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Marrying Structure with Function: The Impact of Novel Renal Biomarkers on Drug Therapy Use

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Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

Learning Objectives

- Identify limitations of existing renal biomarkers
- Explain a method for using cystatin C, to improve medication dosing

Ideal Renal Biomarker

- Easily, rapidly and inexpensively measured
- Detect kidney damage or decreased GFR to a greater degree than current clinical models
- Specific and unaffected by other diseases
- Present early in the course of the disease
- Proportional response to disease severity

Existing Biomarkers

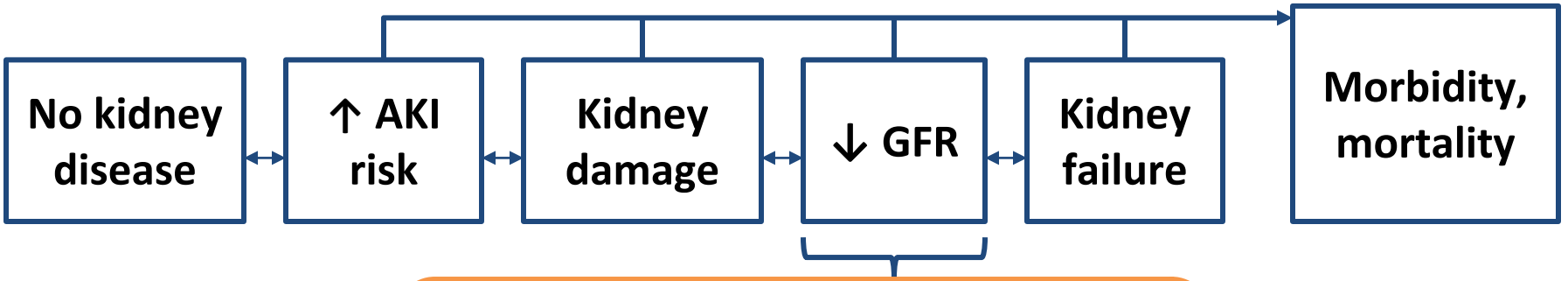
Urine output

- Relatively easy to measure
- Issues when not strict I/O
- Affected by diuretics and hypovolemia
- Qualitative rather than quantitative
- Delayed response

Serum creatinine

- Relatively easy to measure
- Widely available and integrated into care
- Numerous non-renal confounders (e.g. skeletal muscle mass, diet)
- Delayed response

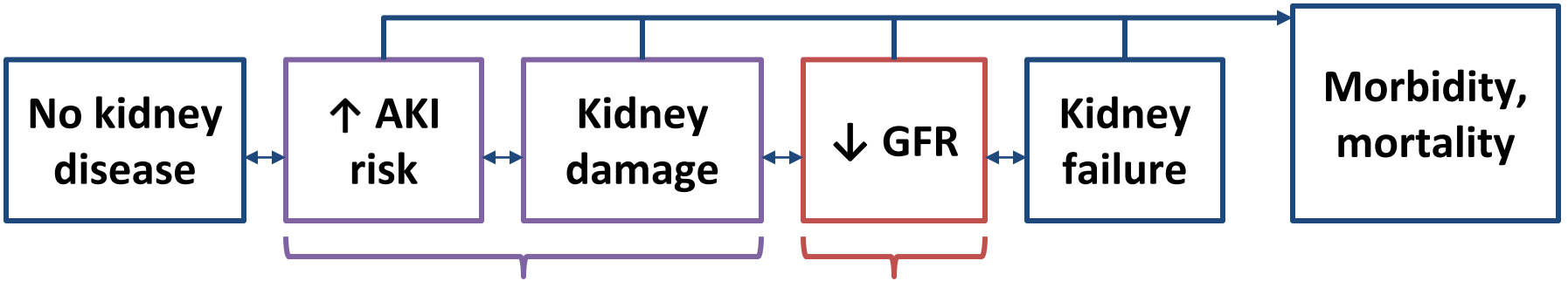
Spectrum of Kidney Disease



Need for new biomarkers to:

- **Better estimate GFR for dosing**
- **Facilitate earlier detection of AKI**

Classes of Novel Biomarkers



Measured GFR

- Generally considered the “gold” standard
- Exogenous compound that is filtered, not secreted/reabsorbed and quantitate its elimination (e.g. inulin, iothalamate, iohexol)
- Single moment in time, often requires urine collection
- Back leak from tubules in AKI
- Generally reserved for research and outpatient use

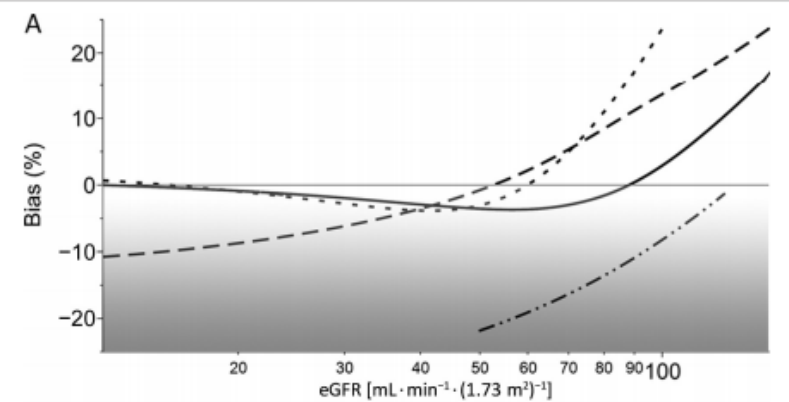
Functional Markers for eGFR

Attributes	Ideal	SCr	CysC
Endogenous	✓	✓	✓
Easily, rapidly, inexpensively measured	✓	✓	✓
Detects even small GFR changes	✓	?	✓
Quick response to changing GFR	✓	✗	?
Few confounders	✓	✗	?

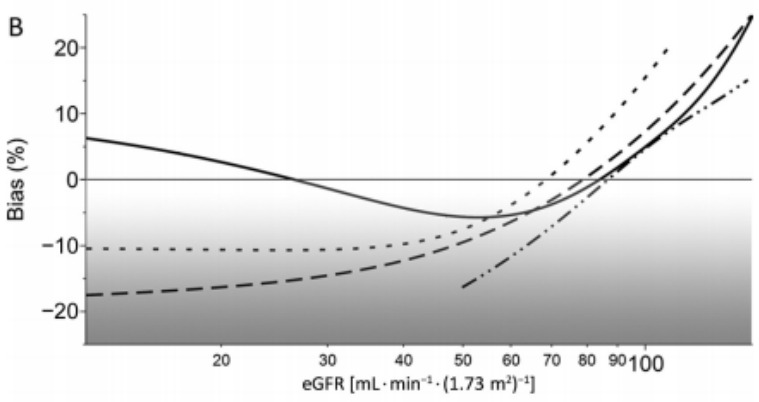
GFR: Glomerular filtration rate; SCr: Serum creatinine; CysC: Cystatin C

Levey A. *Clin Pharmacol Ther*; 2017:102(3):405-419.

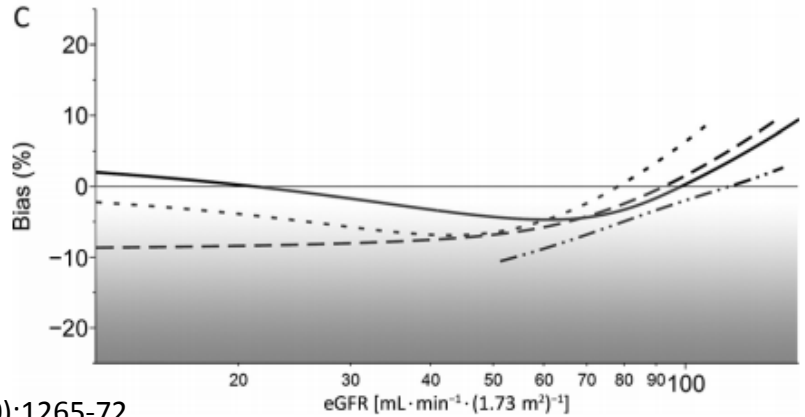
SCr eGFR vs mGFR



CysC eGFR vs mGFR



SCr and CysC eGFR vs mGFR



Meeusen JW, et al. *Clin Chem* 2015;61(10):1265-72.

Medication Use and CysC

Studied Medications	No. of Studies	Renal Elimination (%)
Vancomycin	7	>80
Arbekacin	1	~50
Amikacin	1	68-80
Cefuroxime	1	>90
Carboplatin	2	96
Topotecan	1	~50
Digoxin	3	79-83

Brou N, et al. *Br J Clin Pharmacol* 2015;80(1):20-27.

Vancomycin Use and CysC

Ref.	N	eGFR Equation	
		SCr	CysC
[1]	65	UCrCl	Flodin
[2]	165	CG	Hoek
[3]	25	CG	Hoek
[4]	18	CG, MDRD	Rule, Hoek
[5]	24	CG	Larsson
[6]	678	CG	-
[7]	37	Many	CKD-EPI
[8]	130	CG	Larsson

Findings

- Heterogeneity in equations
- CysC associated vancomycin level and drug clearance
- Drug clearance better predicted by CysC than SCr in most studies
- SCr and CysC not evaluated in combination
- Limited bedside applicability, more simulated models and population studies

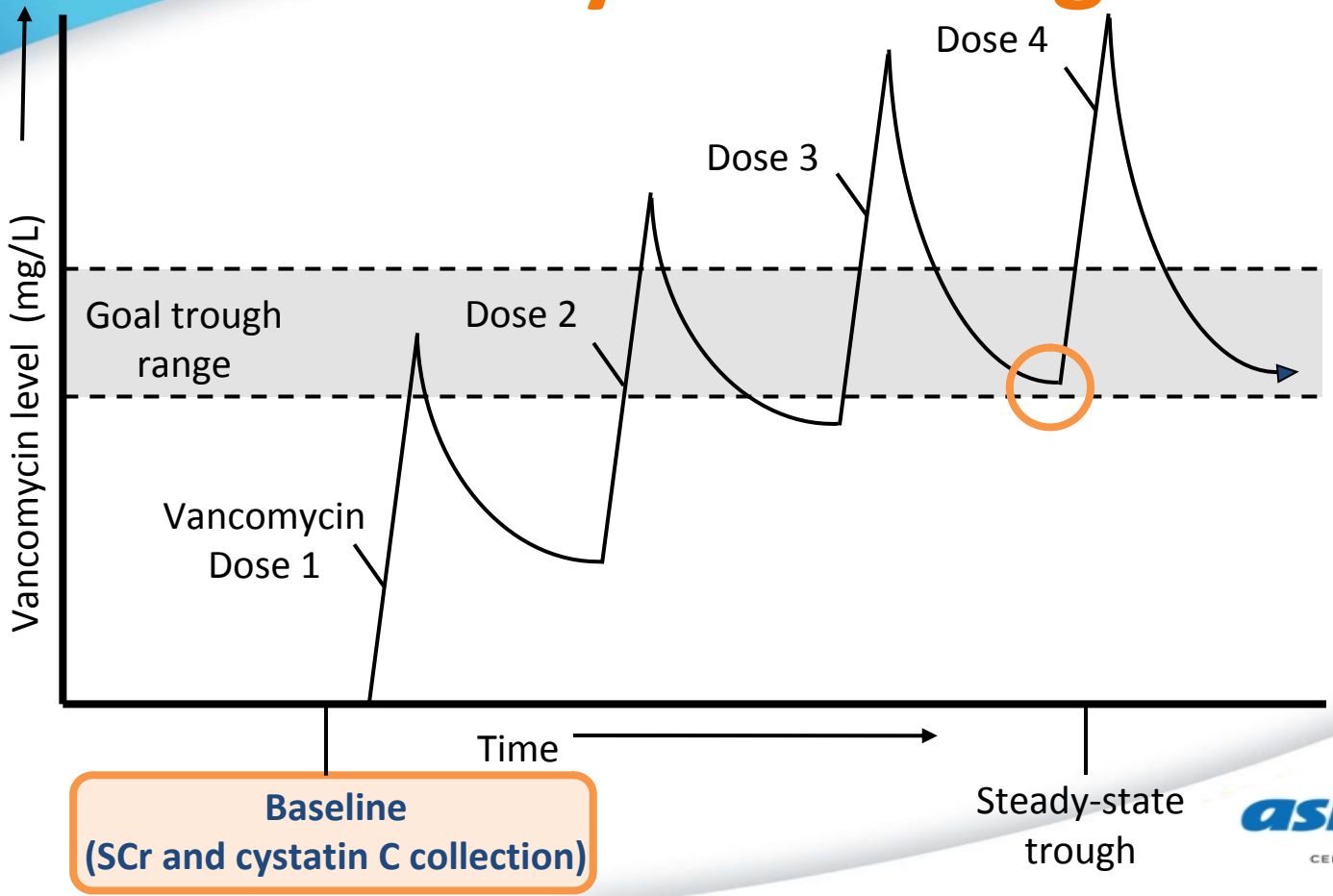
[1] Chen Y, et al. *Int J Clin Pharmacol Ther* 2013;51
[2] Tanaka A, et al. *Ther Drug Monit* 2007;29
[3] Kees MG, et al. *Int J Antimicrob Agents* 2010;36
[4] Suzuki A, et al. *J Pharm Pharmacol* 2010;62
[5] Okamoto G, et al. *Clin Biochem* 2007;40
[6] Chung JY, et al. *J Korean Med Sci* 2013;28
[7] DeCarolis DD, et al. *Ther Drug Monit* 2014;36(5)
[8] Hermida J, et al. *Ther Drug Monit* 2006;28(3)

Vancomycin Dosing at Mayo

- Establish target for source of infection (10-15 or 15-20 mcg/mL)
- Maintenance dose: 15-20 mg/kg
  - 20-25 mg/kg loading dose could be considered
- Interval

CrCl (mL/min)	Dosing Interval (hours)
≥ 90	q8 hours
70-90	q12 hours (q8h if target 15-20 mcg/mL)
35-69	q24 hours (q12h if severe infection)
21-34	q48 hours (q24h if severe infection)

Vancomycin Dosing



Multivariate Models

CrCl with Cockcroft-Gault Model	R^2	Predicted Trough Achievement
• Pre-trough total dose • Dosing interval • CrCl (mL/min)	0.269	33 (26-40%)

CKD $EPI_{Cr\text{-}CysC}$ Model	R^2	Predicted Trough Achievement
• Pre-trough total dose • Dosing interval • CKD-$EPI_{Cr\text{-}CysC}$ (mL/min)	0.580	54 (45-61%)

Frazee E, et al. *Crit Care* 2014;18(3):R110.

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New Nomogram

		Goal 10-15 mg/L			Goal 15-20 mg/L	
		eGFR (CKD-EPI$_{cr\text{-}cys}$ mL/min)				
		60-69	70-79	80-89	90-99	100-109
Weight (kg)	70-79	1500 q24	800 q12	1000 q12	1200 q12	800 q8
		1200 q12	1350 q12	1000 q8	1200 q8	1400 q8
	80-89	1500 q24	800 q12	1000 q12	1200 q12	800 q8
		1200 q12	1350 q12	1000 q8	1200 q8	1400 q8
	90-99	1500 q24	1700 q24	1000 q12	1200 q12	1350 q12
		1200 q12	1350 q12	1000 q8	1200 q8	1400 q8

New Nomogram: Candidacy

Inclusion

- ≥ 18 years
- Hospitalized in one of three ICUs under evaluation
- Prescribed intravenous vancomycin
- Consistent regimen planned with 8, 12, or 24 hour dosing interval

Exclusion

- > 1 dose before ICU admission
- GFR < 20 mL/min
- Dialysis-dependent
- Inappropriate candidate for scheduled dosing (i.e. AKI)
- Weight < 40 kg
- BMI > 40 kg/m^2

Frazee E, et al. *Am J Kidney Dis* 2017;69(5):658-66.

Implementation Logistics

Patient eligibility and need for first vancomycin dose assessed

CysC added to stored serum or drawn

Pharmacist-directed dosing and communication

Steady state level checked

De-escalation and adjustments per usual practice

Frazee E, et al. *Am J Kidney Dis* 2017;69(5):658-66.

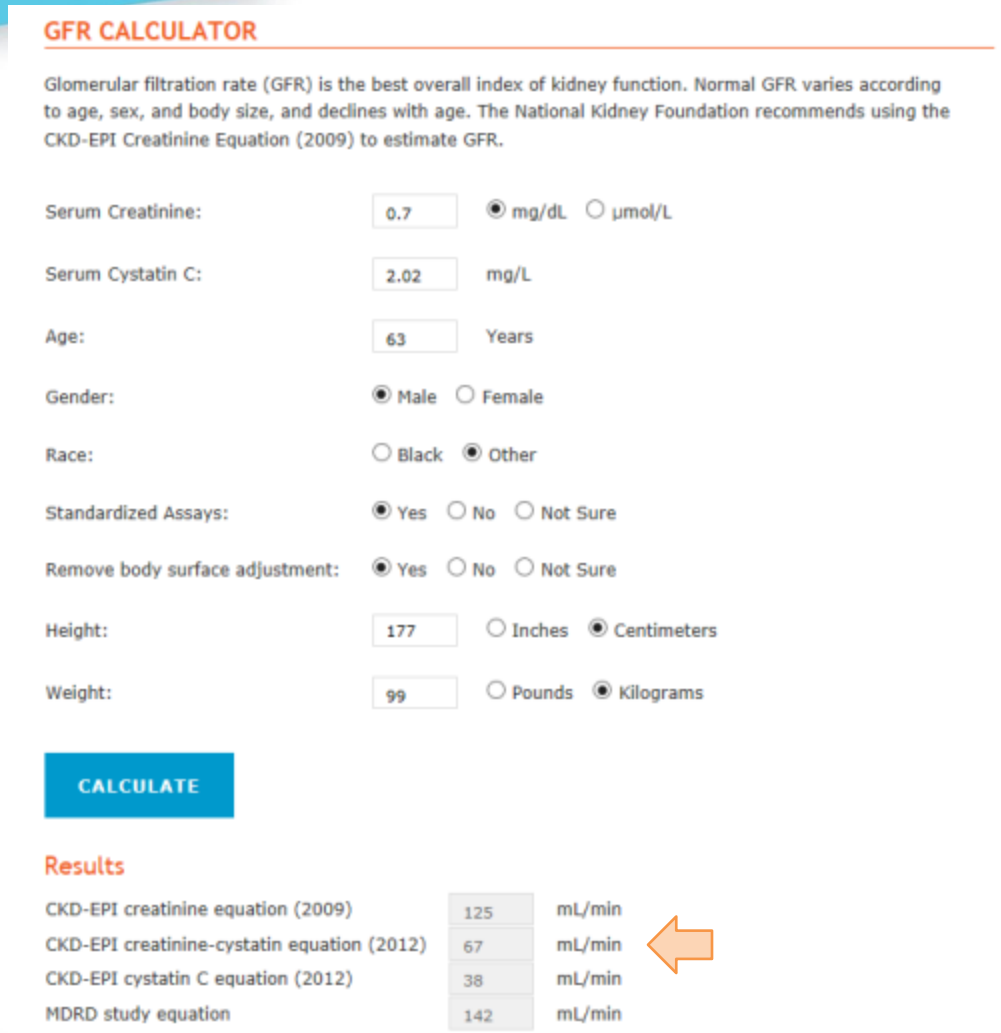
Patient Example

- 63yo white male, 99 kg, BMI 31.6 kg/m^2
  - Goal trough 15-20 mcg/mL (pneumonia)
  - SCr 0.7 mg/dL, $CrCl_{Cockcroft\text{-}Gault}$ = 151 mL/min
  - Corresponding dose: 15-20 mg/kg q8h (1500-2000 mg q8h)
  - Observed trough: **29.7 mg/L**

Frazee E, et al. *Am J Kidney Dis* 2017;69(5):658-66.

Example Case

- 63yo white male, 99 kg, BMI 31.6 kg/m^2
  - SCr 0.7 mg/dL
  - Cystatin C 2.02 mg/L
- CKD EPI$_{cr\text{-}cysC}$ 67 mL/min
- New dose: **1200 mg q12h**



GFR CALCULATOR

Glomerular filtration rate (GFR) is the best overall index of kidney function. Normal GFR varies according to age, sex, and body size, and declines with age. The National Kidney Foundation recommends using the CKD-EPI Creatinine Equation (2009) to estimate GFR.

Serum Creatinine:	0.7	◉ mg/dL ○ µmol/L
Serum Cystatin C:	2.02	mg/L
Age:	63	Years
Gender:		◉ Male ○ Female
Race:		○ Black ◉ Other
Standardized Assays:		◉ Yes ○ No ○ Not Sure
Remove body surface adjustment:		◉ Yes ○ No ○ Not Sure
Height:	177	○ Inches ◉ Centimeters
Weight:	99	○ Pounds ◉ Kilograms

CALCULATE

Results

CKD-EPI creatinine equation (2009)	125	mL/min
CKD-EPI creatinine-cystatin equation (2012)	67	mL/min
CKD-EPI cystatin C equation (2012)	38	mL/min
MDRD study equation	142	mL/min

https://www.kidney.org/professionals/kdoqi/gfr_calculator

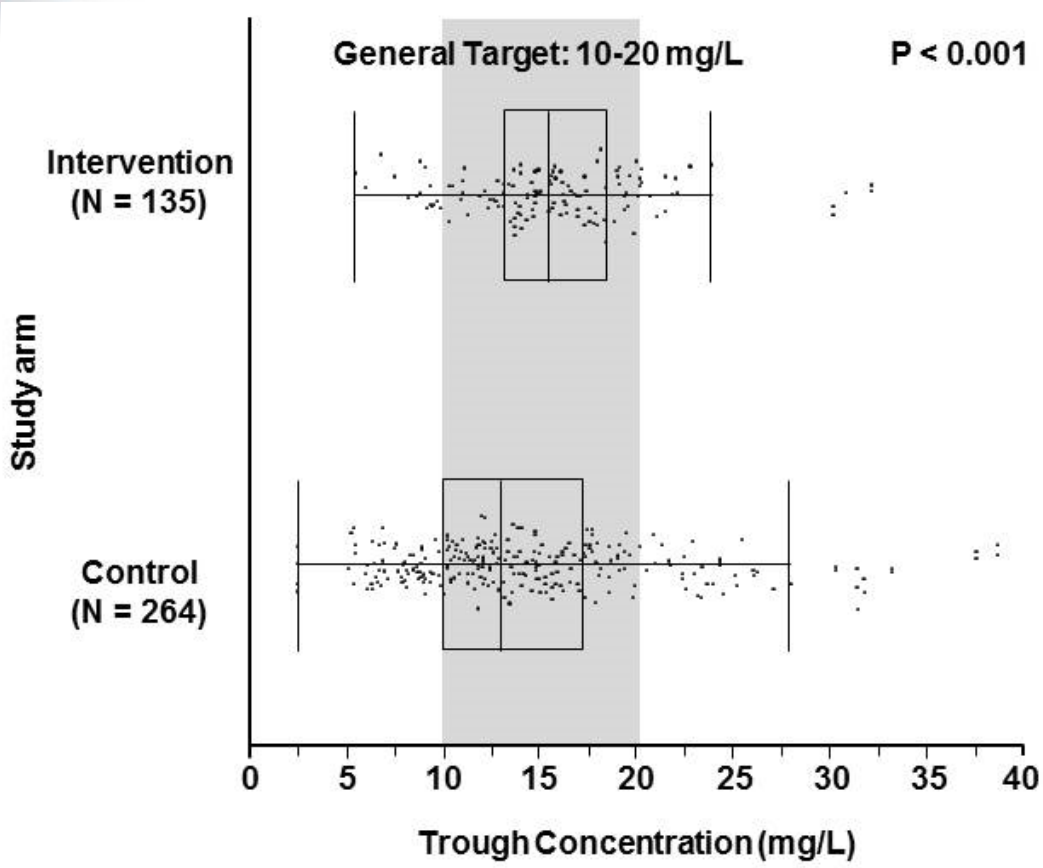
Frazee E, et al. *Crit Care* 2014;18(3):R110.

Comparative Study

- Cohort study
  - Novel dosing nomogram vs historical control with SCr dosing
- Primary endpoint
  - Initial steady state therapeutic vancomycin trough
- Secondary endpoints
  - Clinical failure, in confirmed gram-positive infections
  - ICU, hospital length of stay, 28-day mortality
  - Nephrotoxicity

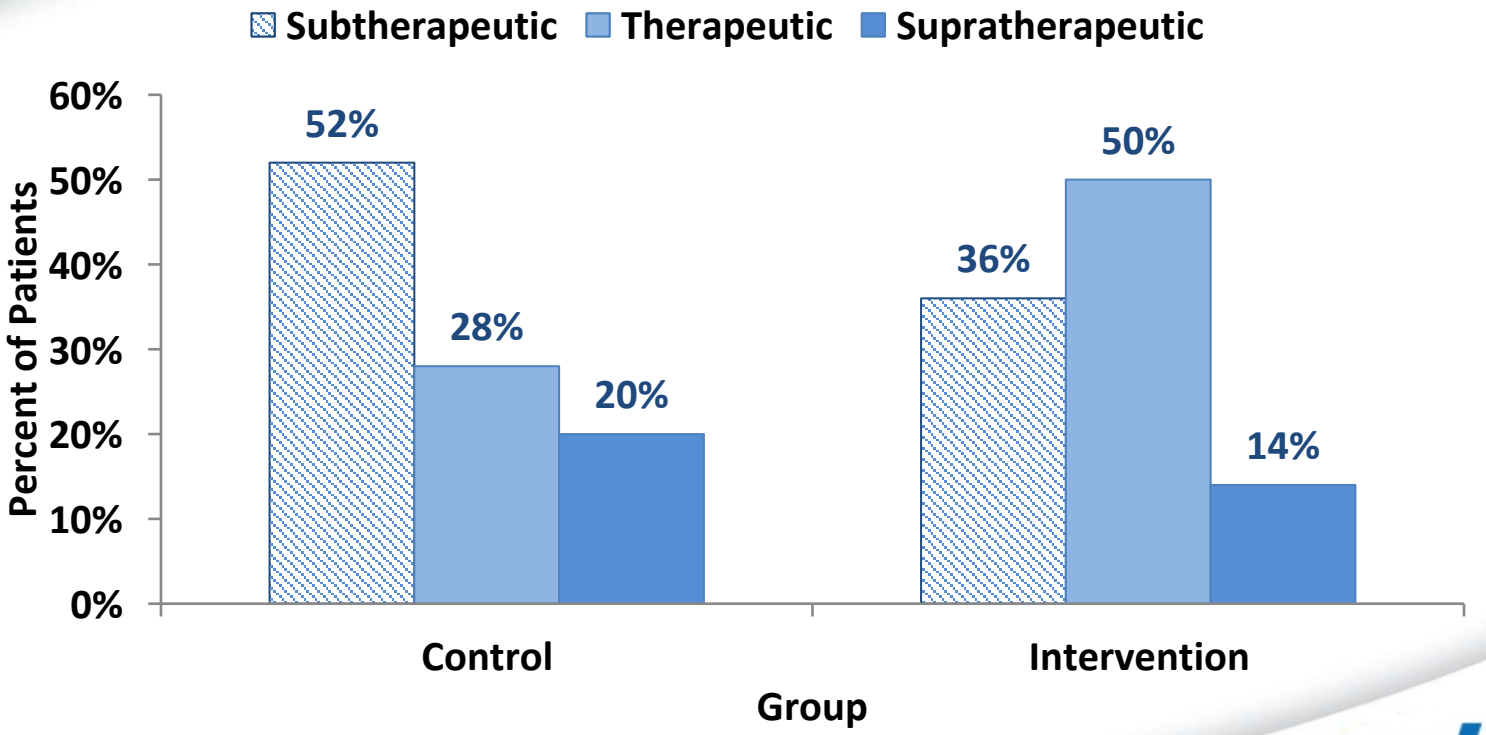
Frazee E, et al. *Am J Kidney Dis* 2017;69(5):658-66.

Trough Distribution



Frazee E, et al. *Am J Kidney Dis* 2017;69(5):658-66.

Target Achievement



Frazee E, et al. *Am J Kidney Dis* 2017;69(5):658-66.

Secondary Endpoints

Characteristic	Control (N = 264)[a]	Intervention (N = 135)[a]	P Value
Composite of nephrotoxicity or death within 7 days of vancomycin (N; %)	38 (14)	17 (13)	0.62
Treatment failure at day 7 (N; %)[b]	37 (34)	12 (29)	0.50
In MRSA patients (N; %)	8 (30)	3 (33)	1.00
Intensive care unit length of stay (days)	2.5 (1.3, 6.5)	2.9 (1.5, 6.4)	0.78
Hospital length of stay (days)	10.9 (5.6, 20.2)	10.3 (6.2, 32.0)	0.16
28-day all-cause mortality (N; %)	35 (13)	24 (18)	0.23

AKI: acute kidney injury; RRT: renal replacement therapy

[a] : Values expressed as median (IQR) unless noted

[b] : N (%) of the 150 individuals (Control: N = 108; Intervention: N = 42) with confirmed gram-positive infections

Frazee E, et al. *Am J Kidney Dis* 2017;69(5):658-66.

Pearls and Key Takeaways

- SCr and UOP have numerous limitations as renal biomarkers
- Operationalizing anything other than SCr-based renal dosing is a multidisciplinary effort
- Automation where possible (lab draw, calculations, resultant dose)
- NKF Calculator can be used to calculate CKD $EPI_{cr\text{-}cysC}$ eGFR (mL/min)
- Drug specific dosing models are needed rather than blind application of a different eGFR formula
- No GFR estimate should replace good clinical judgement

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Marrying Structure with Function: The Impact of Novel Renal Biomarkers on Drug Therapy Use

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Objectives

- Summarize the role for structural biomarkers for the early detection of drug-induced kidney disease (DIKD).
- Explain the application of the structural biomarkers currently available in the United States.

Structural Biomarkers

- Damage biomarkers
  - Indicate injury or at least cellular distress
- Proteins
  - Synthesis is upregulated during AKI
  - Molecules released from injured or distressed cells
  - Byproducts whose filtration, reabsorption or secretion are altered by kidney damage
- So, increase in biomarker concentration (blood, urine) indicative of concern

Characteristics of Structural Biomarkers

Ideal Characteristics

1. Easily measured
2. Present early in the course of the disease
3. Detect to a greater degree
4. Unaffected by other diseases
5. Proportional response to severity

Biomarkers

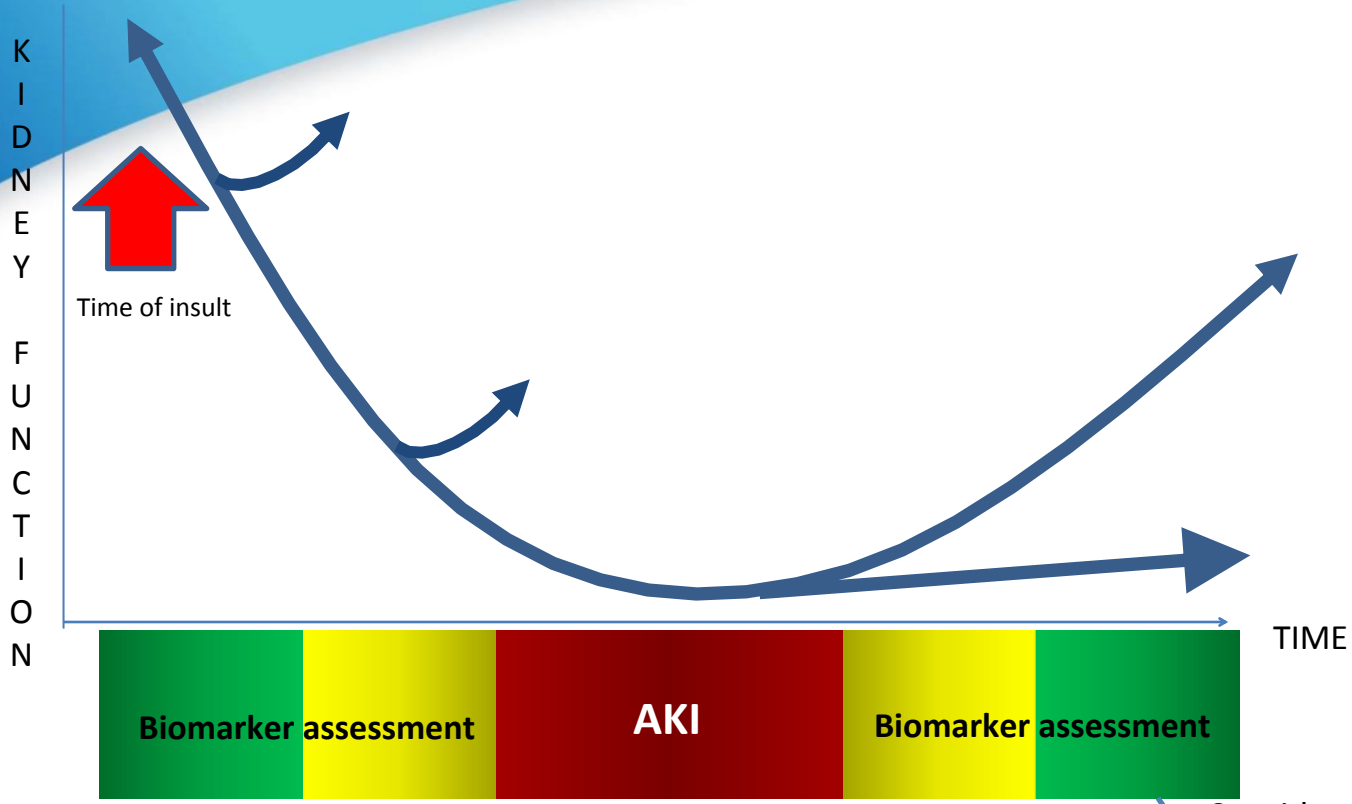
1. Urine and serum
2. Major advantage
3. ? Accuracy of detection
4. Affected by other diseases; varies by biomarker
5. ? Severity

Evidence from Drug Induced Kidney Disease Literature

Kane-Gill et al. Drug Saf 2017;epub ahead of print

Advantage	Example of Evidence
Urine and serum	NGAL: cisplatin induced nephrotoxicity; 4 of 6 studies positive; more favorable for urine than serum; similar for KIM-1 NAG: heterogeneity in reporting (i.e. different unit of measurement)
Presents earlier than current biomarkers	NGAL: evaluated amphotericin inducted AKI and compared NGAL to SCr; NGAL detected AKI 1.7-3.2 days sooner
Detect to a greater degree	NGAL: higher for AKI- related to NSAIDs than hypovolemia and type 1 hepatorenal syndrome and lower than acute tubular necrosis
Affected by other diseases	NGAL: may be elevated in sepsis, malignancy, CKD, UTIs TIMP-2•IGFBP7: may be elevated in diabetes
Severity	KIM-1: higher concentration more kidney damage TIMP-2•IGFBP7: moderate risk > 0.3 to ≤ 2.0 & high > 2.0

Role of Biomarkers and Drug Management



Adapted from
Chawla LS et al. Nat Rev Nephrol 2017;13:241-57

Individualized risk based adjustment
Adjust renally excreted medications
Avoid/Withdraw nephrotoxins
Avoid/Withdraw Meds with renovascular effect

Medication introduction/
Re-introduction

Consider new
renoprotective
medications

Which structural renal biomarker(s) are commercially available in the United States?

A. Liver fatty acid binding protein (L-FABP)
B. Tissue inhibitor of metalloproteinase-2 plus insulin-like growth factor binding protein 7 (TIMP-2•IGFBP7)
C. Neutrophil gelatinase-associated lipocalin (NGAL)
D. Kidney injury molecule-1 (KIM-1)
E. All of the above

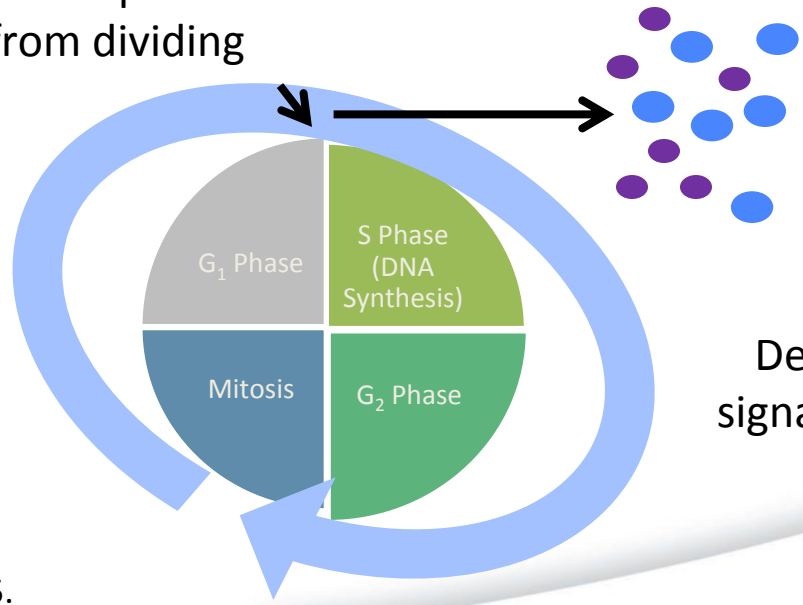
TIMP-2·IGFBP7

(NephroCheck®)

- **"Cell-cycle arrest" markers detected in urine**

Pause in replication to prevent damaged cells from dividing

TIMP-2 and IGFBP7 released



Kidney sustains an insult **(e.g. hypoperfusion)**

Detected in the urine, signal risk for cell damage and AKI

Kashani K, et al. *Crit Care* 2013;17:R25.

TIMP-2·IGFBP7

(NephroCheck®)

- **Sapphire study: Discovery and Validation**
  - Clinical variables (including SCr): AUC 0.81
  - Clinical variables + TIMP-2·IGFBP7: AUC 0.87
- **Opal study: Established clinical cut-offs**
  - Moderate risk > 0.3-2.0: 4+ fold higher risk
  - High risk >2.0: 10+ fold higher risk

Kashani K, et al. *Crit Care* 2013;17:R25.
Hoste E, et al. *Nephrol Dial Transplant* 2014;29:2054-61.
Bihorac A, et al. *Am J Resp Crit Care Med* 2014;189:932-9.

PrevAKI Randomized Controlled Trial

Single-center, randomized trial of 276 cardiac surgery patients with TIMP-2·IGFBP7 ≥0.3

- 138 control patients
- 138 intervention patients

Primary Endpoint: Any AKI at 72-h

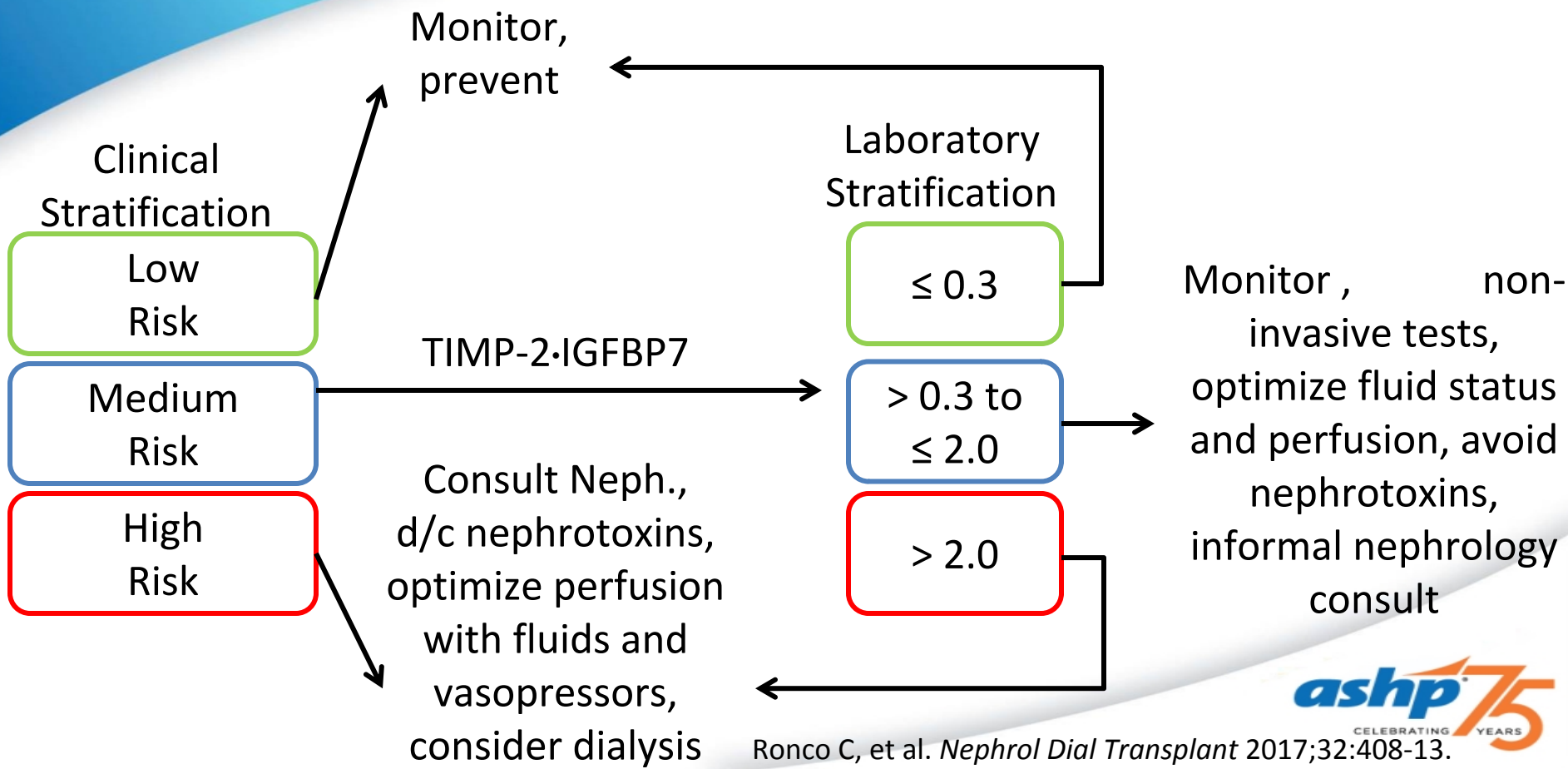
- Any AKI: 72%
  Stage II/III: 45%
- Any AKI: 55%
  Stage II/III: 30%

KDIGO Bundle

- Avoid nephrotoxins
- Withhold ACEI/ARB
- Monitor SCr/UOP
- Glucose < 150 mg/dL
- Limit IV contrast
- Optimize volume status/hemodynamics

Meersch M, et al. *Intensive Care Med* 2017 (Epub ahead of print).

NephroCheck® Rapid Response Team



Ronco C, et al. *Nephrol Dial Transplant* 2017;32:408-13.

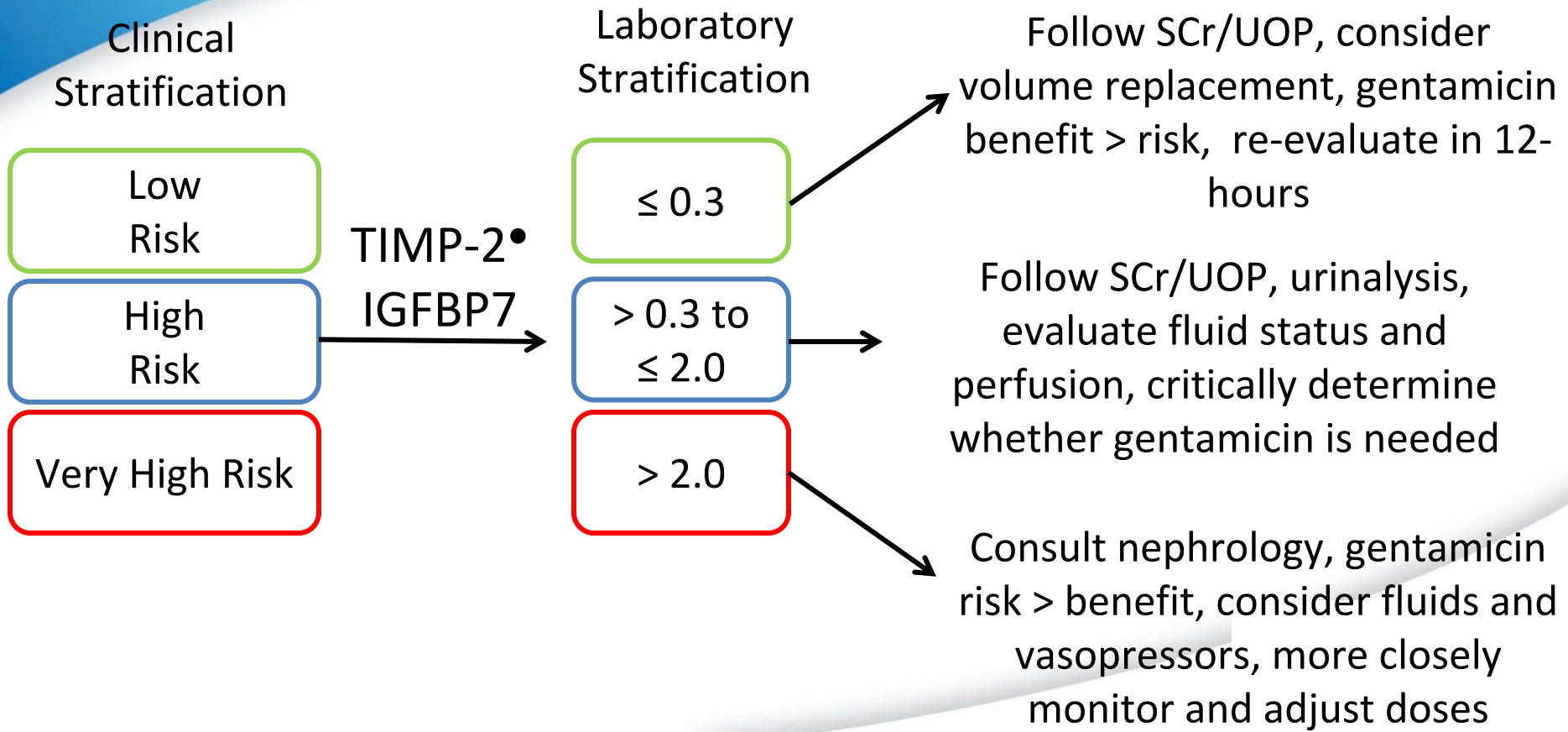
Case: A.B.

- **74 y.o. male admitted for septic shock due to a urinary tract infection (UTI)**
- PMH: Alcoholic cirrhosis, stroke with hemiparesis and urethrocutaneous fistula with recurrent UTIs
- Fluids, vasopressors, cultures were drawn
- Starting cefepime, gentamicin, vancomycin
- **Renal assessment**
  - Serum creatinine (SCr) 0.8 mg/dL (eGFR 92 mL/min)
  - Urine output (UOP) 20 mL/h x 4h (0.25 mL/kg/hr)

What statement best characterizes the use of TIMP-2•IGFBP7 in A.B.?

A. TIMP-2•IGFBP7 is not indicated for use in A.B. given his baseline risk for AKI
B. TIMP-2•IGFBP7 is indicated in A.B. to estimate GFR for renally-dosed medications
C. TIMP-2•IGFBP7 is indicated in A.B. and a level >2.0 would justify holding gentamicin
D. TIMP-2•IGFBP7 is indicated in A.B and requires daily monitoring to optimize medication use

Case: A.B.


Clinical Stratification
Low Risk
High Risk
Very High Risk
TIMP-2•IGFBP7
Laboratory Stratification
≤ 0.3
> 0.3 to ≤ 2.0
> 2.0
Follow SCr/UOP, consider volume replacement, gentamicin benefit > risk, re-evaluate in 12-hours
Follow SCr/UOP, urinalysis, evaluate fluid status and perfusion, critically determine whether gentamicin is needed
Consult nephrology, gentamicin risk > benefit, consider fluids and vasopressors, more closely monitor and adjust doses

Key Takeaways

- Key Takeaway #1
  - Structural biomarkers offer advantages over current clinical models. Data are promising for biomarker use to detect drug induced kidney disease but standard use is premature.
- Key Takeaway #2
  - Data demonstrate TIMP-2•IGFBP7 is associated with cell distress and suggestive of AKI in the next 12-24 hours. Clinical data on the benefit of adjusting medications using this information is needed.

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