

Impact of Renal Function Tests on Critical Care

**Refining Point of Care Testing Strategies for
Critical and Emergency Care**

**Quebec City, Quebec, Canada
September 28-30, 2006**

Renal Function Testing in Critical Care

- **Introduction**
- **Acute Renal Failure**
 - **Implications in critical care**
 - **Defining acute renal failure**
- **Laboratory assessment of acute renal failure**
 - **Creatinine and creatinine-based assessment**
 - **Cystatin C**
 - **Urine markers of renal injury**

Why Measure Renal Function?

- **Screening/ Disease Detection**
- **Disease or Medical Condition Monitoring**
- **Determining Need for Renal Replacement Therapy**
- **Drug Dosage Adjustment**

Laboratory Measurement for Clinical Kidney Disease

What do we measure?

- Estimation of GFR
- Assessment of Proteinuria or other urine markers of renal injury
- Functional assessment of renal function (e.g. Fractional excretion of sodium)
- Urine volume

Acute Renal Failure

- Characterized by deterioration of renal function over a period of hrs to days.
- Wide spectrum of associated conditions
- Mortality rate hasn't decreased significantly over the past 50 yrs.
- Mortality
 - **24-100% in postoperative renal failure**
 - **50-70% in intensive care who require dialysis**
- Acute renal injury is a continuum.

Beginning and Supportive Therapy for the Kidney (BEST) Study

- Prospective multicenter observational study of 29,269 critically ill ICU patients
- ARF defined as oliguria and/or BUN > 84mg/dl (>30mmol/L)
- Incidence of ARF = 5.7%; 2/3 required dialysis
- Septic shock most common contributing factor
- 30% had pre-existing renal dysfunction
- Overall mortality associated with ARF = 60.3%

Limitations in Effective Therapy of Patients with Acute Renal Failure

- **Prevention and dialysis**
- **Barriers:**
 - **Patient and disease heterogeneity**
 - **Risk factor adjustment**
 - **Early diagnosis**
 - **Quantification of ARF severity**
 - **Inability to evaluate early response**
- **Need: Rapid diagnostic tests (for therapeutic studies as well as clinical care)**

Acute Renal Failure

Definitions

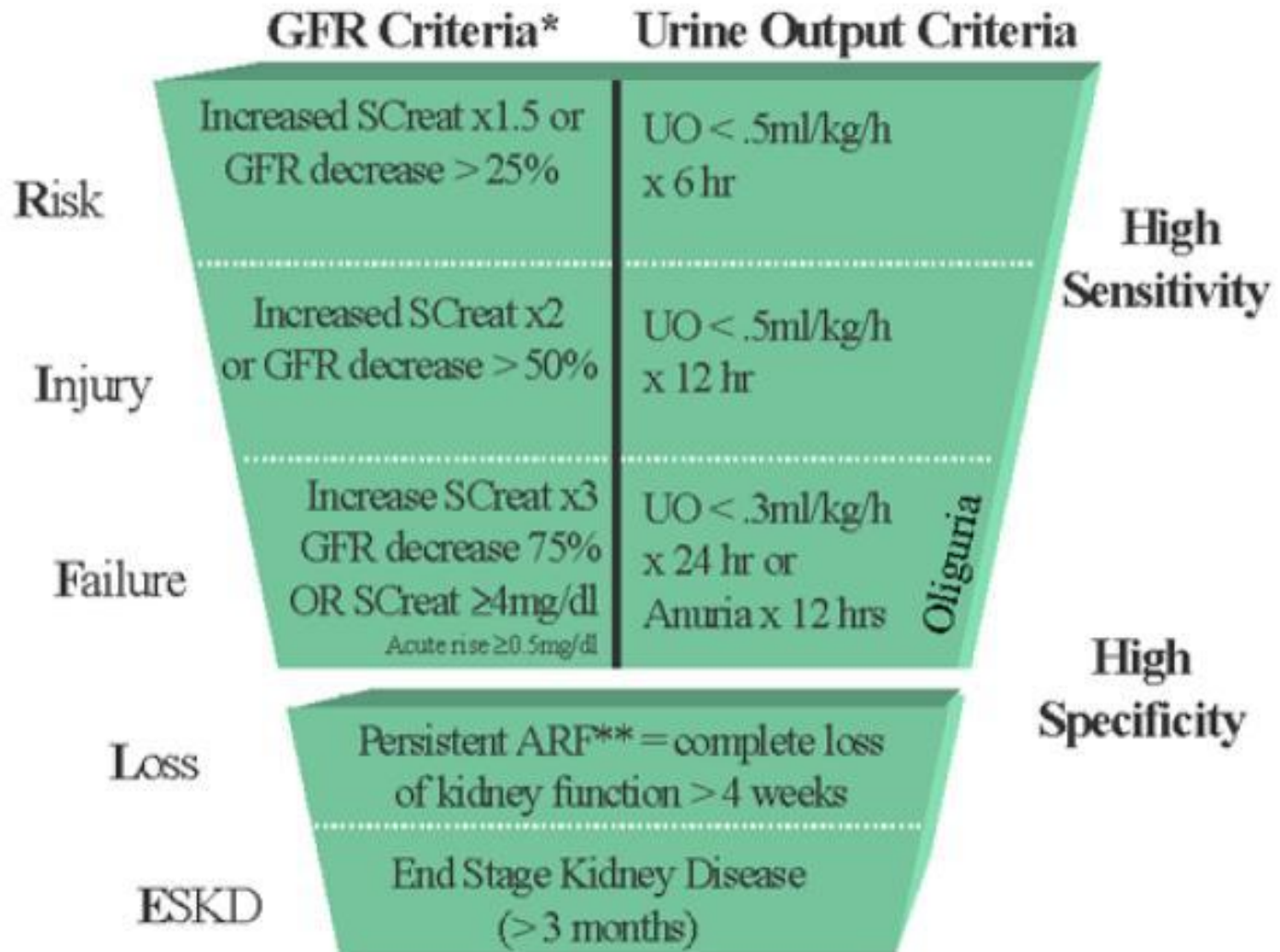
- An abrupt decrease in renal function sufficient enough to result in retention of nitrogenous waste and disrupt fluid and electrolyte homeostasis.
- Increase in creatinine ≥ 0.5 mg/dl within 48 hours of inciting event
- 50% increase to at least SCr of 2.0 mg/dl
- Others.....

Defining Stages of Chronic Renal Disease

Stage	Description	GFR (ml/min/1.73m²)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 (or dialysis)

K/DOQI Clinical Practice Guidelines on Chronic Kidney Disease

RIFLE



Critical Care

Impact of RIFLE criteria on Patient Outcome

- 5,383 intensive care unit patients
- 67% developed acute renal injury
- Maximum RIFLE classification:
 - R 12% Mortality: 8.8%
 - I 27% Mortality: 11.4%
 - F 28% Mortality 26.3%
- More than 50% progressed from 'R' to 'I' or 'F'
- Progressors had worse outcomes than non-progressors

Hoste et al. Critical Care 10:R73, 2006

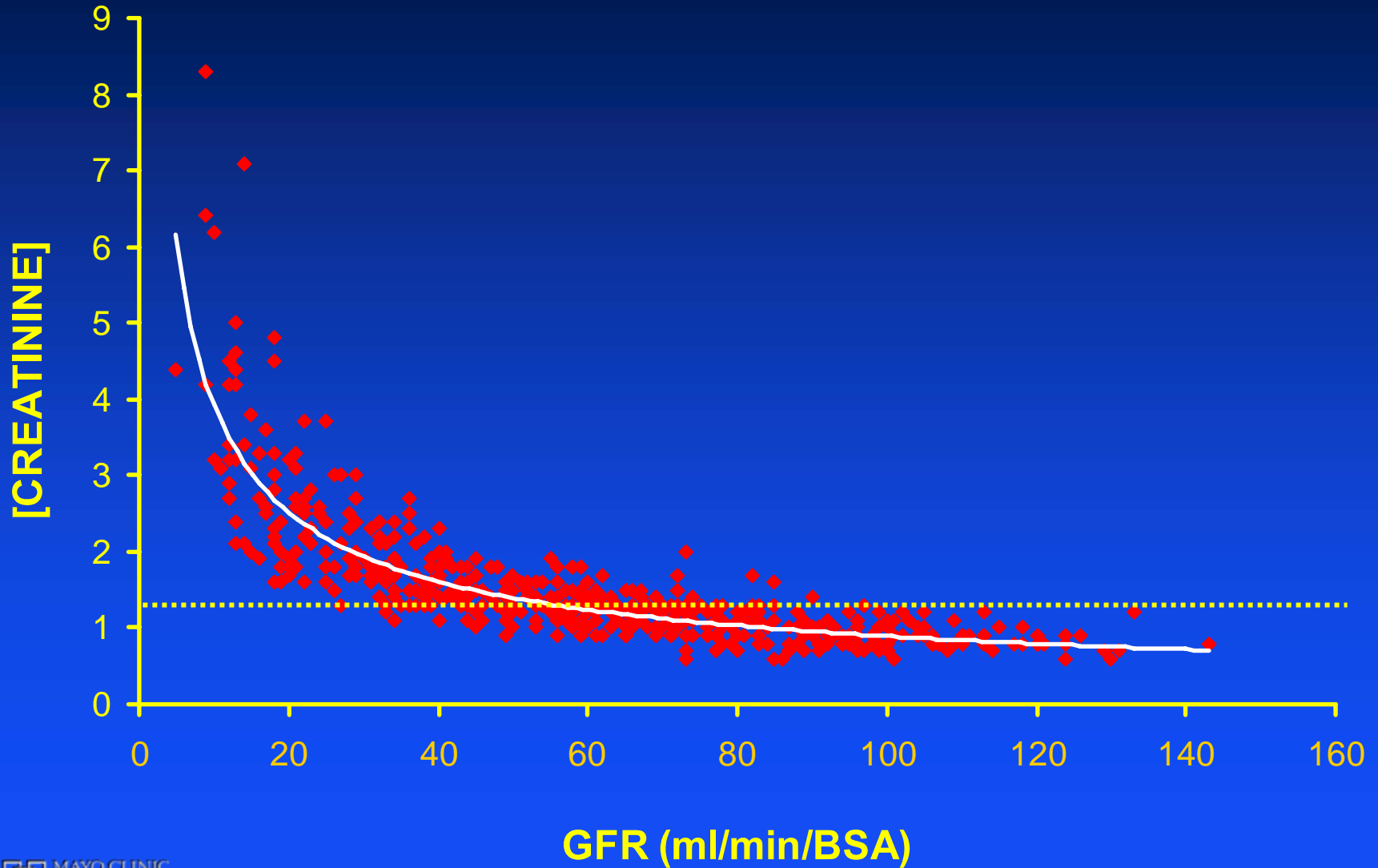
Assessment of GFR

- Inulin Clearance
- Isotopic Clearance
 - ^{125}I -iothalamate ^{51}Cr -EDTA $^{99\text{m}}\text{Tc}$ -DTPA
- Nonisotopic Clearance
 - Iohexol Iothalamate
- Creatinine
- Creatinine Clearance
- Prediction equations
- Cystatin C

Pitfalls in Measurement of GFR in ARF

- **Insensitivity of creatinine to changes in GFR**
- **Equilibration time for creatinine**
 - **Dependent on volume of distribution**
 - **Dependent on production rate**
 - **Tubular secretion of creatinine**
 - **Dependence on muscle mass (equations only roughly adjust for this)**

CREATININE



Assessing Renal Function

Limitations of Creatinine

- Insensitive to early changes in GFR
- Affected significantly by muscle mass
- Does not accurately reflect GFR in nonsteady conditions
- Analytical interferences
- Additional factors can affect production rates (e.g. trauma, steroids, liver disease, etc)

Estimating GFR

- **Cockcroft-Gault Equation**

$$\frac{(140 - \text{Age}) \times \text{Wt}(kg)}{72 \times \text{Cr}} \quad (\text{X } 0.85 \text{ if female})$$

- **MDRD equation**

$$186 \times \text{Cr}^{-1.154} \times \text{Age}^{-0.203} \quad (\text{X } 0.742 \text{ if female})$$

(X .192 if African Amer.)

Clinical Situations in Which Clearance Measures May be Necessary to Estimate GFR

- *Extremes of age and body size*
- *Severe malnutrition or obesity*
- Disease of skeletal muscle
- Paraplegia or quadraplegia
- *Prolonged fasting or non-protein nutrition*
- *Rapidly changing kidney function*
- *Prior to dosing drugs with significant toxicity that are excreted by the kidneys*
- Evaluation of potential kidney donors
- Evaluation of patients receiving maintenance corticosteroids
- *When precise measure of GFR > 60 ml/min is required*

Estimating GFR Rapidly and Accurately

- Preexisting renal disease is a known risk factor for worsening renal function
- Extent of decline in GFR correlates with appearance of oliguria
- Those with most impaired hemodynamics have the least long-term potential for recovery of renal function
- Current estimates of GFR are limited to detecting GFR < 60 ml/min
- Estimates of GFR have large confidence intervals

When is rapid assessment of renal function important in critical care

- Emergency angiography (coronary or otherwise)
- Emergency dosing of drugs with narrow therapeutic window
- Severe CHF or volume overload condition
- Severe hyperkalemia

Importance of harmonization between POCT and central laboratory

- GFR is inversely related to serum creatinine
- Therefore, differences in creatinine at the 'low' end will affect estimated GFR to a greater extent than creatinine differences at the 'high' end.
 - **Creat = 1.3; GFR = 60 ml/min/SA**
 - **Creat = 1.6; GFR = 47 ml/min/SA**
 - **Creat = 3.9; GFR = 17 ml/min/SA**
 - **Creat = 4.2; GFR = 15 ml/min/SA**

**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**
Kost et al. Crit Care Med, 2000

- **4 Medical Centers in U.S.**
- **710 critically ill patients**
- **POCT in ER and OR**
- **Creatinine measured in whole blood using
creatinine substrate-specific electrode
(enzymatic)**

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

Kost et al. Crit Care Med, 2000

- **Creatinine method comparison:**

- Slope = 0.91 - 1.22; y-intercept = -0.07 - 0.15; $r^2 = 0.77 - 1.00$

- **POCT Performance:**

- As performed by ER or OR personnel
- Slope = 0.97 - 0.98; y-intercept = 0.01 - 0.03; $r^2 = 0.98 - 1.00$

Comparability of POC whole-blood electrolyte and substrate testing using a Stat Profile Critical Care Xpress analyzer and standard laboratory methods

Flegar-Mestric; Clin Chem Lab Med 44:898; 2006

- 70 patients in intensive care unit
- Whole blood arterial and venous serum samples
- Comparison with central laboratory analyzer
- Imprecision (CV%) was <5.7% for all analytes except creatinine (CV = 13.8% (low) and = 9.5% (high))
- Comparison: $y = 1.032x + 3.598$ ($r=0.956$)

Evaluation of the i-STAT Portable Clinical Analyzer for POCT in the intensive care units of a university children's hospital

Papadea et al. Ann Clin Lab Sci. 32:231; 2002

- Neonatal and pediatric intensive care units
- Comparison with Vitros 750 chemistry analyzer
- Reproducibility 'satisfactory' for creatinine (CV < 6.5%)
- Linearity and method comparison "clinically acceptable"
- After the PCA was implemented for clinical testing; several discrepant results of creatinine concentrations in neonatal blood samples that would have affected clinical management led to a second creatinine comparison and eventual discontinuation of the PCA creatinine assay.

POCT in an organ procurement organization donor management setting

Baier et al. Clin Transplant 17:48; 2003

- **Compared i-STAT with donor hospital lab**
- **15 consecutive donors**
- **$r = 0.95$ for creatinine**
- **More efficient fluid management of donors**
- **Savings of \$733 per case**

POCT Creatinine

- **POCT whole blood (i-STAT) vs central lab serum testing for radiology**
- **Studies**
 - **Precision**
 - **Linearity**
 - **Method Comparison**
 - **Particular emphasis on 1.5-2.0 mg/dL level**
- **Results needed**
 - **Cr within 0.2 mg/dL of central lab Cr**

POCT Creatinine

- Precision

- Low (0.7 mg/dL) CV=7.3%
- Medium (2.0 mg/dL) CV=3.1%
- High (4.7 mg/dL) CV=2.7%

- Linearity

- Measure/Expected = 94%
(range 0.4 – 15 mg/dL)

POCT Creatinine

Method Comparison

- Target sample population:
 - Mirror the “at risk” group for contrast-induced nephropathy
 - 20 patients > 70 years old
 - 20 patients with diabetes mellitus
 - 20 patients with renal insufficiency/failure

POCT Creatinine

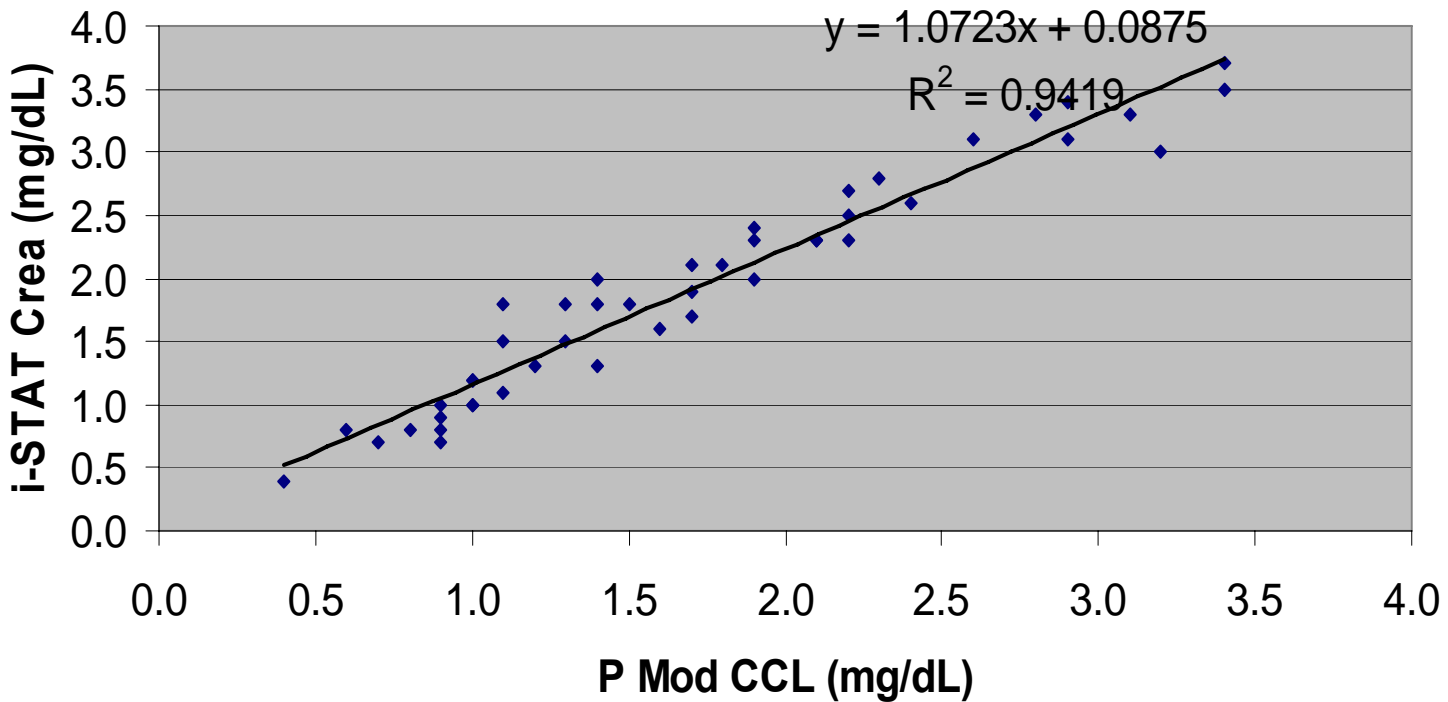
Method Comparison

- **Actual population studied**
 - **14 patients > 70 years old**
 - **13 patients with diabetes**
 - **18 patients with renal insufficiency/failure**

i-STAT Creatinine

Method Comparison

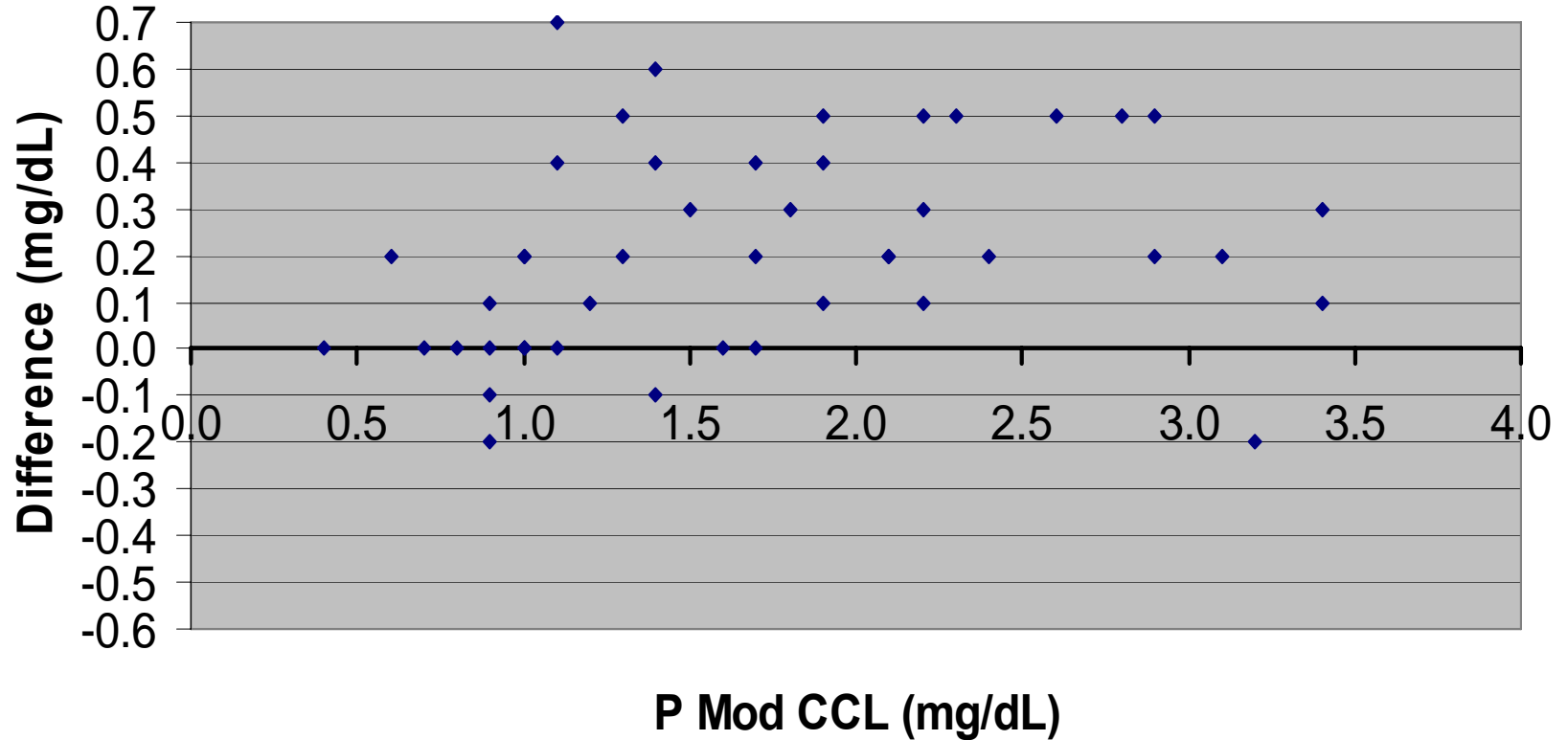
Regression Analysis



POCT Creatinine

Method Comparison

Bias Chart



POCT Creatinine Study

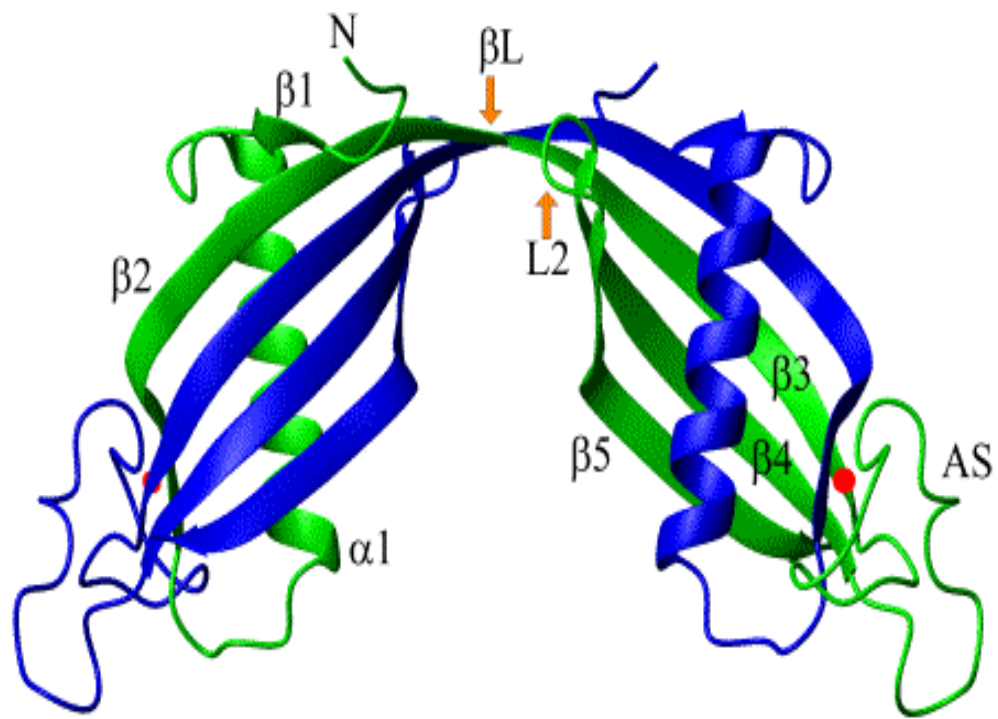
- How many patients are 1.5-2.0 on i-STAT, but normal by CCL
 - **6/21 (28.6%)**
 - **Potential for deferring contrast unnecessarily or over estimating need for preventative intervention**

POCT Creatinine

- How many will the radiologist defer for >2.0 mg/dL Cr on i-STAT where the CCL measurement will be <2.0
 - **4/9 (44.4%)**
 - **Need to compare against current radiologist deferral rate for lack of creatinine results**

POCT Creatinine

- How many samples >2.0 by CCL were >2.0 by i-STAT
 - **15/15 (100%)**
 - **Clearly at risk patients are being properly identified**



Cystatin C

Cystatin C Structure

- **13 kd non-glycosylated basic protein**
- **120 amino acids**
- **Isoelectric point 9.3**
- **Cystatin C gene on chromosome 20**
- **Housekeeping type gene**
- **A point mutation has been described: causes a hereditary form of amyloid angiopathy.**

Cystatin C

Distribution

- **Ubiquitous - Present in all investigated body fluids**
- **High concentrations in CSF and seminal fluid**
- **In blood plasma, contributes only a few percent of total cysteine protease inhibitory capacity.**

Cystatin C

Renal Handling

- **Freely filtered**
- **Metabolized by proximal tubule**
- **No tubular secretion**

Cystatin C

Measurement Methodologies

- **RIA**
- **Enzyme immunoassay**
- **Immunoturbidity (Dako)**
 - Particle-enhanced immunoassay (PETIA)
- **Nephelometry (Dade-Behring)**
 - Particle-enhanced nephelometric immunoassay (PENIA)

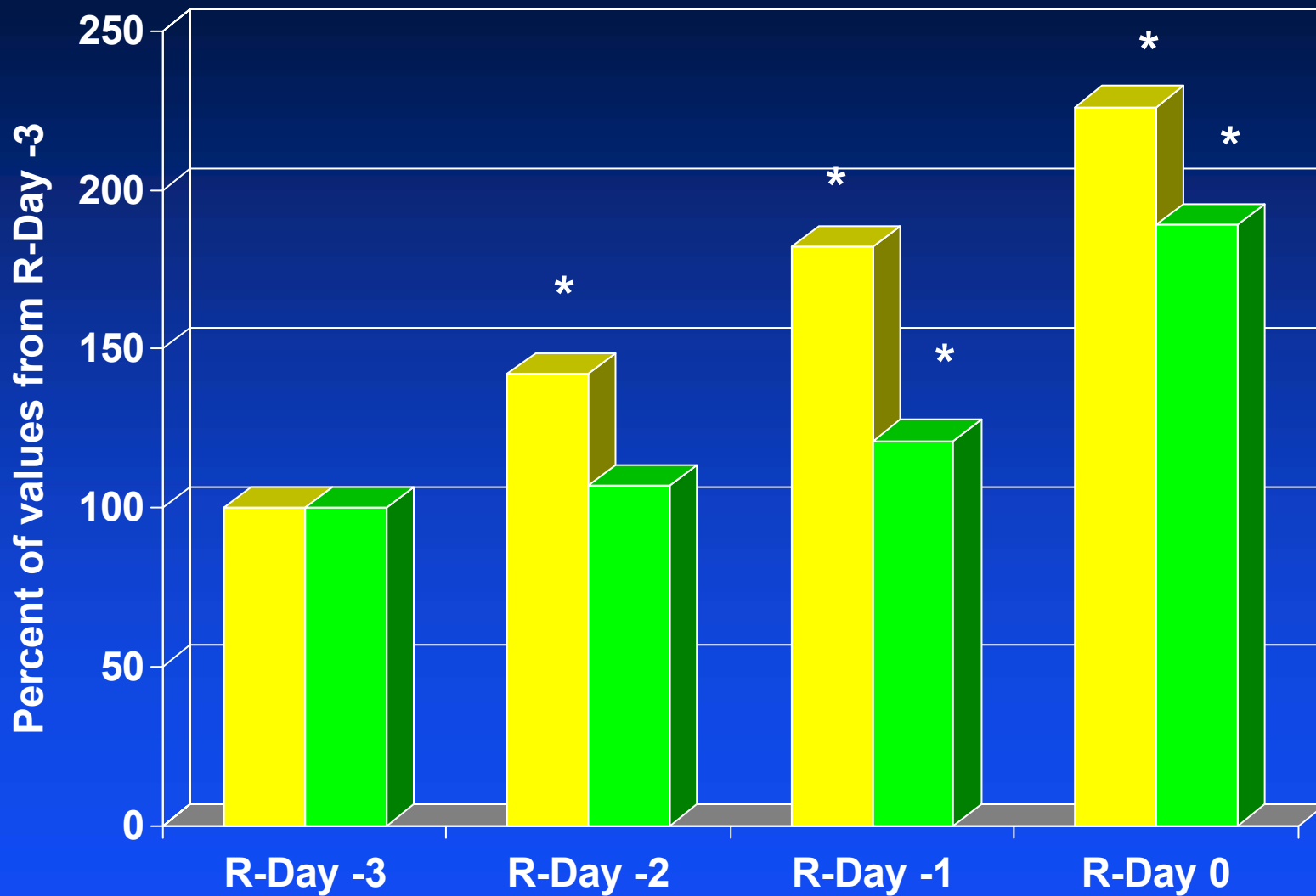
Cystatin C

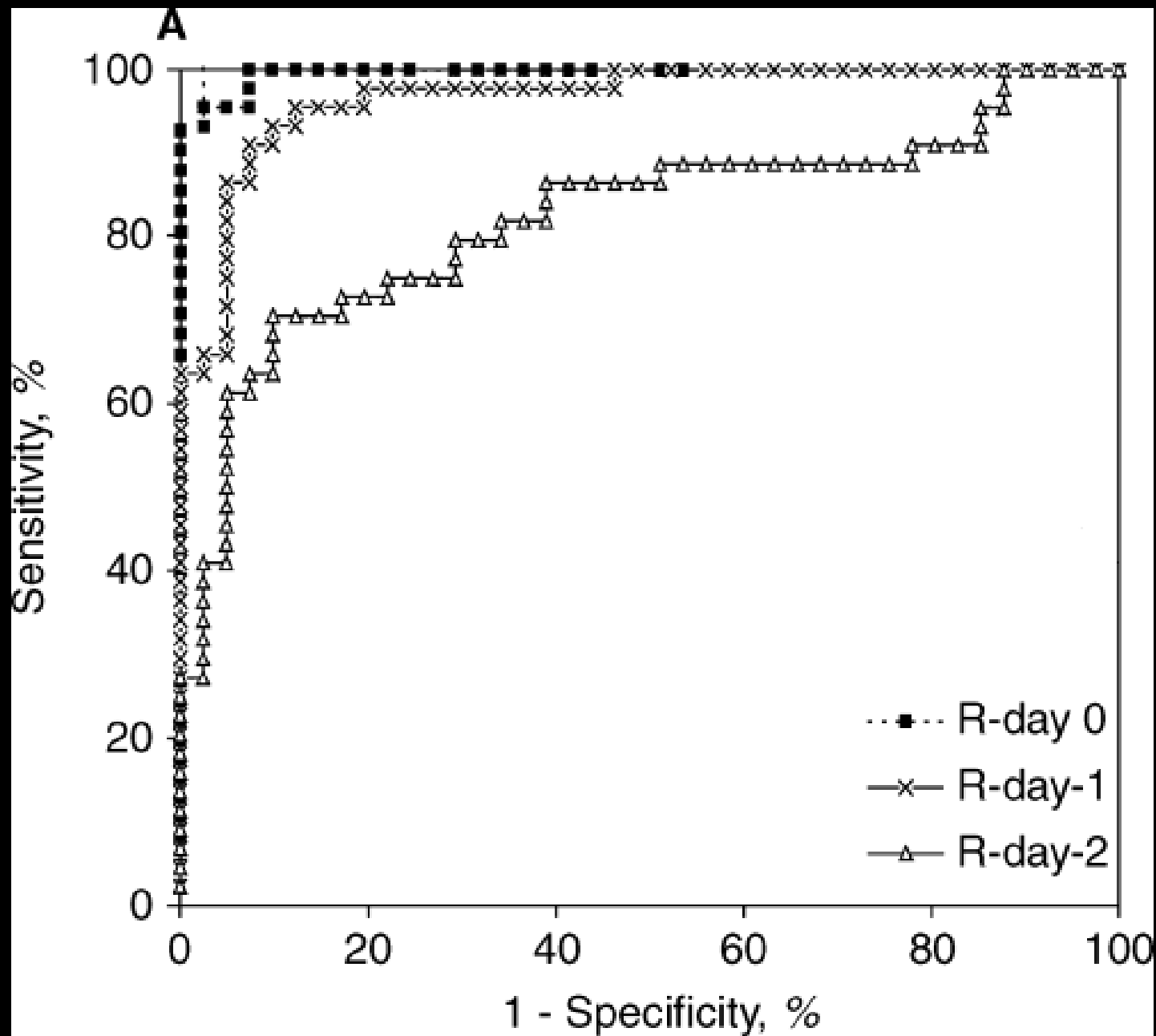
Clinical Utility

- **Multiple comparison studies**
- **Parameters compared: Correlation, ROC, Sensitivity**
- **Most cross sectional studies**
- **Nearly all show Cystatin C equal to or better than serum creatinine**

Cystatin C in Critical Care

■ Cyst C ■ Creat





Renal Failure: Differentiating Acute from Chronic

- **Carbamylated hemoglobin**
 - **Carbamylation of the terminal valine of Hb occurs in direct relationship to duration and magnitude of decrease in GFR**
 - **<80 ug carbamy valine/gram Hb: 96% sensitivity and 84% specificity for differentiating acute from chronic renal failure**

Wynckel et al. Neph Dial Trans 15:1183;2000

Assessment of Renal Function beyond GFR

Fractional Excretion of Sodium

$$FE_{Na}$$

- $FE_{Na} = ((U_{Na} \times P_{Cr}) / (P_{Na} \times U_{Cr})) \times 100$
- Useful only in setting of oliguria (U/O < 400 ml/24 hr or < 20 ml/hr)
- $FE_{Na} < 1\% \Rightarrow$ pre-renal azotemia (80% specificity)
- $FE_{Na} > 1\% \Rightarrow$ acute tubular necrosis or intrinsic renal disease
- Exceptions:
 - Diuretic use
 - Pre-existing chronic renal disease

Traditional Biologic Markers for Early Detection of ARF

Biomarker	Nephron segment
LMwt Proteins	
B2-microglobulin	Proximal tubule
Retinol binding protein	
alpha-1 microglobulin	
HMwt Proteins	
Albumin	Glomerulus
Transferrin	
Immunoglobulin	
Brush border antigens	
Adenosine deaminase binding protein	Proximal tubule
Carbonic anhydrase	
Urinary enzymes	
Neutral endopeptidase	Proximal tubule
Alanine aminotransferase	
Gamma-glutamyltransferase	
N-acetyl-B-D-glucosamine	
B-glucosidase	
Others	
Tamm-Horsfall glycoprotein	Distal tubule

Adapted from Han and Bonventre Curr Opin Crit Care 10:476;2004

New Biologic Markers for Early Detection of ARF

Biomarker	Associated Injury
KIM-1	Ischemic ATN; nephrotoxins
NGAL	Ischemic ATN; nephrotoxins
NHE3	Ischemic ATN; prerenal and post renal
Cytokines (IL-6, IL-8, IL-18)	AKI; delayed graft function
Actin	Ischemic ATN; delayed graft function
Cystatin C	Proximal tubule injury

N-acetyl- β -glucosaminidase (NAG)

- Enzyme located in brush borders of nephron
- Most studies suggest levels are not sensitive or specific enough to warrant routine use

Neutrophil Gelatinase-Associated Lipocalin (NGAL) (1)

- Gene expression upregulated >10X early after ischemic renal injury (mouse)
- Protease resistant
- 25-kD protein covalently bound to gelatinase from human neutrophils
- Located in proliferating cell nuclear antigen-positive proximal tubule cells (?endosomes)

Neutrophil Gelatinase-Associated Lipocalin (NGAL) (2)

- Readily detected in first urine output after ischemia in both mouse and rat models of ARF
- Rate of appearance precedes other markers (N-acetyl-B-D-glucosaminidase and B2-microglobulin)
- May represent an early, sensitive noninvasive urinary biomarker of ischemic and nephrotoxic renal injury

Kidney Injury Molecule-1 (KIM-1)

- **Adhesion molecule involved in renal regeneration**
- **Upregulated 24-48 hr after initial insult (rat model of ischemia)**
- **Detectable in kidney biopsy and urine of patients with ischemic ATN**

Urine Na/H exchanger isoform 3 (NHE3)

- Is the most abundant apical sodium transporter in the renal tubule
- Localized in the apical membrane of renal proximal tubular and thick ascending limb cells.
- Is not detected in the urine of normal individuals.

Urine Na/H exchanger isoform 3 (NHE3) cont'd

- Detected in membrane fractions from patients with prerenal azotemia, postrenal ARF and ATN.
- Not seen in other intrinsic causes of AKI such as transplant rejection, primary GN, interstitial and inflammatory nephritis.
- Levels are much higher in patients with severe AKI – no overlap between prerenal azotemia and ATN groups, therefore may be useful in differentiating prerenal azotemia from other causes of AKI.

Urinary cytokines

- Inflammation plays an important role in the pathophysiology of AKI associated with ischemia, sepsis, and many nephrotoxicants.
- AKI is associated with increased production of proinflammatory and anti-inflammatory cytokines.
- IL-6 is a predominant cytokine in the kidney (26-kDa glycoprotein).

Urinary cytokines cont'd

- **IL-6: early marker for acute renal allograft rejection and might predict sustained ATN after renal transplantation.**
- **IL-8: 8-kDa chemokine whose production is implicated in various glomerular diseases and acute pyelonephritis.**
- **IL-18: significantly increased in ischemic ATN and increases within 24 hours after kidney transplantation in patients with delayed allograft dysfunction.**

Urinary actin

- **Actin is the most abundant cellular cytoskeletal protein.**
- **Damage to the actin cytoskeleton has been identified in various animal and tissue culture conditions after ischemia or ATP depletion.**
- **Actin is elevated after transplantation in those individuals destined to develop sustained renal failure and may reflect overall cellular damage in the kidney.**

Urinary glutathione-S-transferases (GSTs)

- Soluble cytosolic enzymes in the proximal tubule (α subtype) and distal tubule (π subtype).
- Participate in detoxifying many compounds.
- Presence in the urine has been measured in different forms of renal injury.
- Renal transplant patients --- π GST in acute rejection; α GST in CSA toxicity. Transplant ATN had elevations in both isoforms.
- Increases occur 1 to 2 days before sCr increased.

What is needed?

- **Identify biomarkers that distinguish ATN from other causes of ARF**
- **Develop early or 'real-time' markers of acute renal dysfunction**
- **Apply electronic or other means to notify clinicians of modest decreases in renal function (increases in creatinine) to encourage early evaluation**

Summary

- Acute renal failure is common in critical care situations and is associated with significant morbidity and mortality
- The RIFLE Classification provides standardization for acute renal failure
- Early detection of acute renal failure or acute renal injury is desirable
- Creatinine remains the mainstay for detecting acute renal failure
- There are several potential new markers of renal injury that are in need of rigorous clinical validation

Thank you

Prediction of ARF by “bedside formula” in medical and surgical intensive care patients

Coritsidis et al; Renal Failure; 22:235; 2000

- Prospective study of 115 consecutive medical ICU patients and 123 patients in surgical ICU
- Empiric formula using serum albumin, urine osmolality and presence of sepsis
- ‘Bedside formula’ was more accurate than APACHE II in predicting ARF in medical but not surgical ICU.