urine AND pregnancy AND bedside AND limited to human and English language = 7
3 urine AND hCG AND pregnancy AND test AND rapid AND limited to human and English language = 12
4 home pregnancy AND limited to human and English language = 39
Abstracts = 78
Systematic Review = 12
12 citations in final recommendations

Literature Search 98

Guideline 174. hCG Literature Search

Databases Searched:
Medline OVID (1975–September Week 2, 2003)
Search Criteria:
1 hCG AND pregnancy AND home AND limited to human and English language = 23
2 urine AND pregnancy AND bedside AND limited to human and English language = 7
3 urine AND hCG AND pregnancy AND test AND rapid AND limited to human and English language = 12
4 home pregnancy AND limited to human and English language = 39
Abstracts = 78
Systematic Review = 12
0 citations in final recommendations

Literature Search 99

Guideline 175. hCG Literature Search

Databases Searched:
Medline OVID (1975–September Week 2, 2003)
Search Criteria:
1 hCG AND pregnancy AND home AND limited to human and English language = 23
2 urine AND pregnancy AND bedside AND limited to human and English language = 7
3 urine AND hCG AND pregnancy AND test AND rapid AND limited to human and English language = 12
4 home pregnancy AND limited to human and English language = 39
Abstracts = 78
Systematic Review = 12
3 citations in final recommendations

Literature Search 100

Guideline 176. Urine LH Ovulation Testing Literature Search

Databases Searched:
Medline OVID (1975–October Week 3, 2003)
Search Criteria:
1 Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertility limited to human and English language = 55
2 Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fecundity limited to human and English language = 7
3 Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertilization limited to human and English language = 12
4 Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND ambulatory care OR clinic visits limited to human and English language = 2
Abstracts = 72
Systematic Review = 13
13 citations in final recommendations

Literature Search 101

Guideline 177. Urine LH Ovulation Testing Literature Search

Databases Searched:
Medline OVID (1975–October Week 3, 2003)
Search Criteria:
1 Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertility limited to human and English language = 55
2 Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fecundity limited to human and English language = 7
3 Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertilization limited to human and English language = 12
4 Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND ambulatory care OR clinic visits limited to human and English language = 2
Abstracts = 72
Systematic Review = 13
11 citations in final recommendations

Literature Search 102

Guideline 178. Urine LH Ovulation Testing Literature Search

Databases Searched:
Medline OVID (1975–October Week 3, 2003)
Search Criteria:

1	Ovulation detection OR urine LH test OR home ovulation OR [urine AND luteinizing hormone] AND pregnancy outcomes limited to human and English language	= 8
2	Ovulation detection OR urine LH test OR home ovulation OR [urine AND luteinizing hormone] AND pregnancy limited to human and English language	= 151
3	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertility limited to human and English language	= 55
4	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fecundity limited to human and English language	= 7
5	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertilization limited to human and English language	5 12
6	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND ambulatory care OR clinic visits limited to human and English language	5 2

Abstracts = 223
Systematic Review = 0
0 citations in final recommendations

Literature Search 103

Guideline 179. Urine LH Ovulation Testing Literature Search

Databases Searched:
Medline OVID (1975–October Week 3, 2003)
Search Criteria:

1	Ovulation detection OR urine LH test OR home ovulation OR [urine AND luteinizing hormone] AND pregnancy outcomes limited to human and English language	= 8
2	Ovulation detection OR urine LH test OR home ovulation OR [urine AND luteinizing hormone] AND pregnancy limited to human and English language	= 151
3	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertility limited to human and English language	= 55
4	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fecundity limited to human and English language	= 7
5	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertilization limited to human and English language	= 12
6	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND ambulatory care OR clinic visits limited to human and English language	= 2

Abstracts = 223
Systematic Review = 8
8 citations in final recommendations

Literature Search 104

Guideline 180. Urine LH Ovulation Testing Literature Search

Databases Searched:
Medline OVID (1975–October Week 3, 2003)
Search Criteria:

1	Ovulation detection OR urine LH test OR home ovulation OR [urine AND luteinizing hormone] AND pregnancy limited to human and English language	= 151
2	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertility limited to human and English language	= 55
3	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fecundity limited to human and English language	= 7
4	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertilization limited to human and English language	= 12
5	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND ambulatory care OR clinic visits limited to human and English language	= 2

Abstracts = 216
Systematic Review = 0
1 citations in final recommendations

Literature Search 105

Guideline 181. Urine LH Ovulation Testing Literature Search

Databases Searched:
Medline OVID (1975–October Week 3, 2003)
Search Criteria:

1	Ovulation detection OR urine LH test OR home ovulation OR [urine AND luteinizing hormone] AND pregnancy limited to human and English language	= 151
2	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertility limited to human and English language	= 55
3	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fecundity limited to human and English language	= 7
4	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND fertilization limited to human and English language	= 12
5	Ovulation detection OR urine LH test OR home ovulation test OR [urine AND luteinizing hormone] AND ambulatory care OR clinic visits limited to human and English language	= 2

Abstracts = 216
Systematic Review = 1
0 citations in final recommendations

Literature Search 106

Guideline 182. Urine LH Ovulation Testing Literature Search

Databases Searched:
Medline OVID (1975–October Week 3, 2003)
Search Criteria:

1	Fertility monitor limited to human and English language	= 13
2	Cue AND ovulation limited to human and English language	= 11
3	New Method AND ovulation limited to human and English language	= 14
4	ferning AND ovulation detection limited to human and English language	= 5

Abstracts = 43
Systematic Review = 10
8 citations in final recommendations

Literature Search 107

Guideline 183. pH/Nitrazine Testing for PROM Literature Search

Databases Searched:
Medline OVID (1970–September Week 2, 2003)
Search Criteria:
fetal membranes, premature rupture OR premature rupture of membranes OR ruptured membranes OR PROM AND pH OR hydrogen-ion concentration limited to English language = 77
Abstracts = 65
Systematic Review = 1
1 citations in final recommendations

Literature Search 108

Guideline 184. pH/Nitrazine Testing for PROM Literature Search

Databases Searched:
Medline OVID (1970–September Week 2, 2003)
Search Criteria:
1 fetal membranes, premature rupture OR premature rupture of membranes OR ruptured membranes OR PROM AND pH OR hydrogen-ion concentration limited to English language = 77
2 fetal membranes, premature rupture OR premature rupture of membranes OR ruptured membranes OR PROM AND nitrazine limited to English language = 24
Abstracts = 87
Systematic Review = 12
10 citations in final recommendations

Literature Search 109

Guideline 185. pH/Nitrazine Testing for PROM Literature Search

Databases Searched:
Medline OVID (1970–September Week 2, 2003)
Search Criteria:
1 fetal membranes, premature rupture OR premature rupture of membranes OR ruptured membranes OR PROM AND nitrazine AND pregnancy outcome limited to English language = 1
2 fetal membranes, premature rupture OR premature rupture of membranes OR ruptured membranes OR PROM AND pH Or hydrogen-ion concentration AND pregnancy outcome limited to English language = 14
Abstracts = 12
Systematic Review = 0
0 citations in final recommendations

Literature Search 110

Guideline 186. Fern Testing for PROM Literature Search

Databases Searched:
Medline OVID (1970–September Week 2, 2003)
Search Criteria:
1 fetal membranes, premature rupture OR premature rupture of membranes OR ruptured membranes OR PROM AND pH OR hydrogen-ion concentration limited to English language = 77
2 fetal membranes, premature rupture OR premature rupture of membranes OR ruptured membranes OR PROM AND nitrazine limited to English language = 24
Abstracts = 87
Systematic Review = 12
5 citations in final recommendations

Literature Search 111

Guideline 187. fFN for Preterm Labor Literature Search
Databases Searched: Medline OVID (1998–October Week 1, 2003) **Search Criteria:** 1 fetal fibronectin = 169 2 limited to human and English language = 105 Abstracts = 102 Systematic Review = 24 **0 citations in final recommendations**

Literature Search 112

Guideline 188. fFN for Preterm Labor Literature Search
Databases Searched: Medline OVID (1998–October Week 1, 2003) **Search Criteria:** 1 fetal fibronectin = 169 2 limited to human and English language = 105 Abstracts = 102 Systematic Review = 24 **0 citations in final recommendations**

Literature Search 113

Guideline 189. fFN for Preterm Labor Literature Search
Databases Searched: Medline OVID (1998–October Week 1, 2003) **Search Criteria:** 1 fetal fibronectin = 169 2 limited to human and English language = 105 Abstracts = 102 Systematic Review = 24 **0 citations in final recommendations**

Literature Search 114

Guideline 190. fFN for Preterm Labor Literature Search
Databases Searched: Medline OVID (1998–October Week 1, 2003) **Search Criteria:** 1 fetal fibronectin = 169 2 limited to human and English language = 105 Abstracts = 102 Systematic Review = 24 **4 citations in final recommendations**

Appendix **C**

Acknowledgements

Development and publication of these guidelines were supported by grants from the American Association for Clinical Chemistry and Radiometer Copenhagen.

The organizing committee would like to thank the following professional societies for their contributions to the guidelines:

- Clinical microbiologists from the American Society for Microbiology reviewed and commented on the infectious diseases-related content of the guidelines.
- The College of American Pathologists (CAP) POCT Checklist Committee reviewed and commented on the guidelines.
- The IFCC C-EBLM Committee reviewed and commented on the first draft of the guidelines.

The organizing committee would like to thank the following companies whose professional staff dedicated time to work on these practice guidelines:

- Abbott Point-of-Care, East Windsor, NJ, USA
- ARC Consulting, Perth, Western Australia
- Bayer Diagnostics, Tarrytown, NY, USA
- Instrumentation Laboratory, Lexington, MA, USA
- International Technidyne Corporation, Edison, NJ, USA
- Nanosphere, Northbrook, IL, USA
- Nova Biomedical, Waltham, MA, USA
- Quidel Corporation, San Diego, CA, USA
- Respironics, Murrysville, CA, USA

The authors would like to thank Dr. Stanley Cernosek, Director, Corporate Business Development, Beckman Coulter, Inc. for assistance in the early stages of this project.

The authors would like to express appreciation to the following individuals for their critical review:

- Dr. Jared Block, Director, Point of Care Services, Carolinas Medical Center, Charlotte, NC, USA
- Dr. Paula Santrach, Vice Chair, Clinical Operations, Department of Laboratory Medicine & Pathology, Mayo Clinic, Rochester, MN, USA
- Dr. Frank LaDuca, Senior Director, Regulatory Affairs, Bayer Healthcare Diagnostics Division, Tarrytown, NY, USA