

FROM THE MIND OF THE CHAIR



Hi again everyone!
Thanks for viewing the
July 2019 edition on the
PMF newsletter! This
issue is jam packed with
lots information about the
upcoming 71th AACC
Annual Scientific Meeting
& Clinical Laboratory
Expo in Anaheim. In
particular, we highlight

many of the pediatric and maternal fetal
medicine related sessions that are available for
meeting attendees! I am looking forward to
seeing many at one or more to the PMF
sponsored events! Please plan to attend our
annual **Joint division mixer on Sunday night,
August 4 at 8:00 PM!** Here you can catch up
with old friends from the PMF, Clinical
Translational Sciences, and History Divisions,
and honor our award winners! As in past years,
we have two abstract awards winners, **William
Phipps** (Student/Young Investigator)
and **Christopher Hamilton** (Best Abstract).
The 2019 award winner for **Outstanding
Contributions to Pediatric and Maternal
Fetal Laboratory Medicine** is **Dr. Uttam Garg**.
Please join me in congratulating each of our
award winners on their outstanding
contributions to our field!

Along with the joint division mixer, there will be
a networking event on Sunday evening at the
opening mixer! Like last year, the **Division
networking event at the opening mixer** will
give interested attendees a chance to mingle
with Division board members, play games, and
even join new divisions! Please stop by the
PMF table to network, play PMF related games
and even register for prizes, like dinner with the
PMF board or a free round table session!

Once again, the PMF Division is hosting a
special hot topics session. This year Dennis
Dietzen and Hubert Vesper will discuss ongoing
work by the AACC on pediatric reference
intervals! There are also several scientific
sessions sponsored by the PMF division
including a special PMF ePoster session
highlighting this year's top scoring abstracts.
We are also presenting the PMF developed
session entitled "**33110 Challenges in the
Diagnosis and Management of Polycystic
Ovary Syndrome: Multifaceted
Perspectives**". Please see the section at the
end of the newsletter for more details!

Also in this issue, we continue our ABC's of
Pediatric Laboratory Medicine series with our D
installment on neonatal toxicology. Our
excerpts from the literature focuses on sweat
testing and other Cystic Fibrosis testing.

I hope you find the content of this newsletter
both interesting and helpful! Thank you for your
ongoing support of the efforts of the PMF
Division! See you in Anaheim!

Alison Woodworth

Chair, AACC PMF Division

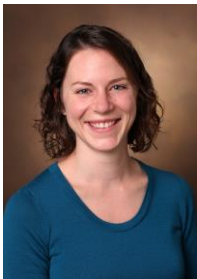
Table of Contents

From the Mind of the Chair.....	1
The ABC's of Pediatric Laboratory Medicine...2	
References.....	5-6
Excerpts From The Literature.....	6
PMF Division Awardees.....	8



THE ABC'S OF PEDIATRIC LABORATORY MEDICINE:

“D” is for DOA: Neonatal toxicology testing



Jennifer M. Colby, PhD
Department of Pathology,
Microbiology, and Immunology,
Vanderbilt University Medical
Center, Nashville, TN



Steven W. Cotten, PhD
Department of Pathology and
Laboratory Medicine, University of
North Carolina at Chapel Hill,
Chapel Hill, NC

Introduction

Substance abuse is a growing concern in the United States. Use or abuse of prescription medications, particularly opioids, has increased substantially in the past ten years. Use of prescription and illicit drugs is also increasing in sensitive populations like pregnant women. Maternal drug use also exposes the developing fetus to drugs, which has a number of deleterious consequences, including the development of a withdrawal syndrome known as neonatal abstinence syndrome. Mothers who use drugs while pregnant may also be subject to legal consequences, including loss of custodial rights. Toxicology testing on specimens collected from the neonate is often required to demonstrate *in utero* exposure, due

to the potentially severe medicolegal consequences. Development of a comprehensive testing protocol, with guidance on specimen selection, specimen collection, and result interpretation is important for proper care. Such testing provides an opportunity for laboratorians to significantly contribute towards to better care of mother-baby dyads.

Possible Specimen Types

Urine

Although urine is the most commonly encountered specimen in toxicology testing in adults, it is used far less frequently in neonates. Collecting urine from a neonate can be quite challenging. Removal of urine directly from the diaper is difficult, and other absorbent material (e.g. cotton balls) may be used instead. Removal of urine that has saturated an absorbent material could allow residual chemicals from the polymer to contaminate the urine and may lead to artifactual results. Better practices include collecting urine in specialized neonatal collection bags. However, collecting adequate sample volume for drug testing may be time consuming, because most neonates produce very little urine in their first few days of life (1).

In addition to the issues issue related to specimen collection, urine drug testing can be difficult to interpret in neonates. Most urine drug screens performed by clinical laboratories are optimized for workplace drug testing in adults. This means that the tests detect metabolites and drug concentrations expected in adult drug users, which may not be relevant to neonates (2). In addition, urine typically provides a window of drug detection that spans several days. Although this is extended slightly in the neonate's first void, even first void urine has low sensitivity for more remote exposures (3,4).

Meconium

Meconium, the stool formed during gestation, is a very common specimen for neonatal drug testing. Many waste products, including drugs

and metabolites, accumulate in meconium, which begins to form around the 12th week of gestation and accumulates slowly throughout the second trimester. More than half of a baby's meconium is produced in the final 8 weeks of pregnancy. As a result, meconium reflects exposures in most of the 3rd trimester, and in some cases, may reflect exposures in the later 2nd trimester (5,6). Meconium is generally most sensitive for repeated or more severe exposures (7).

Although it has a long history of use and is often considered the gold standard, meconium poses a number of operational challenges. Like neonatal urine, collecting meconium is not trivial. It is often passed in stages, which requires multiple collections, and the passage can be delayed several days after birth. In neonates with opioid exposures, passage can be delayed even longer. Meconium is also a heterogenous matrix. Each passage must be collected and combined prior to testing. Storage and mixing of specimens introduces an opportunity for labeling errors and degradation, but use of only a partial collection may lead to false negative results. An inadequate collection may not provide enough material for necessary confirmation testing, which is frustrating for clinicians. Finally, meconium may also be expelled in utero, in which case it is unobtainable.

Umbilical Cord Tissue

Umbilical cord tissue toxicology testing is rapidly gaining acceptance in the U.S., due in part to its operational advantages. Chiefly, cord tissue is available immediately at birth, and the collection process is simple. Because cord tissue is considered a homogenous matrix, multiple collections are not necessary. Toxicology testing of cord tissue can proceed promptly after birth, thus it often has a decreased turnaround time relative to toxicology testing in meconium (8). However, several studies have demonstrated that drugs and metabolites are present at lower concentration in cord tissue than in meconium (9). Not surprisingly, the window of drug detection using a cord tissue sample is shorter

than meconium, and cord tissue may not capture as many exposures as meconium (9–12).

Pre-Analytical Testing Challenges

Presently, hospitals use two major approaches for neonatal drug testing. The first, universal screening, involves consistently testing all newborns born at an institution. This strategy is costly but may reduce the potential for bias in test ordering. The alternative, a risk-based screening approach, involves testing only in scenarios that meet pre-defined criteria. Criteria may include factors like maternal history or signs of drug use, social risk factors, limited or absent prenatal care, and symptoms of withdrawal in the neonate. This strategy is less expensive than universal screening but may require careful consideration of inclusion criteria and regular audits to avoid bias.

Analytical Testing Considerations

All neonatal toxicology analyses of meconium or umbilical cord tissue are regulated as laboratory developed tests. For laboratories, this means increased demands during test development and validation. Both specimens require extensive pre-analytical sample preparation, which may include homogenization by blender or tissue grinder. Owing to the amount of labor required to process the specimen, these processes can be very expensive. Due to the extensive sample clean-up that is required, the recovery of target analytes can be low, and the limit of detection for a given drug can vary substantially from one laboratory to another. Analytes included in a method can also vary from laboratory to laboratory. This means that a test result from one laboratory or one specimen type is not necessarily interchangeable with results from another laboratory or testing performed on an alternate matrix (9–12).

Importance of Turnaround Time

In addition to being one of the main indicators of a lab's performance, achieving an

appropriate turnaround time also has implications on the utility of a result. Toxicology results are used by a variety of stakeholders to make a determination about the discharge of the neonate, and depending on the results, may prompt additional legal proceedings. Because discharge decisions may rest on the results, it is important that neonatal toxicology test results are available quickly, ideally within 48h of birth. Delaying discharge until results are available is not always possible, and this may pose problems for the hospital and for the neonate. For example, if positive results concerning ongoing maternal substance abuse arrive after the neonate has been discharged, the baby may experience additional preventable trauma before the mother has been re-contacted, or the baby may be lost to follow-up entirely.

Stakeholders and Result Utilization

A critical review of any neonatal drug testing program reveals impacts on a spectrum of providers and stakeholders, including physicians and nursing in OB-GYN, Labor and Delivery, Neonatal Intensive Care Units (NICU) and Social Services. Each stakeholder may have different expectations related to testing and be concerned with different aspects of the total testing process: pre-analytical, analytical or post-analytical. Prior to testing, providers in OB-GYN should be mindful of the institution's neonatal drug policy, which specifies the testing strategy. If risk-based testing has been implemented, proper assessment of risk factors must be completed by the OB-GYN team and communicated to Labor and Delivery. The decision for or against testing should ideally be made prior to delivery to ensure proper collection of the desired specimen. Providers in Labor and Delivery, Well-Baby Nursery, and NICU must also be aware of their role related to specimen collection. Ease of specimen collection is one factor that can influence the selection of screening tests.

In addition to collection, the analytical performance of the test and the panel of drugs detected can impact how stakeholders view the clinical performance. All providers (and clinical

laboratorians!) would prefer a rapid, affordable test with 100% sensitivity and specificity. However, real-world constraints dictate compromises related to sensitivity, cost and turnaround time. Several publications have demonstrated that specimen type can influence the specific drugs detected due to differences in distribution and deposition in the matrix (9). Additionally the analytical method and the limit of detection for target compounds prevent a specific specimen type or method from being ideal for all applications. For example, healthcare providers in the NICU and Well-baby nursery may consider detection of opioids (illicit or prescribed) the most important component of the toxicology results profile, whereas Social Services caseworkers may be concerned with other abused drugs such as cannabis, benzodiazepines, or gabapentin.

Turnaround time has a large impact on how different stakeholders use neonatal toxicology results. Most hospital laboratories will be able to provide same day results for urine drug screens, and providers in Well-baby, NICU, and Social Services will be able to make clinical decisions rapidly. Meconium and umbilical cord tissue specimens are often sent to an outside laboratory for analysis, introducing additional transit time. The increased turnaround time can impact the timely discharge of the neonate. Performing the analysis in-house is one strategy to decrease turnaround time relative to referral testing (8).

Laboratory Stewardship related to Neonatal Drug Testing

The laboratory can play an integral role in helping stakeholders understand the complexities of neonatal drug testing. Two major areas of expertise that laboratorians can contribute include the choice of specimen type and the method for analysis. Choosing the specimen that meets the needs of an institution's neonatal drug testing program can be challenging. Issues related to turnaround time and cost (both direct and indirect) should also be discussed when developing a plan. The laboratory can also assist in the integration of

toxicology results from multiple patients (mother and newborn), multiple specimen types (urine, meconium, hair, and umbilical cord), along with each patient's medication list, and maternal history to help interpret the findings. The laboratory can troubleshoot unexpected results by providing critical evaluation of the total testing process and leveraging expertise in toxicology testing.

Conclusions

The creation of an effective neonatal testing program requires careful consideration of the pre-analytic, analytic, and post-analytic phases of testing. The unique specimen types associated with neonates are distinct from those used for other toxicology testing applications. These differences require careful consideration to preserve specimen integrity and produce accurate, timely results. Laboratorians can assume a prominent role in the care of drug-exposed newborns, a role that has important medicolegal implications, and highlights the strength of the laboratory in facilitating quality, cost-effective healthcare.

Acknowledgements

The authors would like to thank CLN for allowing this revised version of their previously published article (<https://www.aacc.org/publications/cln/articles/2018/march/facing-challenges-in-neonatal-drug-testing>) to be re-printed for the PMF Division Newsletter.

References

1. Kasamatsu A, Ohashi A, Tsuji S, Okada H, Kanzaki H, Kaneko K. Prediction of urine volume soon after birth using serum cystatin C. *Clin Exp Nephrol*. 2016 Oct 1;20(5):764–9.

2. Barakauskas VE, Davis R, Krasowski MD, McMillin GA. Unresolved discrepancies

between cannabinoid test results for infant urine. *Clin Chem*. 2012 Sep;58(9):1364–7.

3. Halstead AC, Godolphin W, Lockitch G, Segal S. Timing of specimen collection is crucial in urine screening of drug dependent mothers and newborns. *Clin Biochem*. 1988;21(1):59–61.

4. Kwong TC, Ryan RM. Detection of intrauterine illicit drug exposure by newborn drug testing. *National Academy of Clinical Biochemistry. Clin Chem*. 1997 Jan;43(1):235–42.

5. Himes SK, Tassiopoulos K, Yogev R, Huestis MA. Antiretroviral Drugs in Meconium: Detection for Different Gestational Periods of Exposure. *J Pediatr*. 2015 Aug;167(2):305–311.e3.

6. Gray TR, LaGasse LL, Smith LM, Derauf C, Grant P, Shah R, et al. Identification of Prenatal Amphetamines Exposure by Maternal Interview and Meconium Toxicology in the Infant Development, Environment and Lifestyle (IDEAL) Study: *Ther Drug Monit*. 2009 Dec;31(6):769–75.

7. Joya X, Marchei E, Salat-Batlle J, García-Algar O, Calvaresi V, Pacifici R, et al. Drugs of abuse in maternal hair and paired neonatal meconium: an objective assessment of foetal exposure to gestational consumption: Drugs of abuse in maternal hair and paired neonatal meconium. *Drug Test Anal*. 2016 Aug;8(8):864–8.

8. Labardee RM, Swartzwelder JR, Gebhardt KE, Pardi JA, Dawsey AC, Brent Dixon R, et al. Method performance and clinical workflow outcomes associated with meconium and umbilical cord toxicology testing. *Clin Biochem*. 2017 Sep;50(18):1093–7.

9. Concheiro-Guisan A, Concheiro M. Bioanalysis during pregnancy: recent advances and novel sampling strategies. *Bioanalysis*. 2014 Dec;6(23):3133–53.

10. Concheiro M, Lendoiro E, de Castro A, González-Colmenero E, Concheiro-Guisan A, Peñas-Silva P, et al. Bioanalysis for cocaine, opiates, methadone, and amphetamines exposure detection during pregnancy: Bioanalysis for cocaine, opiates, methadone and amphetamines exposure detection during pregnancy. *Drug Test Anal.* 2017 Jun;9(6):898–904.

11. Colby JM. Comparison of umbilical cord tissue and meconium for the confirmation of in

utero drug exposure. *Clin Biochem.* 2017 Sep;50(13–14):784–90.

12. Colby JM, Adams BC, Morad A, Presley LD, Patrick SW. Umbilical Cord Tissue and Meconium May Not Be Equivalent for Confirming in Utero Substance Exposure. *J Pediatr* [Internet]. 2018 Oct [cited 2019 Jan 23]; Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0022347618313763>

Excerpts from the Literature



Brenda Suh-Lailam, PhD, DABCC, FAAC, Assistant Director, Clinical Chemistry and Mass Spectrometry, Ann & Robert H. Lurie Children's Hospital of Chicago. Assistant Professor of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Sweat Chloride Testing

McCarthy C, Clancy JP, Brewington J.

JAMA. 2019 Jan; 321(7):701–702.

Two editions ago, we discussed updates to the consensus guidelines from the Cystic Fibrosis (CF) Foundation for the diagnosis of CF. The main changes of concern to laboratorians were changes in the terms used to describe the different reference interval partitions for the interpretation of sweat chloride results, as well as changes in the reference interval limits for different age groups.

Sweat chloride testing is the standard diagnostic test for CF and should be the initial test performed when CF is suspected. Most CF cases are diagnosed after sweat chloride testing following abnormal newborn screening

(NBS). However, in certain cases, mild CF is missed by NBS leading to later diagnoses. Most of these cases give indeterminate sweat chloride results when tested. The goal of this publication was to describe such a case and what follow up testing to perform in these situations. In this case, CF was not identified by NBS and sweat chloride test results obtained when the patient started having gastrointestinal (GI) symptoms at age 5 gave indeterminate results on 3 separate occasions. Further genetic testing using a 97-mutation CF transmembrane conductance regulator (CFTR) test panel also gave a negative result. It took whole genome sequencing analysis to identify one CF-causing mutation (c.2249C>T) which was not sufficient to make a diagnosis since less than 2 well-characterized disease-causing mutations were identified.

When faced with such a case, what do you do next? "Alternative CFTR functional testing" is the next diagnostic step in such a case. The authors describe 2 types of alternative CFTR functional tests. The first is using electrodes and sequential perfusion of compounds that affect sodium and chloride transport to measure the nasal potential difference across the nasal epithelium. In this case, this test could not be performed because of lack of cooperation from the patient. The second functional test is intestinal current measurement. Similar to the first test, compounds affecting sodium and chloride transport are used to stimulate

epithelium obtained from rectal biopsy samples and then electrical current which indicates CFTR-dependent ion transport is measured. This test demonstrated that the patient had minimal CFTR function (<5% normal function), far below the CF diagnostic threshold (<25% normal function), allowing for a diagnosis to be made. The patient was treated with pancreatic enzyme replacement therapy (PERT) resulting in an improvement of the GI symptoms.

Laboratorians should be aware of the limitations of the different laboratory tests used for the diagnosis of CF and the alternative functional testing available for cases that cannot be diagnosed using these laboratory tests.

2019 AACC Annual Scientific Meeting and Clinical Lab Expo: PMF Sessions of Interest and Meeting Highlights

AUGUST 4-8, 2019 IN ANAHEIM, CALIFORNIA

Sunday, August 4th

Opening Plenary:

David Walt, PhD

11001 Biomarker Discovery: From Technology Development to Clinical Applications

Monday, August 5th

Plenary Session:

Julie Korenberg

12001 Translating Genes, Brain and Behavior: A Next Generation Human Framework

Roundtable:

42102 or 52202 Interferences with Thyroid Function Tests: Where Do We Stand?

42110 or 52210 Thrombotic Disorders in the Pediatric Population: Current Issues in Diagnosis and Management

42112 or 52212 Follow-up of Positive Newborn Screen Positive Results for Metabolic Disorders (Developed with PMF Division)

42115 or 52215 Utility of Procalcitonin Measurement: Current Evidence and Clinical Utility in Pediatric and Adult Populations

42120 or 52220 Clinical Laboratory Management of Dyslipidemia in Children and Adolescents: Standing Plasma Test to Genetic Testing

42125 or 52225 Pearls and Pitfalls of Estradiol and Testosterone Testing (PMF Board Member)

42131 or 52231 Genetic Testing for Immunodeficiency Disorders

Scientific Sessions:

32106 Predicting and Diagnosing Gestational Diabetes Mellitus (GDM): Are We Making Progress?

32431 Highlighting the Emerging Role of Anti-Müllerian Hormone (AMH) in Ovarian Reserve, Assisted Reproduction, Polycystic Ovary Syndrome (PCOS), and Other Diseases

Tuesday, August 6th

Plenary Session:

Virginia Kaklamani, MD, DSc.

13001 Using Biomarkers to Tailor Treatment for Breast Cancer

Roundtable:

43115 or 53215 Non-invasive Prenatal Testing: Utilization of Cell-free DNA in Fetal Aneuploidy Screening and Beyond

43116 or 53216 Preeclampsia Screening and Diagnosis: A Novel Approach

43126 or 53226 Thyroid Testing During Pregnancy: Current Recommendations and Pitfalls

Scientific Sessions:

33106 Integrating Laboratory Results to Increase Quality Care for Affected Newborns Identified Through Newborn Screening: What is the Optimal Workflow?

33110 Challenges in the Diagnosis and Management of Polycystic Ovary Syndrome: Multifaceted Perspectives (Developed with the PMF Division)

Special Presentation:

Pediatric and Maternal-Fetal Session: The Importance of Developing Accurate Pediatric Reference Intervals

1:00 PM – 2:30 PM, Anaheim Marriott, Platinum 4 Room

Wednesday, August 7th

Plenary Session:

Euan Ashley, BSc, MB ChB, FRCP, DPhil, FAHA, FACC, FESC

14001 Towards Precision Medicine

Roundtable:

44115 or 54215 Umbilical Cord Testing - Moving Beyond Blood Gases (PMF Board Member)

44120 or 54220 LC-MS/MS for Pediatric Steroid Hormone Measurement: Overview and Practice

44126 or 54226 Diagnosing Inborn Errors of Metabolism: Challenging Cases in Biochemical Genetics

44129 or 54229 Reference Intervals for Thyroid Function Tests during Pregnancy

**PMF Division ePoster session
2:00-2:45 PM, Anaheim Convention Center, Expo Hall A, Poster Theater**

Thursday, August 8th

Plenary Session:

Carl Wittwer, MD, PhD

15001 Extreme Molecular Diagnostics

Please Join Us!

Event: Opening Mixer. Sunday 8/4 6:45-8:00 PM. Anaheim Convention Center, Grand Plaza

Event: Joint Section Mixer (with the History and Clinical Translational Science Divisions). Sunday 8/4 8:00-9:30 PM. Hilton Anaheim, Oceanside

PMF Division Awardees

Please help us congratulate the winners of this year's PMF Division Awards. The awards will be presented during the Pediatric and Maternal-Fetal Mixer.

Best Abstract by a Student or Young Investigator:

- **William Phipps**, UT Southwestern, Dallas, TX
- Title: Quantitative Amino Acid Analysis by LC-MS/MS using a Low-Cost Derivatization Approach and Automated Liquid Handler

Best Abstract:

- **Christopher Hamilton**, Penn State Health, Hershey, PA
- Title: Comparison of Five Bioavailable Testosterone Testing Methods

Outstanding Contributions to Pediatric Maternal-Fetal Laboratory Medicine:



Uttam Garg, PhD, Division Director, Laboratory Medicine: Director, Clinical Chemistry, Toxicology and Biochemical Genetics, Children's Mercy, Professor of Pediatric Pathology, University of Missouri-Kansas City School of Medicine, Kansas City, MO

2019 PMF Division Executive Board:

Chair

Alison Woodworth, PhD

Chair Elect

Angela Ferguson, PhD

Past Chair

Shannon Haymond, PhD

Members At Large

Joseph Wiencek, PhD

Amy Karger, PhD

Jane Dickerson, PhD

Mark Kellogg, PhD

Secretary

Christina Lockwood, PhD

Treasurer

Amy Pyle-Eiola, PhD

Webmaster

Olajumoke Oladipo, PhD

Newsletter Editor

Van Leung-Pineda, PhD

Newsletter Editorial Board

Brenda Suh-Lailam, PhD

Kelly Doyle, PhD

Fellow Representative

Laura Smy, PhD (July 2018-July 2019)

Erin Schuler, PhD (July 2019-July 2020)

