Workup and Management of Acute Kidney Injury

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KIDNEY RESEARCH INSTITUTE

A collaboration between
Northwest Kidney Centers and UW Medicine

Division of Nephrology
University of Washington

Objectives

1. Review common and some uncommon causes of acute kidney injury (AKI) in hospitalized patients
2. Discuss practical diagnostic evaluation for the hospitalized patient with AKI
3. Discuss prevention and management of select AKI etiologies

Case 1

HPI:

- 43 y/o woman with a history of chronic HCV, presents to ED with abdominal pain, vomiting x 3 days
- Temp 38, BP 95/60, HR 100
- Exam shows abdominal tenderness, 1+ LE edema
  - Receives 1 liter LR, vancomycin and cefepime x 1
  - F/u BP 105/70 → admitted to medicine

PMH:

- H/o wrist fracture 1 year ago, creatinine 0.7 mg/dL

Laboratory/imaging evaluation

134	102	20	94
4.2	21	1.2	

Urinalysis: 1+ RBCs, 1+ protein
Urine protein/creat: 0.5 g/g

CBC: WBC 14k, Hgb 10, Platelets 110k

HCV viral load: 800,000 IU/L

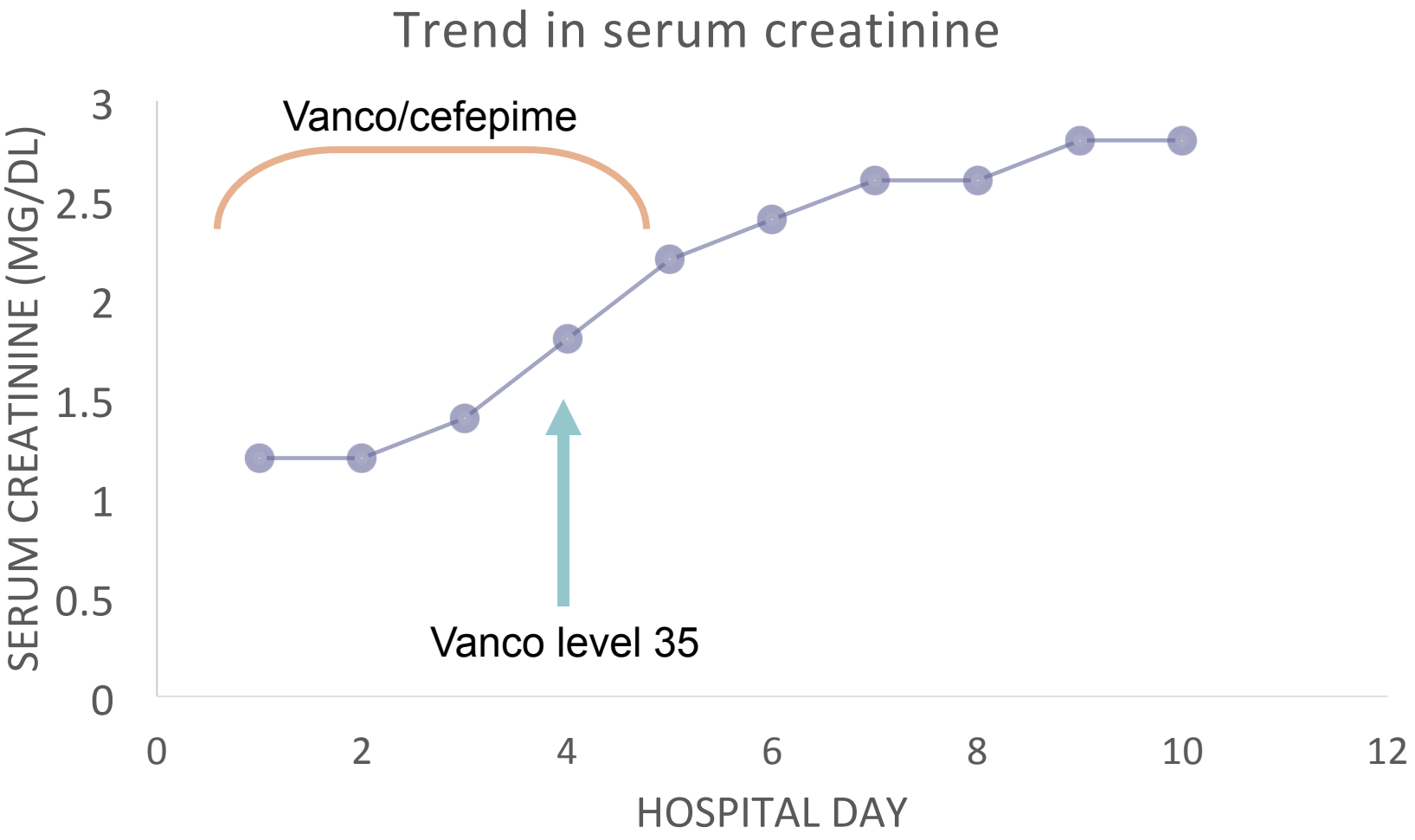
C3, C4 both low

INR: 1.4

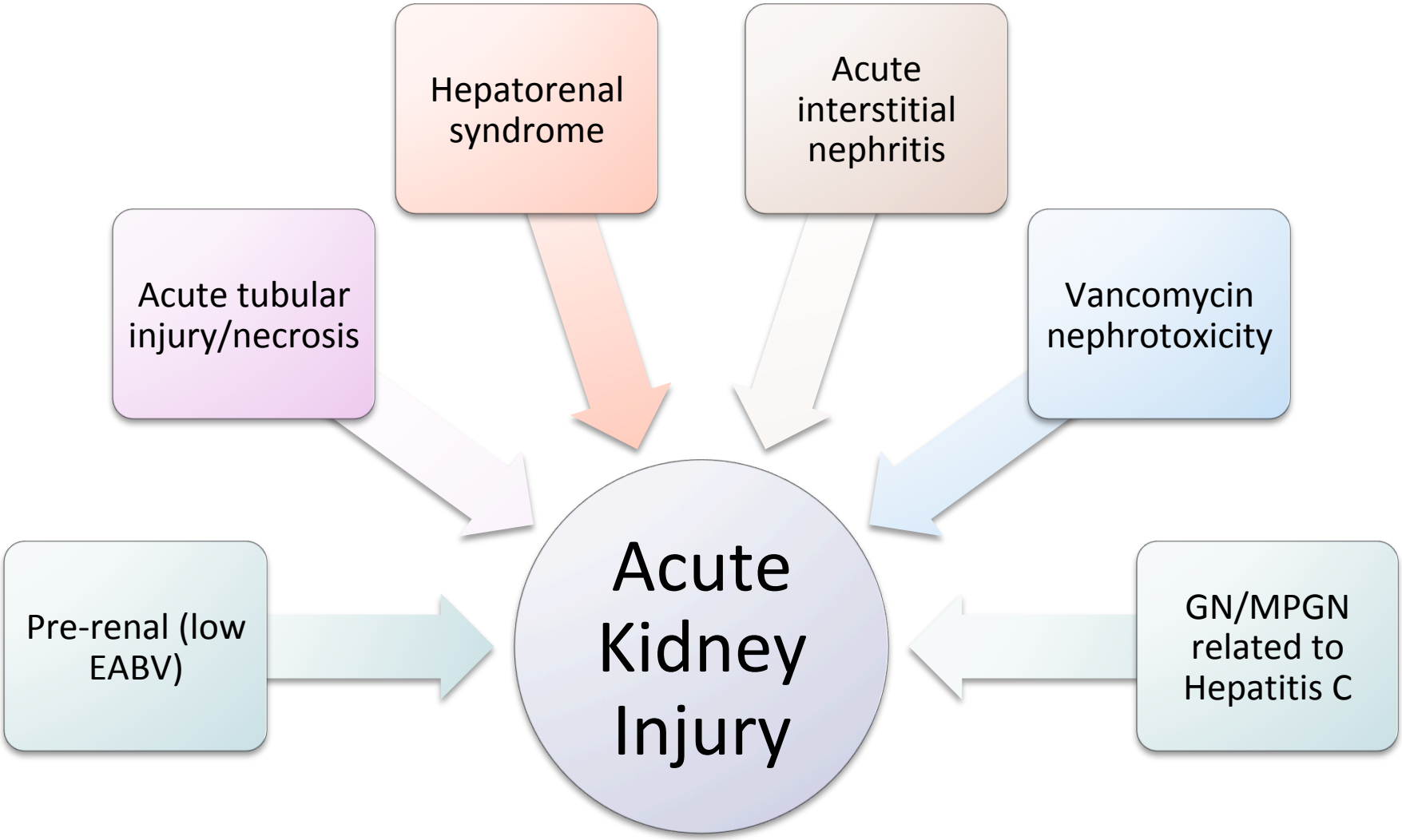
AST/ALT: 110/90

Total bilirubin: 2.0 mg/dL

Case 1, continued



What is causing this patient's AKI?



“Acute Kidney Injury" is a clinical syndrome

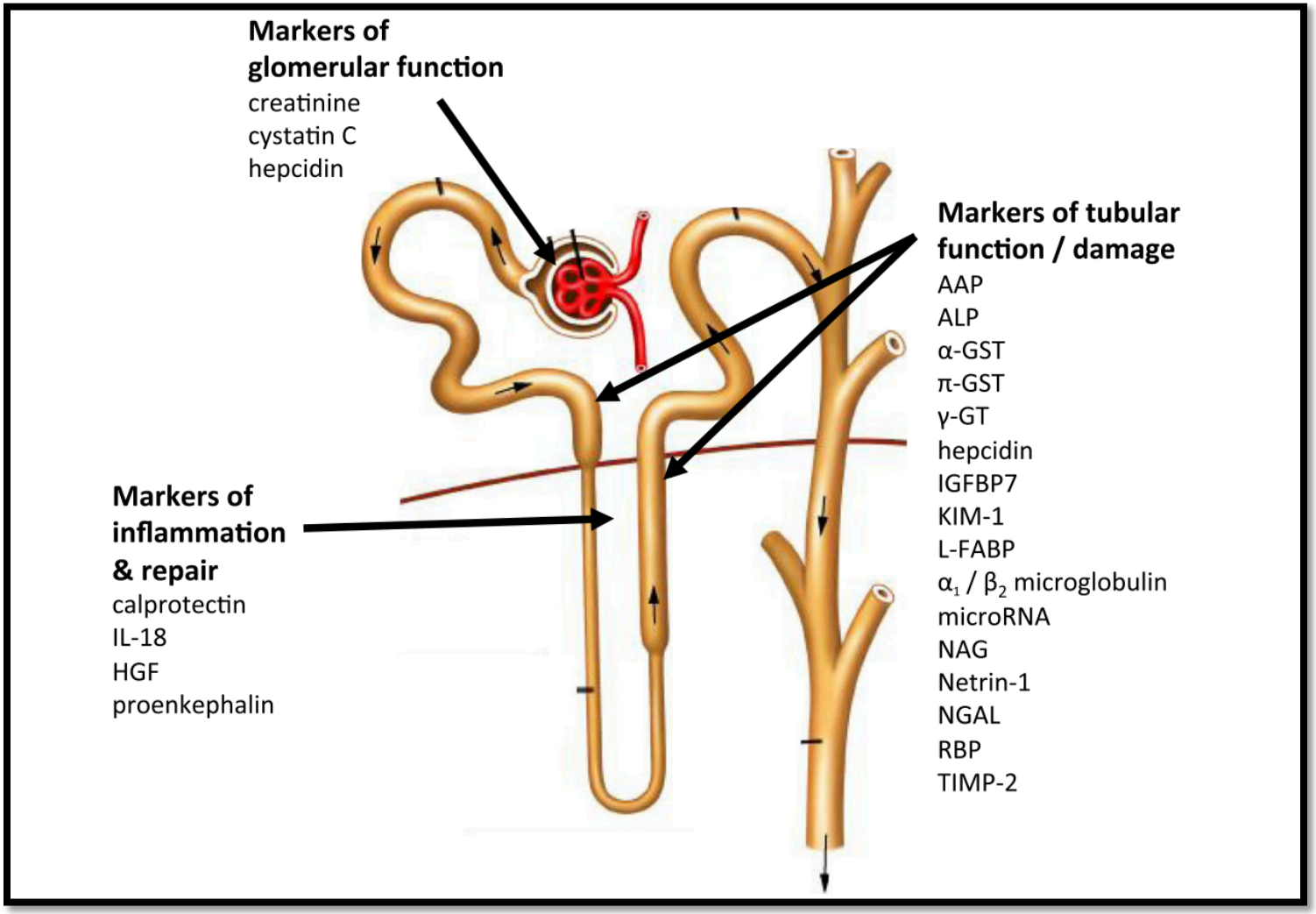
Elevated Creatinine/ Decreased eGFR

Low urine output

Stage	Serum Creatinine	Urine output
1	1.5-1.9 times baseline within 1 wk or ≥ 0.3 mg/dl increase within 48 hrs	<0.5ml/kg/h for 6-12 hrs
2	2.0-2.9 times baseline	<0.5ml/kg/h for ≥ 12 hrs
3	3.0 times baseline or increase in serum creat to ≥ 4.0 mg/dl or initiation of RRT or in patients < 18 yrs, decrease in eGFR to <35ml/min per 1.73 m^2)	<0.3ml/kg/h for ≥ 24 hrs or Anuria for ≥ 12 hrs

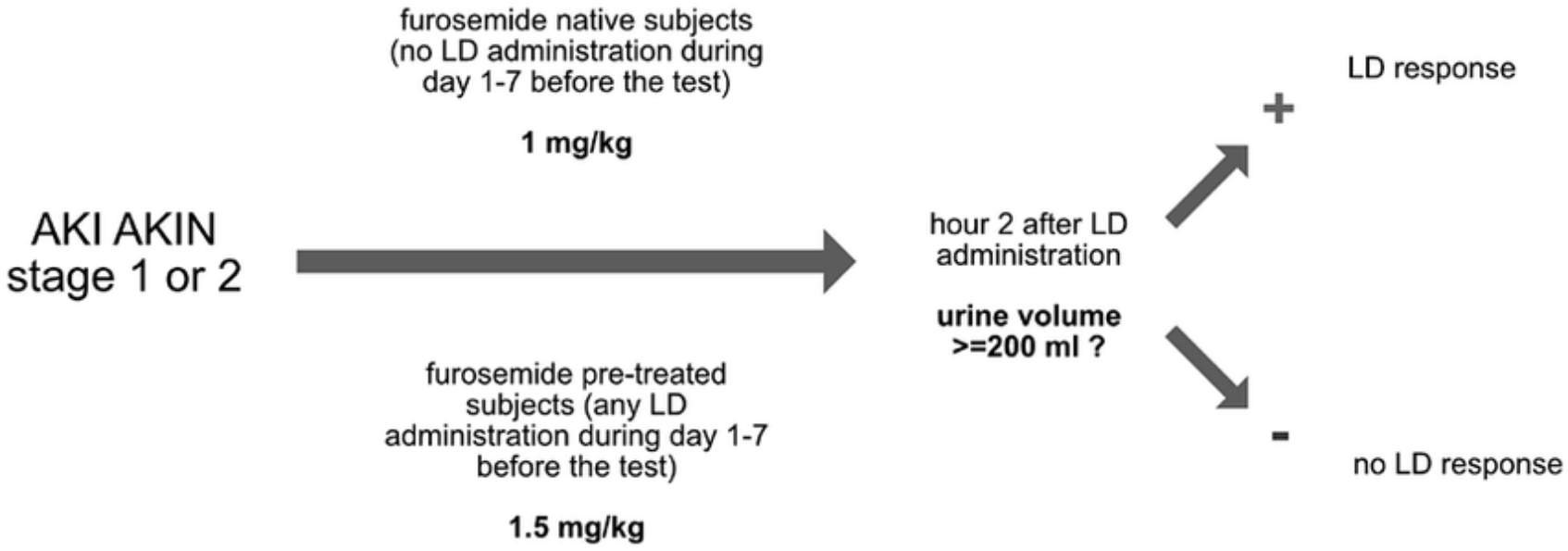
KDIGO AKI Guidelines, 2012

Urinary biomarkers for AKI – NOT YET!



Ostermann M, et al.. Crit Care. 2016.

Tubular function as a stress test

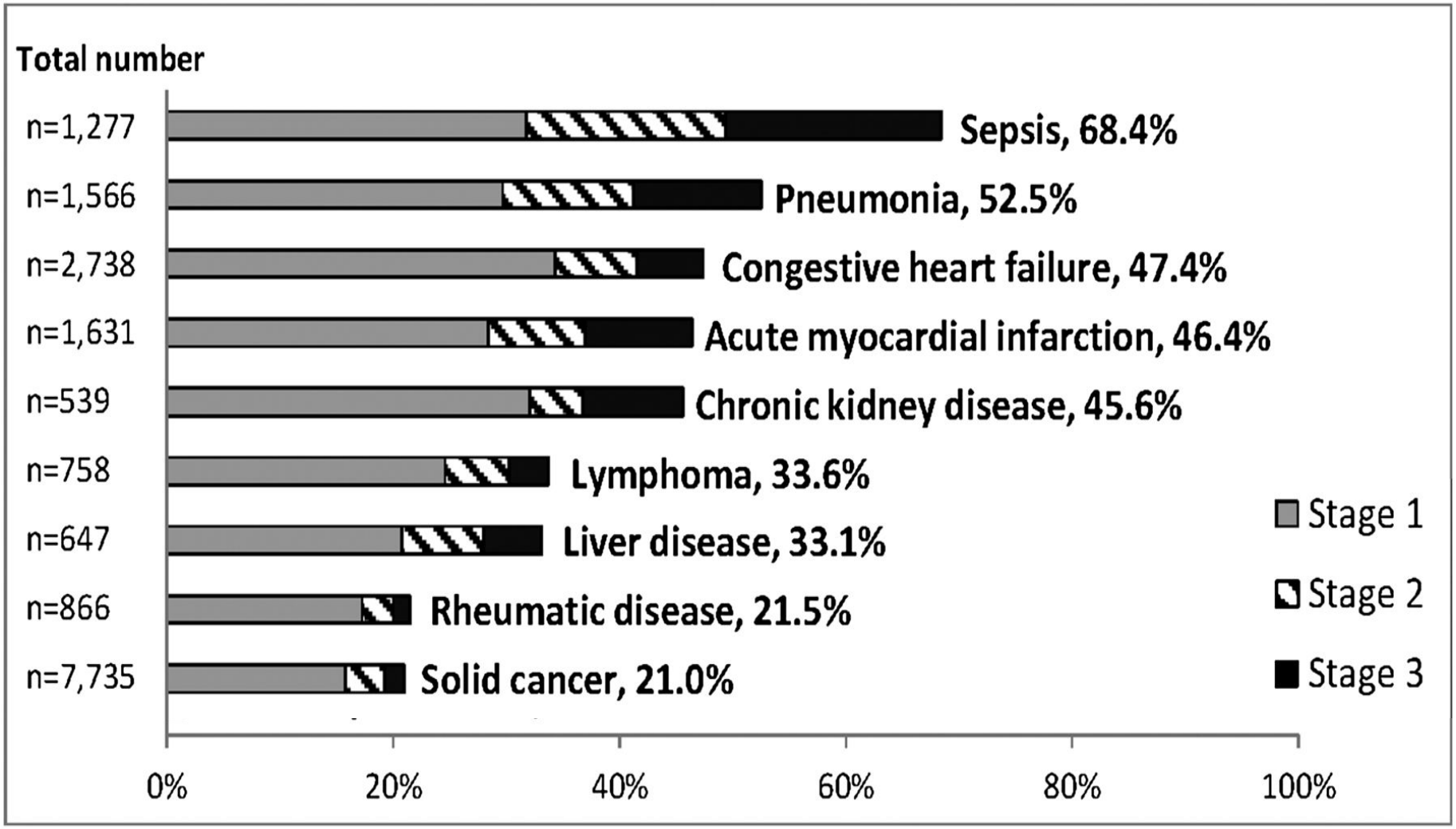


77 patients with AKI who received FST → followed for development of stage 3 AKI, RRT, death

FUROSEMIDE OUTPERFORMED URINARY BIOMARKERS FOR ALL OUTCOMES

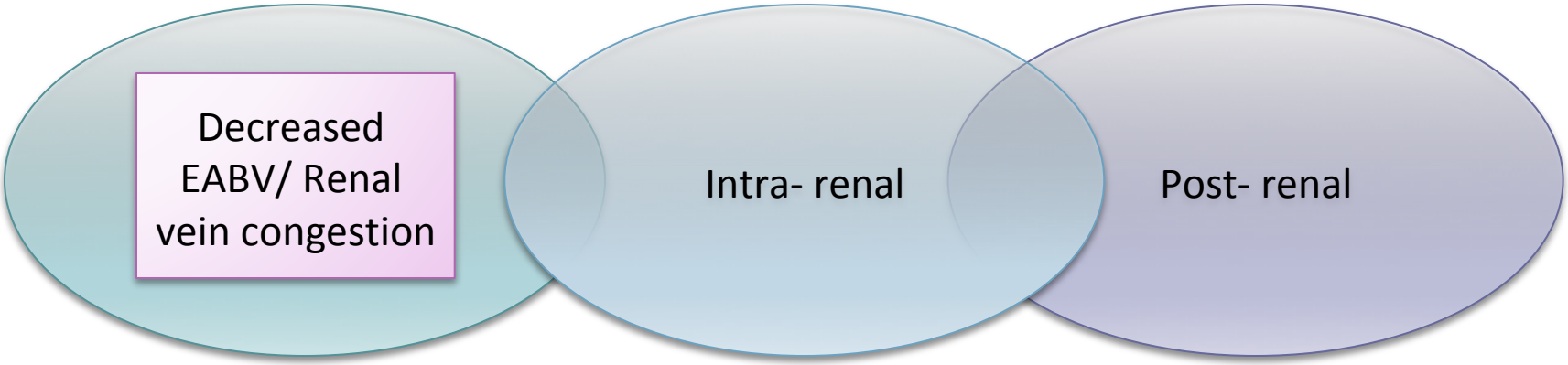
Koyner et al, JASN, 2015

AKI is common in hospitalized patients!



Zeng et al, CJASN, 2014

Causes of AKI

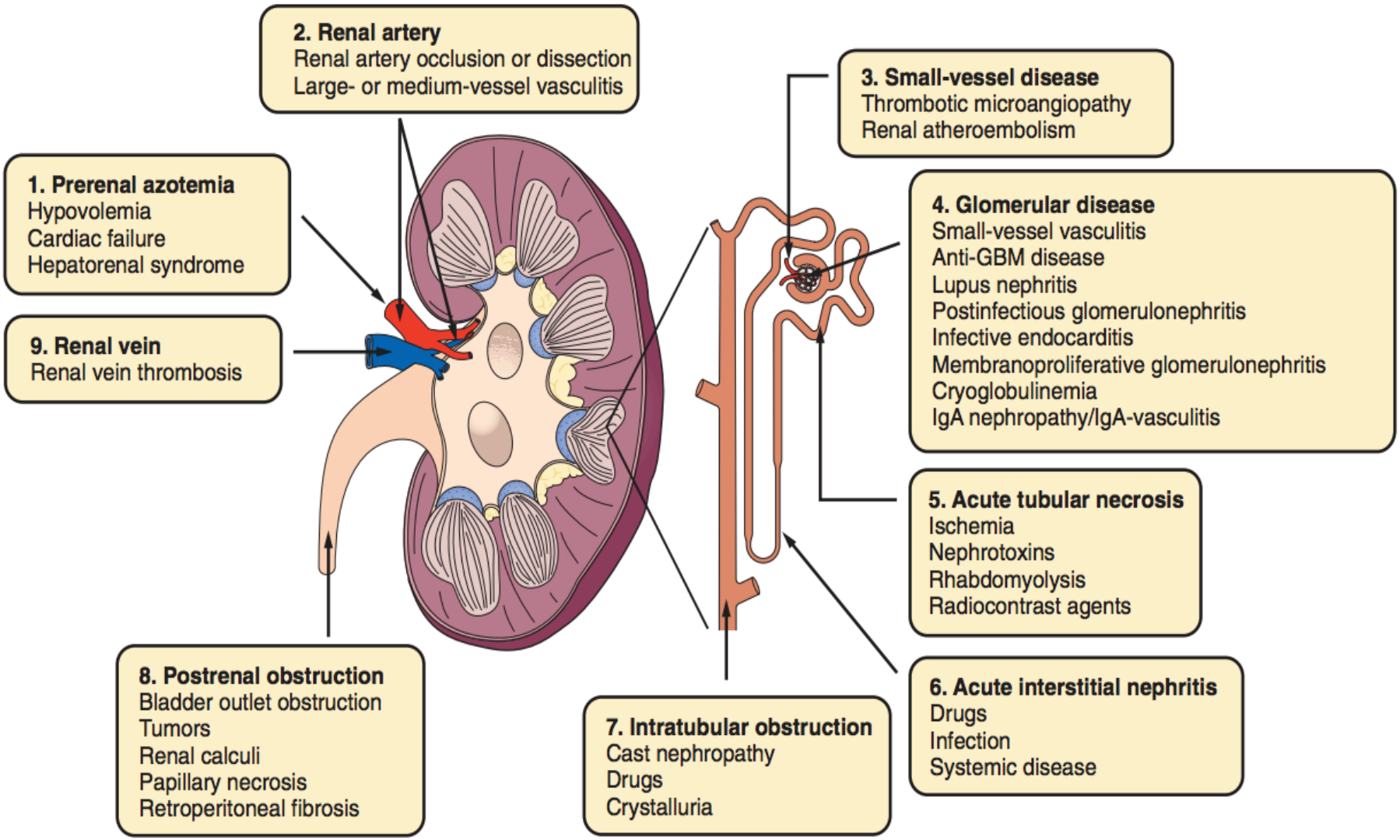


- Volume depletion
- Cardiorenal syndrome
- Hepatorenal syndrome
- Abdominal compartment syndrome
- Renal artery occlusion/
- Dissection
- Renal vein thrombosis

- Glomerular disorders
- Microvascular disorders
- Tubulointerstitial Disorders
- Acute tubular necrosis

- Ureteral obstruction
- Bladder outlet
- Obstruction

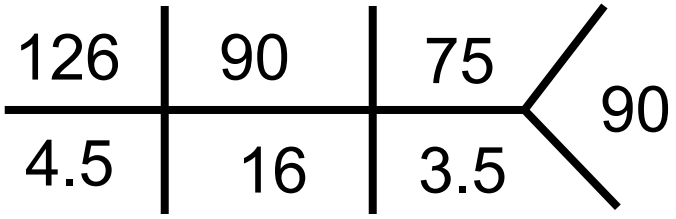
Causes of AKI – An Anatomic Approach



Jefferson, Haseley. Comprehensive Clinical Nephrology. Chapter 66, Sixth edition.

Case 2

- 20 y/o man hospitalized for volume depletion after returning from Mexico
- Reports 5 days of 6-10 loose stools/day, nausea, poor PO intake
- BP is 80/50, dizzy with standing
- Creatinine 1 year ago 0.9.

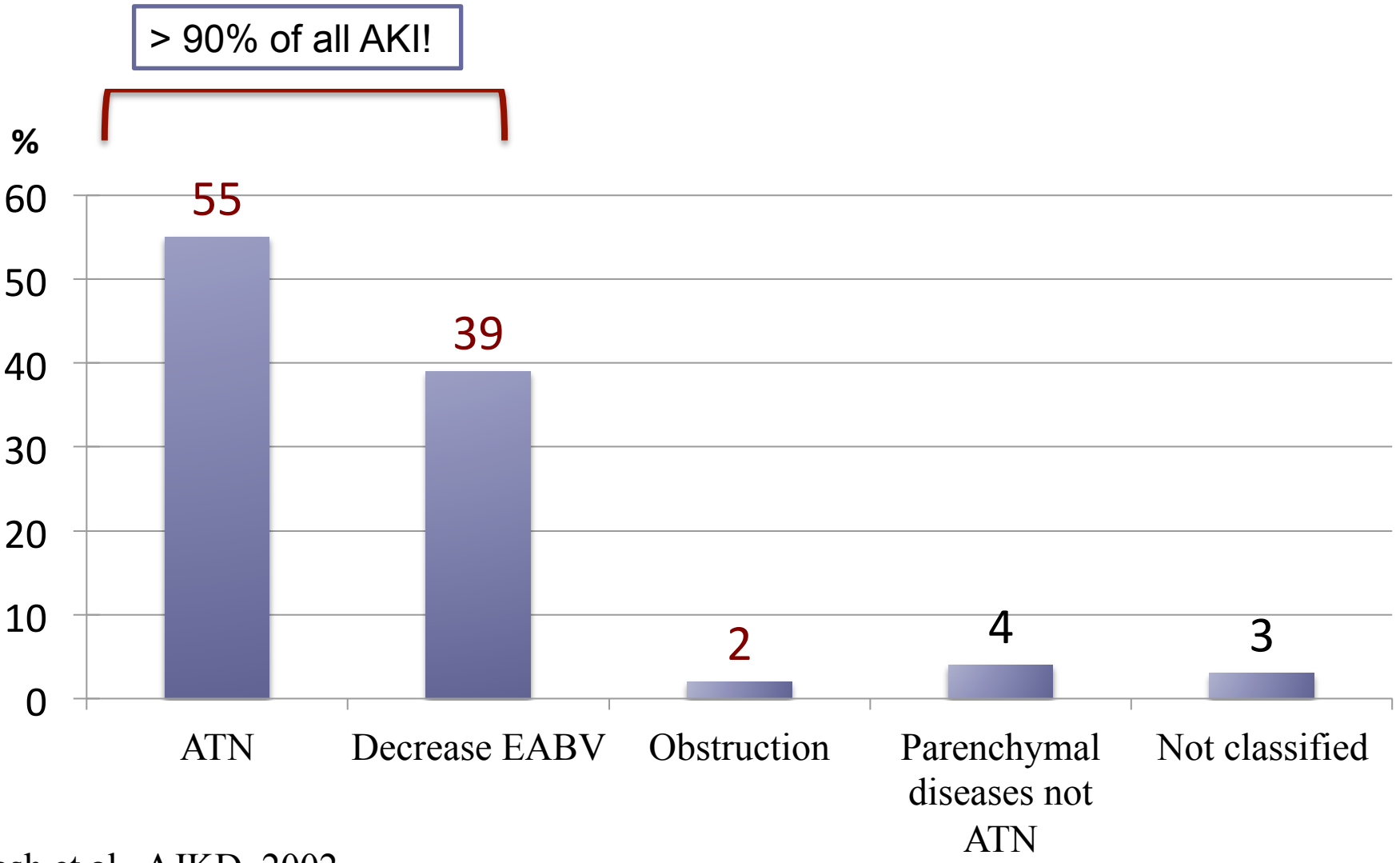


Urine:

U_{Na}	8 mEq/L
Ucreat:	35 mg/dL
Uosm:	560 mOsm/kg
Fe Na	0.6%

Urine sediment: Bland

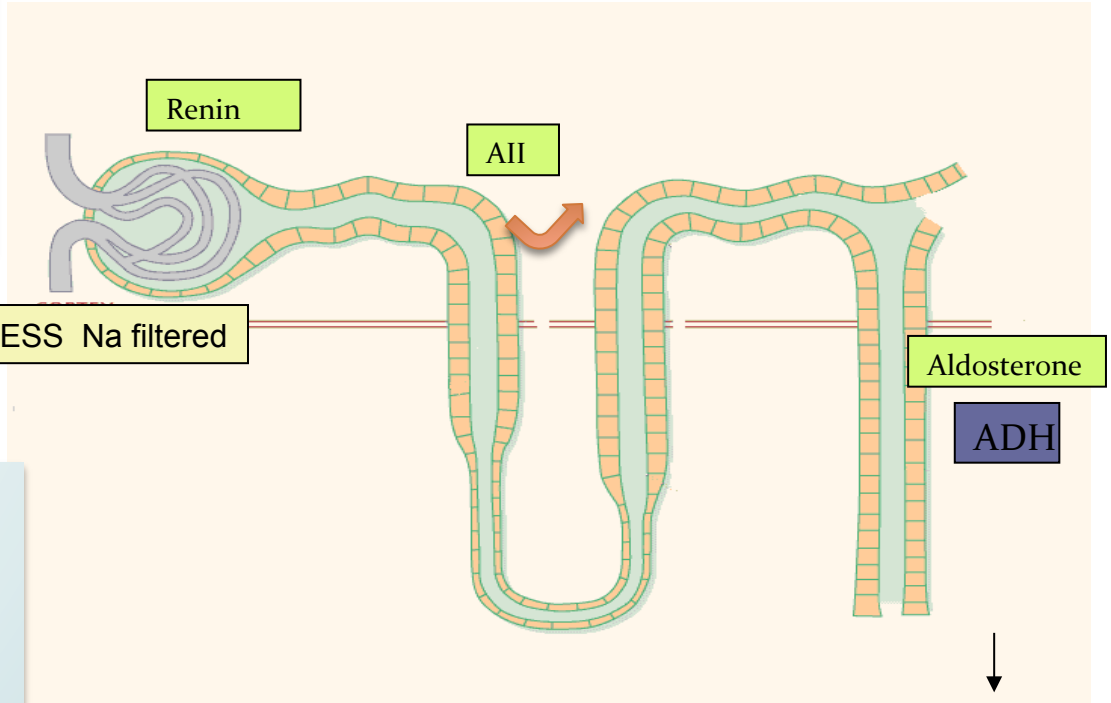
Causes of AKI in hospitalized patients



Nash et al., AJKD, 2002

Pathophysiology of low EABV-related AKI

Impaired renal perfusion
→
↓ Glomerular capillary filtration pressure →
Activation of RAAS



- ↓RBF → GFR
- Incr Na, H20, urea reasbsorption in PCT
- ↑Aldosterone→ ↑Na reabsorption
- ↑ADH →↑H_2O reabsorption

1. Decr U volume ~oliguria
2. Decr U Na - <10, FeNa < 1%

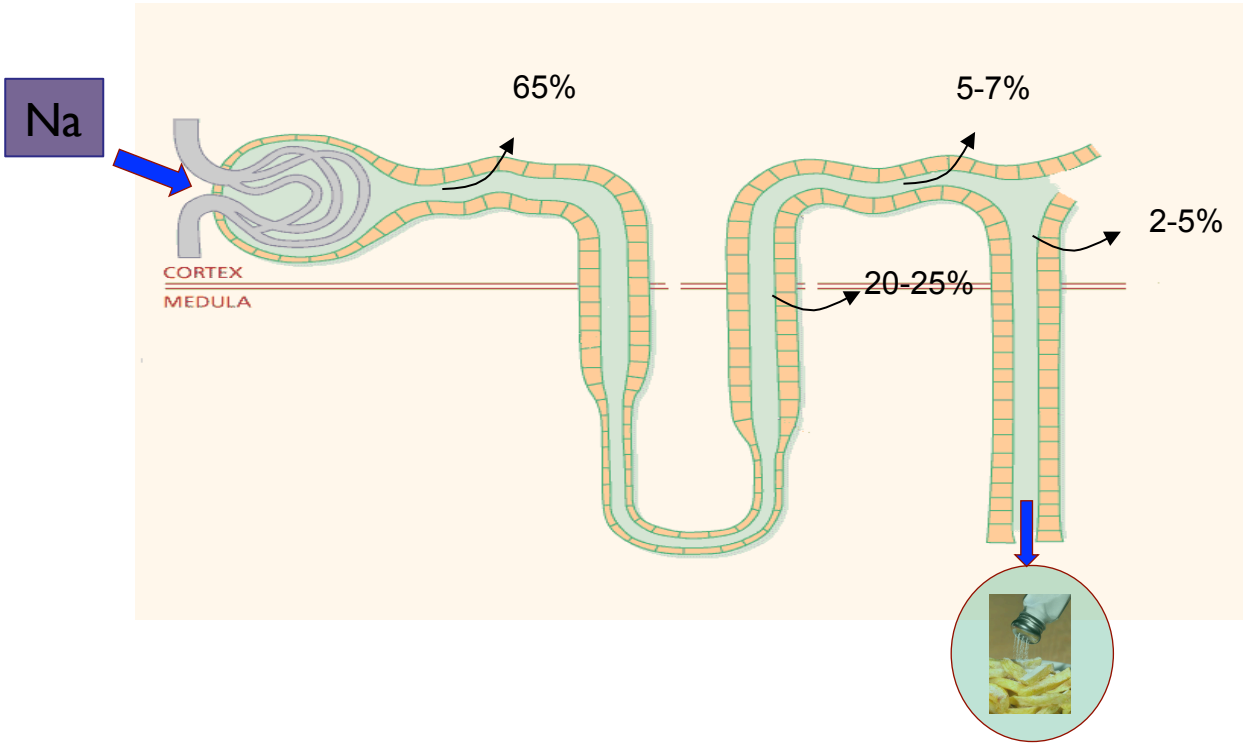
(or FEUrea < 35% if on diuretics)

Decreased EABV AKI – more than "pre-renal"

Intravascular volume depletion
Hemorrhage
GI or renal losses
Reduced cardiac output
CHF/cardiogenic shock
Pericardial diseases
Systemic vasodilation
Sepsis
Cirrhosis
Anaphylaxis
Renal Vasoconstriction
Hepatorenal syndrome
Acute hypercalcemia
Drugs – ACEI, NSAIDS, calcineurin inhibitors

Pre- renal	ATN
UOP/hemodynamics respond quickly to fluids if given enough	UOP/hemodynamics do not respond to fluids
BUN out of proportion to Cr	BUN/ Cr < 20: 1
UOP < 15 ml/ hr but not anuric	Can be anuric
Course improved with intervention	Course unaffected by intervention provided further insult avoided
Urine sodium low (<10 meq/L), FeNa low (<1%)	Urine sodium NOT low (>20 meq/L), FeNa not low (>2%)
Some cases have considerable overlap	

FENa



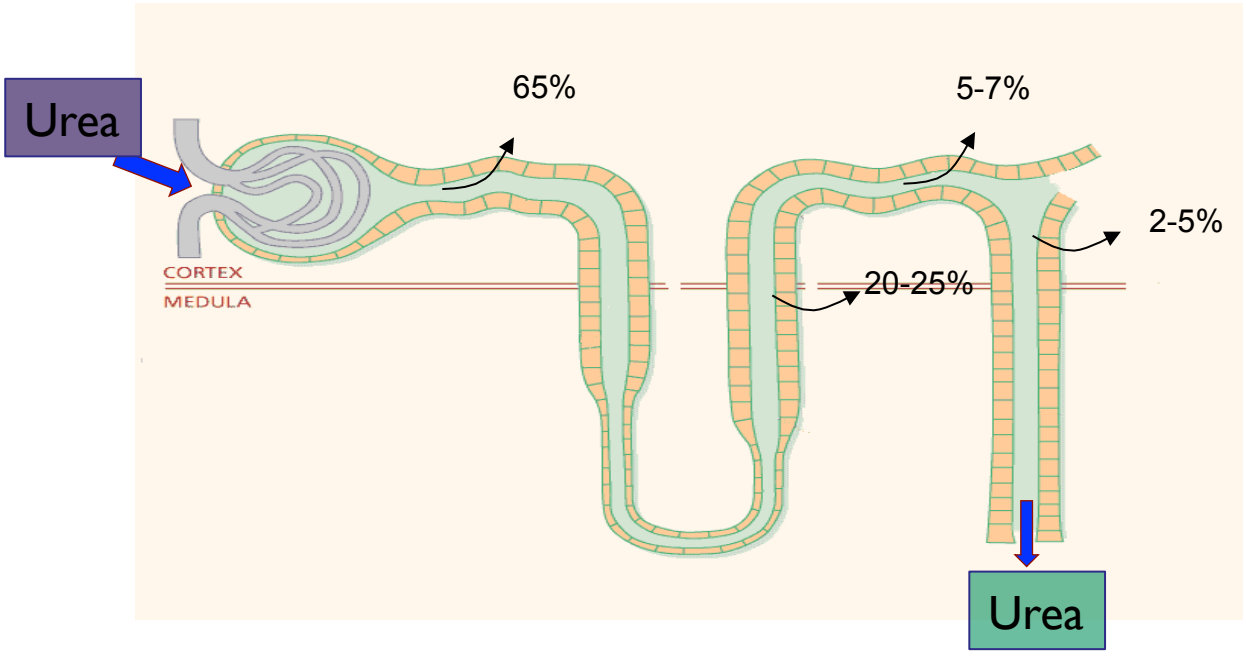
$$= \frac{\text{Excreted Na}}{\text{Filtered Na}}$$

$$= \frac{\text{Urine Na} \times \text{Serum Cr}}{\text{Serum Na} \times \text{Urine Cr}} \times 100$$

- FENa <1% prerenal azotemia
  - Sensitivity: 90%
    Specificity: 93%
- FENa > 1% ATN
  - Sensitivity: 93%
    Specificity: 90%

Espinel. JAMA. 1976:236(579-581)
Miller et al. Ann Int Med. 1978;89(47-50)

ON DIURETICS?
✔FEUrea



$$= \frac{\text{Excreted Urea}}{\text{Filtered Urea}}$$

$$= \frac{\text{Urine Urea x Serum Cr}}{\text{Serum Urea x Urine Cr}} \times 100$$

- Normal FE Urea 50-65 %
- Prerenal Azotemia < 35%

What's wrong with fractional excretion measures?

Table 1. Limitations of fractional excretion of sodium

Scenarios with FeNa < 1%	Scenarios with FeNa > 2%
normal kidney function with low or moderate salt intake	normal kidney function with high salt intake or IV saline
acute GN	late urinary obstruction
early AIN	late AIN
acute urinary obstruction	glucosuria
transplant rejection	bicarbonaturia
FeNa < 1% despite ATN	FeNa > 2% despite prerenal AKI
AKI with liver failure or CHF	use of diuretics
sepsis-associated AKI	CKD
radiocontrast nephropathy	FeNa after IVF therapy
nonoliguric ATN	glucosuria
myoglobinuric ATN	bicarbonaturia
hemoglobinuric ATN	salt-wasting disorders

FeNA, fractional excretion of sodium; AIN, acute interstitial nephritis; ATN, acute tubular necrosis; CHF, congestive heart failure; IV, intravenous; IVF, intravenous fluid.

Perazella et al. CJASN 2012

MANAGEMENT OF PRERENAL AKI

- Restore renal perfusion/treat underlying condition

Other common low EABV AKI conditions

Type 1 cardiorenal syndrome

Hepatorenal syndrome (HRS)

Cardiorenal syndromes

Type 1 (acute) – Acute HF results in acute kidney injury

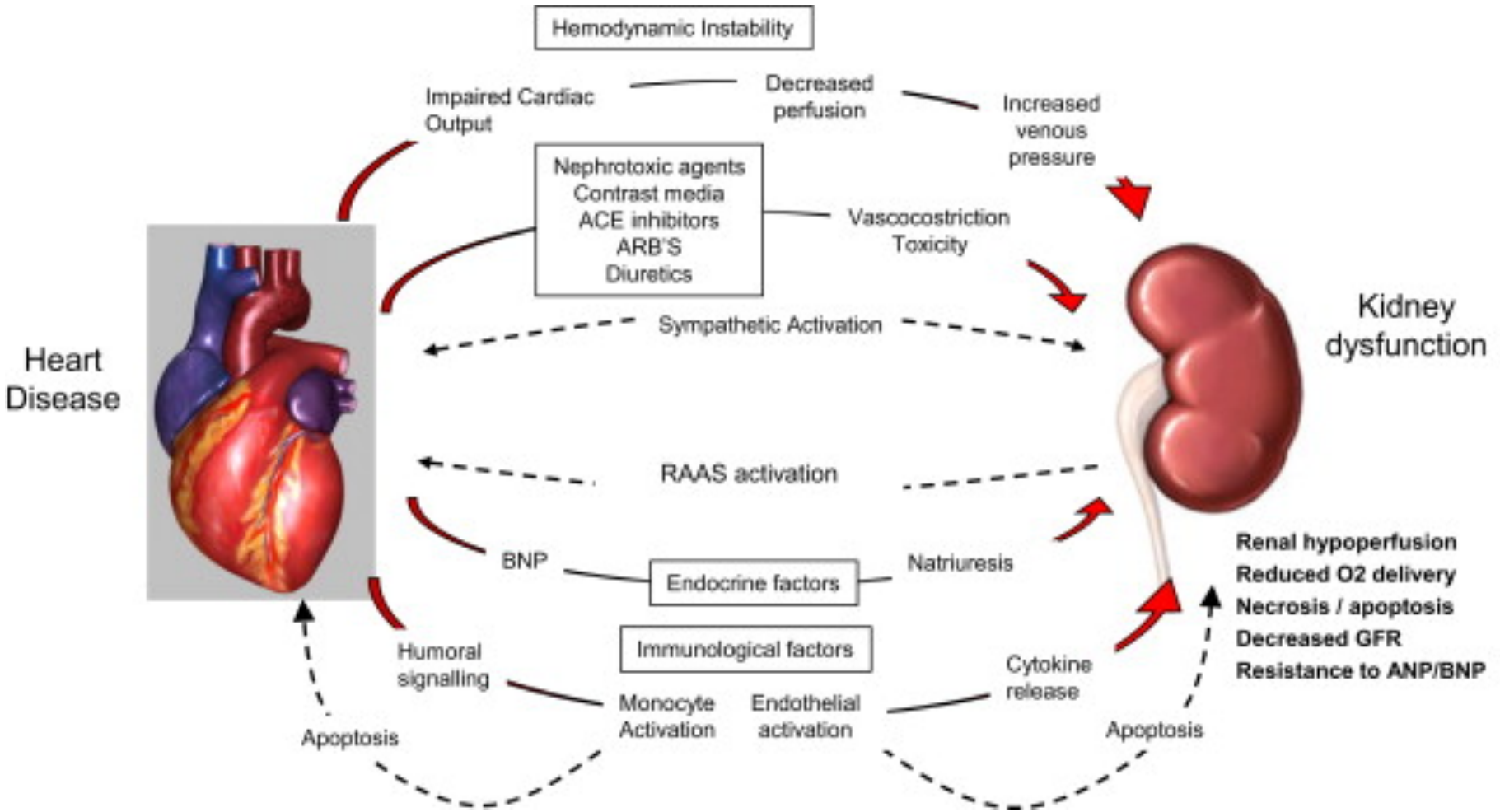
Type 2 – Chronic cardiac dysfunction (eg, chronic HF) causes progressive CKD.

Type 3 – Abrupt and primary worsening of kidney function due, for example, to renal ischemia or glomerulonephritis causes acute cardiac dysfunction, which may be manifested by HF.

Type 4 – Primary CKD contributes to cardiac dysfunction, which may be manifested by coronary disease, HF, or arrhythmia.

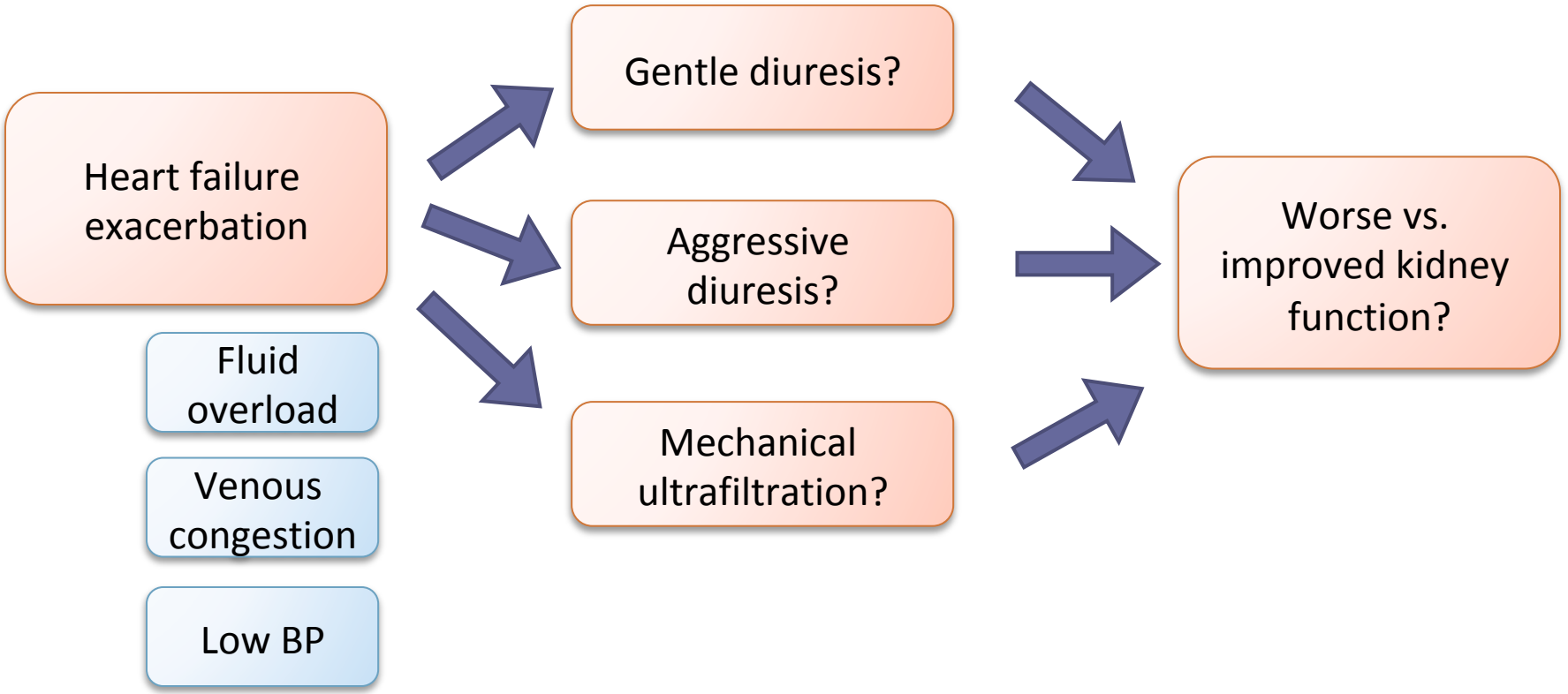
Type 5 (secondary) – Acute or chronic systemic disorders (eg, sepsis or diabetes mellitus) that cause both cardiac and renal dysfunction.

Mechanisms of CRS



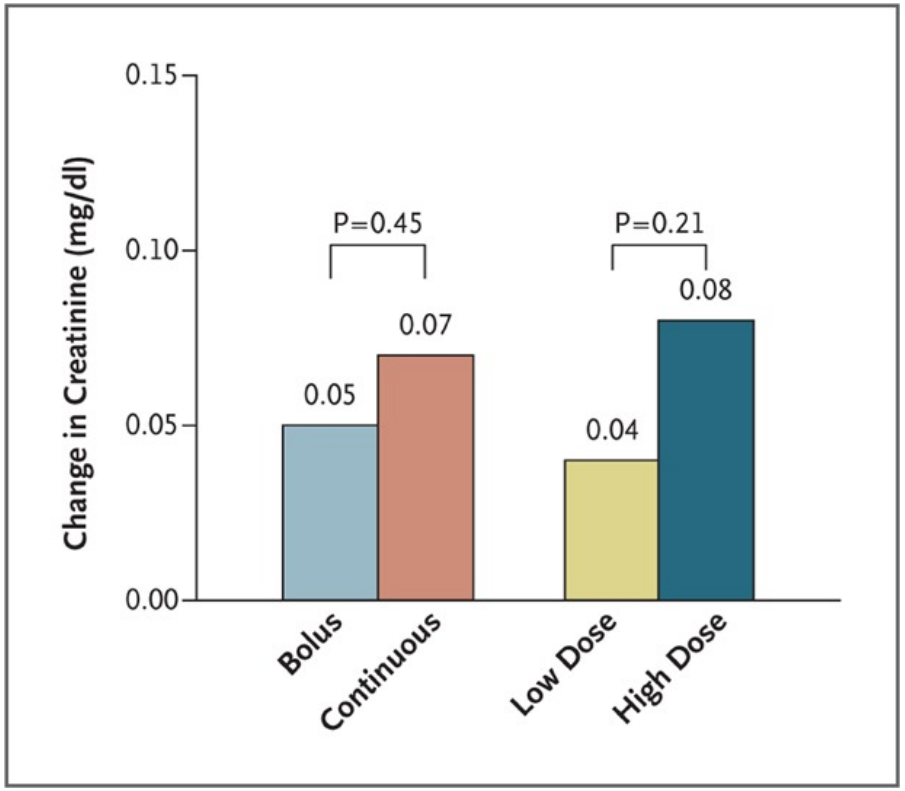
Soni *Clinical Queries: Nephrology* 2014

Clinical conundrum with acute cardiorenal syndrome, type 1



Diuretic dosing

- **DOSE trial**
- **308 patients with acute decompensated heart failure**
- **Randomized to furosemide IV bolus q12 hours vs. infusion and at either low dose (equivalent to home oral dose) vs. high dose (2.5x home oral dose)**
- **No difference in the groups**

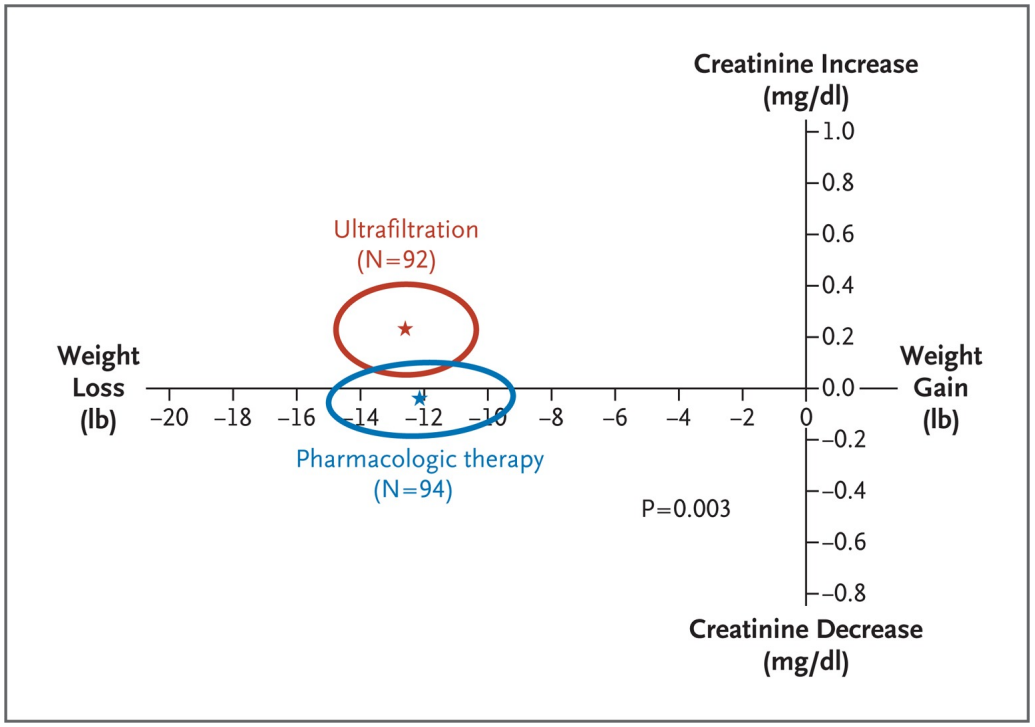


Take home message: diuretic dosing is flexible

Felker *NEJM* 2011

Ultrafiltration

- **CARRESS-HF trial**
- **188 patients with acute decompensated heart failure, AKI and persistent congestion**
- **Stepped pharmacologic therapy (IV diuretics) vs. ultrafiltration**
- **No difference in weight loss between groups**
- **Higher rate of adverse events and greater increase in Cr in UF group**



Take home message: diuresis is likely a safer strategy (vs. UF)

Bart *NEJM* 2012

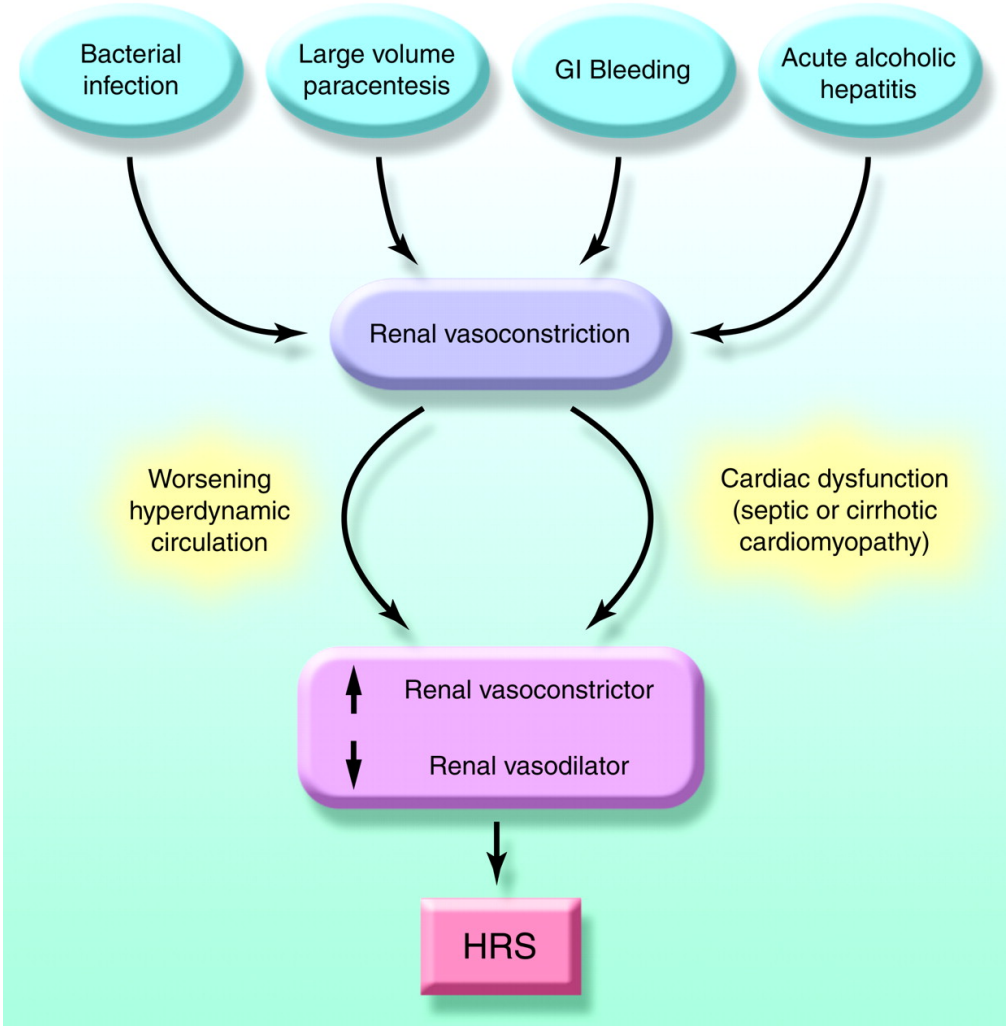
HEPATORENAL SYNDROME

Reversible functional renal impairment that occurs in patients with advanced liver disease.

- Low GFR
- Absence of shock, current infection, fluid losses, nephrotoxic drugs
- No improvement in renal function after diuretic withdrawal and expansion of volume
- Proteinuria <500 mg/d
- No obstruction
- No intrinsic renal disease (no ATN, no GN)

→ Typically IV albumin 1g/kg of body weight x 2 days

Precipitating factors in HRS



3 interrelated pathways:

1. Splanchnic vasodilation decreasing EABV
2. Renal sympathetic stimulation
3. Cardiac dysfunction leading to renal hypo-perfusion

Wadei et al, CJASN, 2006

HRS Treatment

In critically ill patients:

- Norepinephrine IV to raise MAP by 10 mmHg until no response or resolution of AKI (at least 2 days)

In non-critically ill patients:

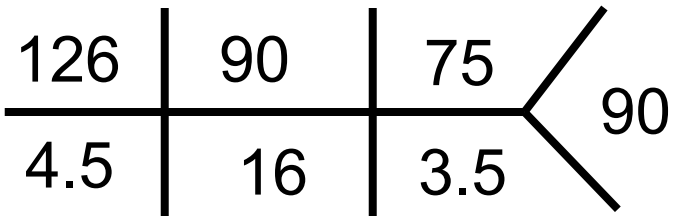
- Midodrine 7.5-15mg TID
- Octreotide 100mcg-200mcg TID
- Trial x 2 days

In non-responders:

- Consider TIPS (controversial)
- If liver transplant candidate, dialysis as bridge to transplant

Case 3

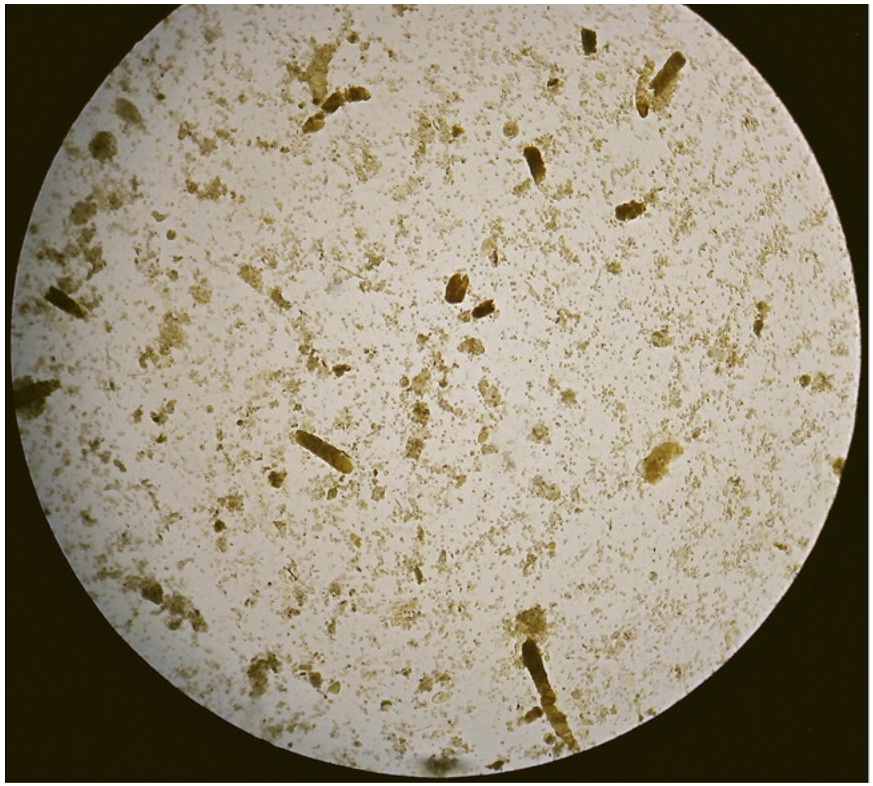
- 20 y/o man hospitalized for volume depletion after returning from Mexico
- Reports 5 days of 6-10 loose stools/day, nausea, poor PO intake
- BP is 80/50, dizzy with standing
- Creatinine 1 year ago 0.9.

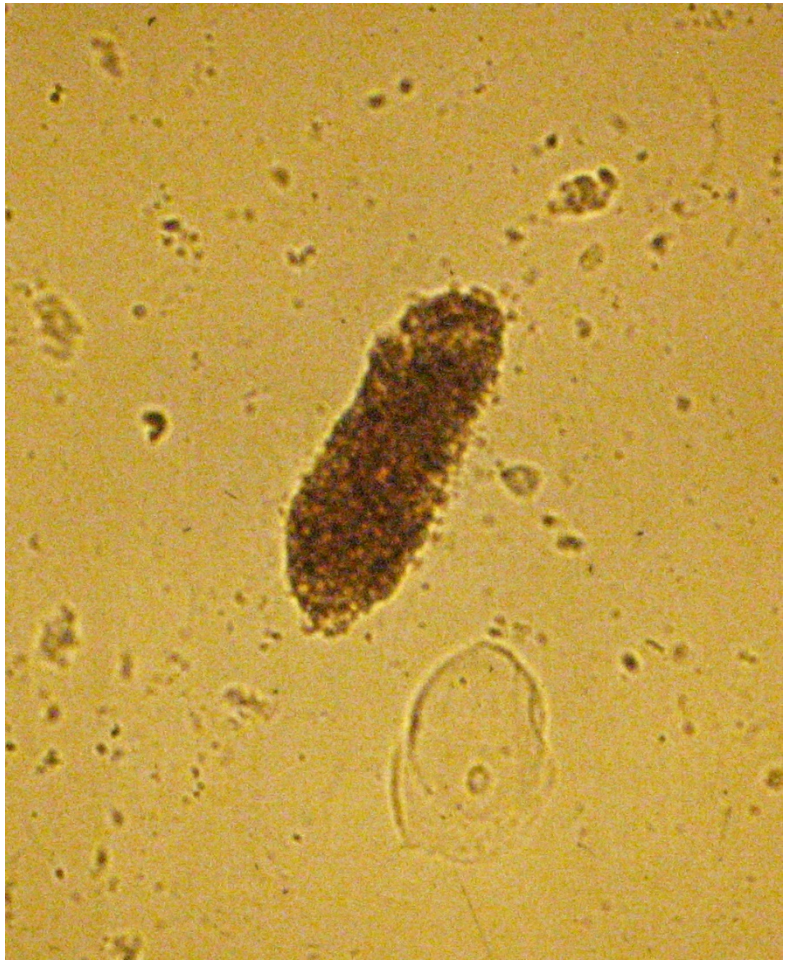


Urine:

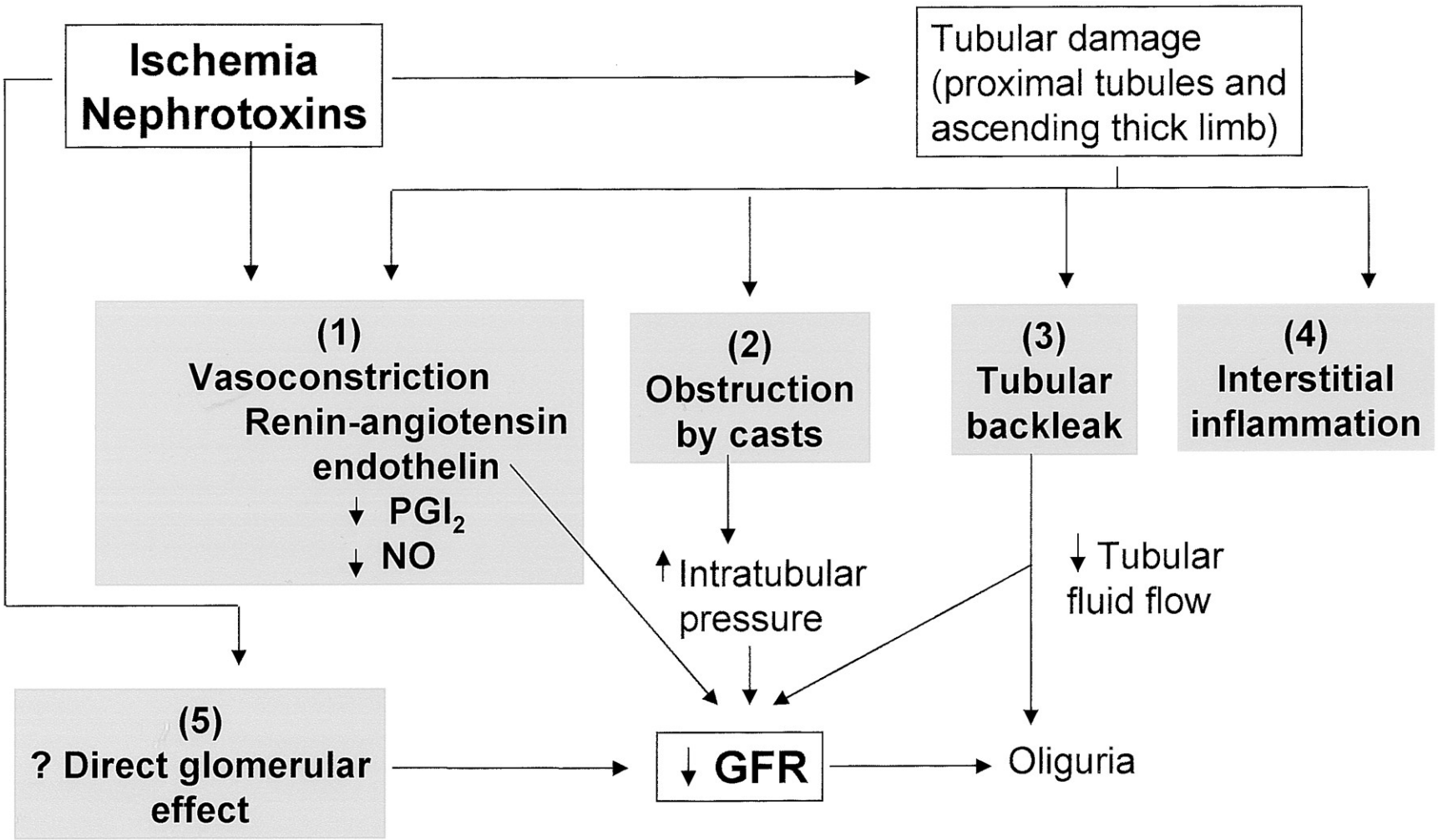
U_{Na}	30 mEq/L
Ucreat:	42 mg/dL
Uosm:	300 mOsm/kg
Fe Na	2%

Case 3: urine sediment





Why does ATN cause elevated creatinine?



Lameire and Vanholder, JASN, 2001

Value of Urine Sediment

Table 2. Likelihood ratios for prerenal AKI and acute tubular necrosis based on urine microscopy (14)

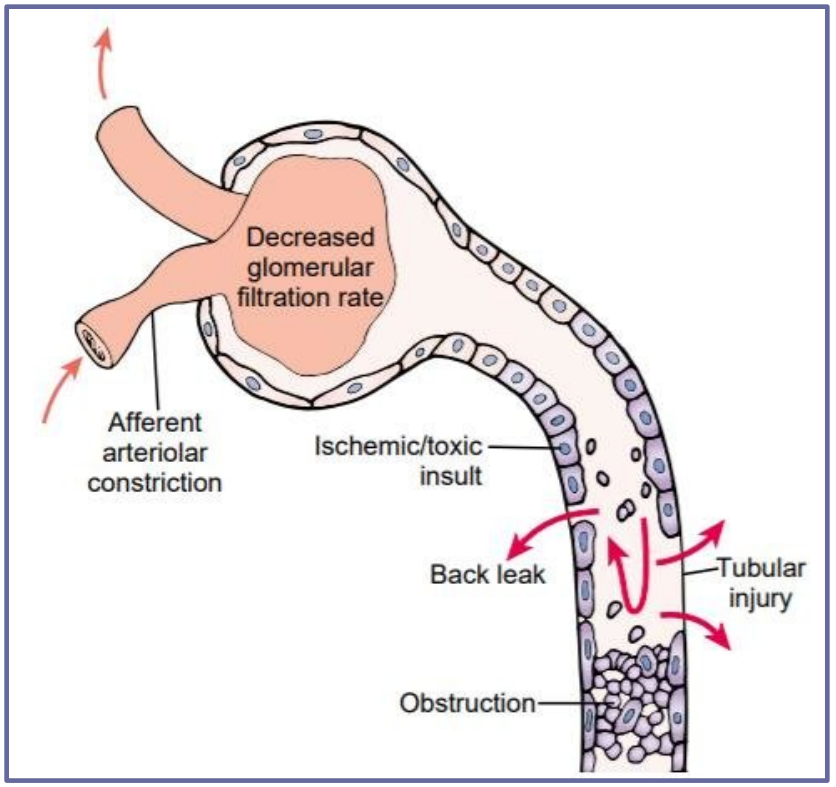
Urine Findings	ATN	Prerenal AKI	Likelihood Ratio	
			ATN	Prerenal AKI
Granular casts/LPF				
0	23	84	0.23	4.35
1–5	73	21	2.97	0.34
6–10	23	2	9.68	0.10
>10	8	0	∞	0
total	125	106		

Estimated % change in probability	+LR Power to RULE IN	SHIFT IN POST-TEST PROBABILITY	−LR Power to RULE OUT	Estimated % change in probability
10 = 45% ↑	10	← LARGE →	< 0.1	0.1 = 45% ↓
5 = 30% ↑	5-10	← MODERATE →	.1-.2	0.2 = 30% ↓
2 = 15% ↑	2-5	← SMALL → (but sometimes important)	.2-.5	0.5 = 15% ↓

Perazella et al. CJASN 2012

ISCHEMIC ATN

- Failure to restore renal blood flow (RBF) during low EABV stage → tubular cell injury.

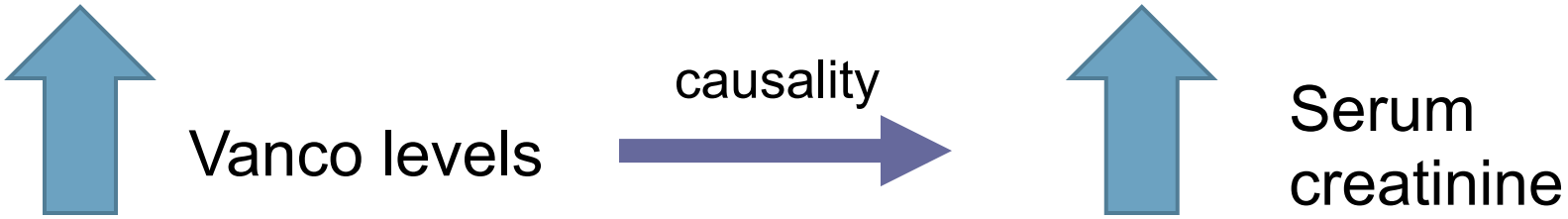


NEPHROTOXINS AND ATN

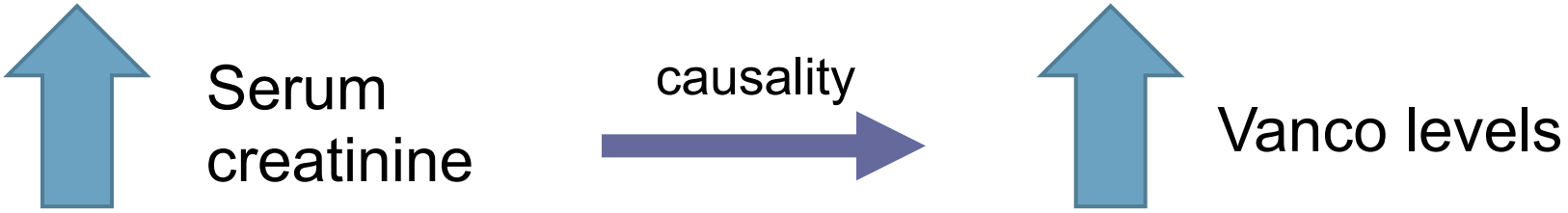
Endogenous	Exogenous/Drugs
Myoglobin (Rhabdomyolysis) Uric acid (Tumor Lysis Syndrome) Hemoglobin (Hemolysis)	Amphotericin Aminoglycosides Cisplatin Ifosfamide Acetaminophen Salicyclates Radiocontrast agents (?) Intravenous immunoglobulin Zolendronate **Vancomycin**

Is vancomycin nephrotoxic?

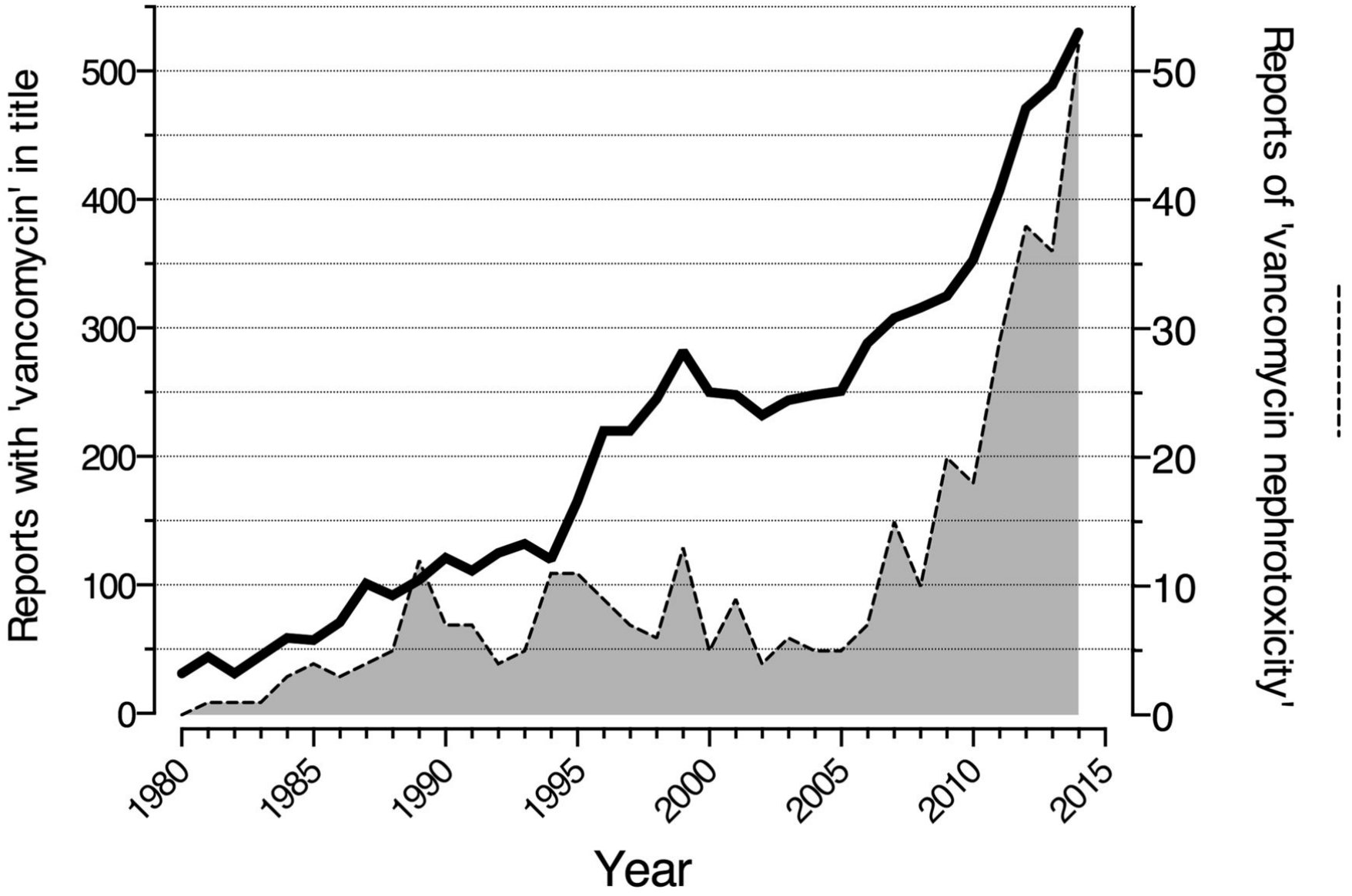
- Is it this?



- Or is it this?



Not amenable to randomized controlled trial!



Nolin, CJASN 2016

Vancomycin nephrotoxicity

7 randomized and controlled trials
N = 4033

6 – vancomycin vs linezolid
1 – vancomycin vs certaroline

6/7 – vancomycin associated with higher risk of AKI

RR 2.45 (95% confidence interval, 1.69 to 3.55)

Article

Vancomycin and the Risk of AKI: A Systematic Review and Meta-Analysis

Abhisekh Sinha Ray, Ammar Haikal,* Kassem A. Hammoud,† and Alan S.L. Yu**

Abstract

Background and objectives Vancomycin has been in use for more than half a century, but whether it is truly nephrotoxic and to what extent are still highly controversial. The objective of this study was to determine the risk of AKI attributable to intravenous vancomycin.

Design, setting, participants, & measurements We conducted a systematic review of randomized, controlled trials and cohort studies that compared patients treated with intravenous vancomycin with a control group of patients given a comparator nonglycopeptide antibiotic and in which kidney function or kidney injury outcomes were reported. PubMed and Cochrane Library were searched from 1990 to September of 2015. Two reviewers extracted data and assessed study risk of bias, and one reviewer adjudicated the assessments. A meta-analysis was conducted on seven randomized, controlled trials (total of 4033 patients).

Results Moderate quality evidence suggested that vancomycin treatment is associated with a higher risk of AKI, with a relative risk of 2.45 (95% confidence interval, 1.69 to 3.55). The risk of kidney injury was similar in patients treated for skin and soft tissue infections compared with those treated for nosocomial pneumonia and other complicated infections. There was an uncertain risk of reporting bias, because kidney function was not a prespecified outcome in any of the trials. The preponderance of evidence was judged to be indirect, because the majority of studies compared vancomycin specifically with linezolid.

Conclusions Our findings suggest that there is a measurable risk of AKI associated with vancomycin, but the strength of the evidence is moderate. A randomized, controlled trial designed to study kidney function as an outcome would be needed to draw unequivocal conclusions.

Clin J Am Soc Nephrol 11: 2132–2140, 2016. doi: 10.2215/CJN.05920616

Divisions of *Nephrology and Hypertension and †Infectious Diseases, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas

Correspondence: Dr. Alan S.L. Yu, The Kidney Institute, University of Kansas Medical Center, 3901 Rainbow Boulevard, Mail Stop 3018, Kansas City, KS 66160. Email: ayu@kumc.edu

Ray et al, CJASN 2016

Vancomycin nephrotoxicity as a function of trough level

Trough concentration (mg/L)	Toxicity
5 – 10	5%
10.1 – 15	3%
15.1 – 20	11%
20.1 – 35	23%
>35	82%

Horey et al. Ann Pharmacother. 2012;46:1477-83

What about "contrast nephropathy?"

- 6,000,000 hospitalized pts; no AKI on admit, LOS < 10 d
- Evaluated for hospital-acquired AKI

Contrast	No Contrast	
5.5%	5.6%	(unadjusted)
5.6%	5.1%	(adjusted)

CLINICAL EPIDEMIOLOGY www.jasn.org

Estimating the Risk of Radiocontrast-Associated Nephropathy

Emilee Wilhelm-Leen, Maria E. Montez-Rath, and Glenn Chertow

Department of Medicine, Division of Nephrology, Stanford University School of Medicine, Palo Alto, California

Conclusions: "…our analyses suggest that the incremental risk of AKI that can be attributed to radiocontrast is modest at worst, and almost certainly overestimated by patients, physicians, surgeons, radiologists, and other decision-makers."

Prevention of contrast-nephropathy

My approach:

- If eGFR >45 mL/min, no change in management with any iodinated contrast scan
- If eGFR 30-45 mL/min, USUALLY no change in management → evaluate for risk factors for AKI
- If eGFR <30
  - If can tolerate fluid, give 1cc/kg/hr isotonic fluid (NS versus LR) for 6 hours pre-procedure, and for 6 hours post-procedure
  - Do not give NAC, do not withhold ACEI/ARB, statins

MANAGEMENT OF ATN

- Restore renal perfusion/treat underlying condition
- Avoid further insults if possible; if drug-related, withdrawn the offending drug
- Manage accompanying volume/electrolyte/acid-base abnormalities
- Adjust renally–excreted meds to current level of kidney function
- Watch for uremic manifestations, or other indications for initiation of dialysis

Obstructive nephropathy, an uncommon cause of AKI

Intrarenal obstruction

- Stones
- Transitional cell carcinoma
- Clots
- Papillary necrosis

Ureteral obstruction

- Stones
- Transitional cell carcinoma
- External compression
  - Tumors
  - RP fibrosis
  - Lymph nodes

Bladder outlet obstruction

- BPH
- Neurogenic bladder

- Evaluation:
  - Bladder scan, bladder catheterization
  - Renal u/s

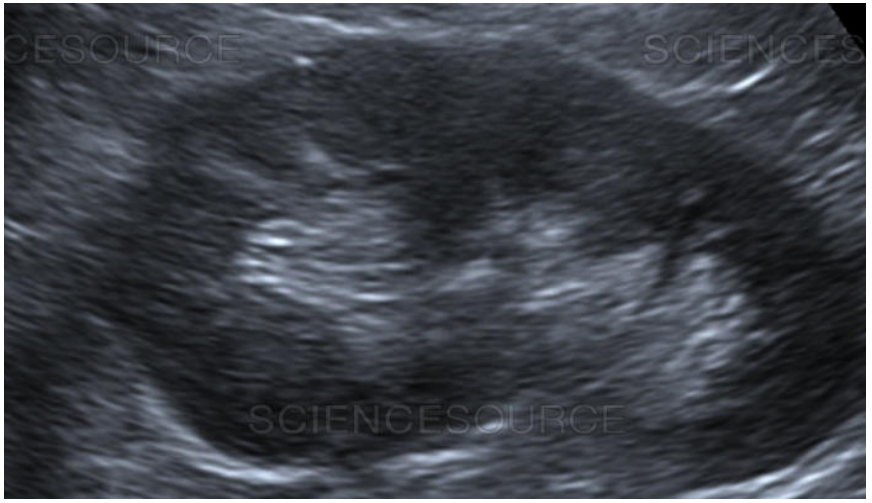
MANAGEMENT OF OBSTRUCTIVE NEPRHOPATHY

- If related to nephrolithiasis, sometimes ureteral stent
  - Sometimes requires surgical intervention
- If BPH → bladder catheterization
- If due to bladder malignancy, or external compression, generally requires percutaneous nephrostomy tube placement (IR typically)
- Watch for post-

Should you get a renal ultrasound in all AKI?

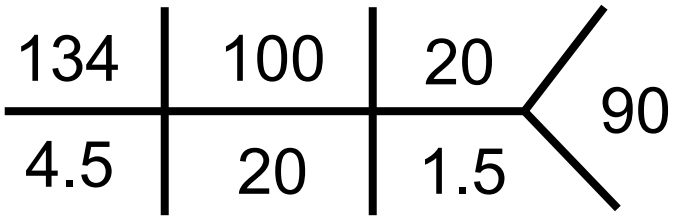
No, but you should at least consider….

- Large kidneys- amyloid (other infiltrative disease), AIN, HIV, diabetes
- Small kidneys- likely chronic process, unlikely to benefit from treatment
- Polycystic kidney disease
- Single kidney
- RP stranding/ fibrosis
- Biopsy considerations



Case 4

- 55 y/o man hospitalized for sepsis, found to have MRSA bacteremia 2/2 severe soft tissue infection
- Treated with IV vancomycin
- Initial labs:



C3: low C4: WNL

Urine:

U_{Na} 20 mEq/L

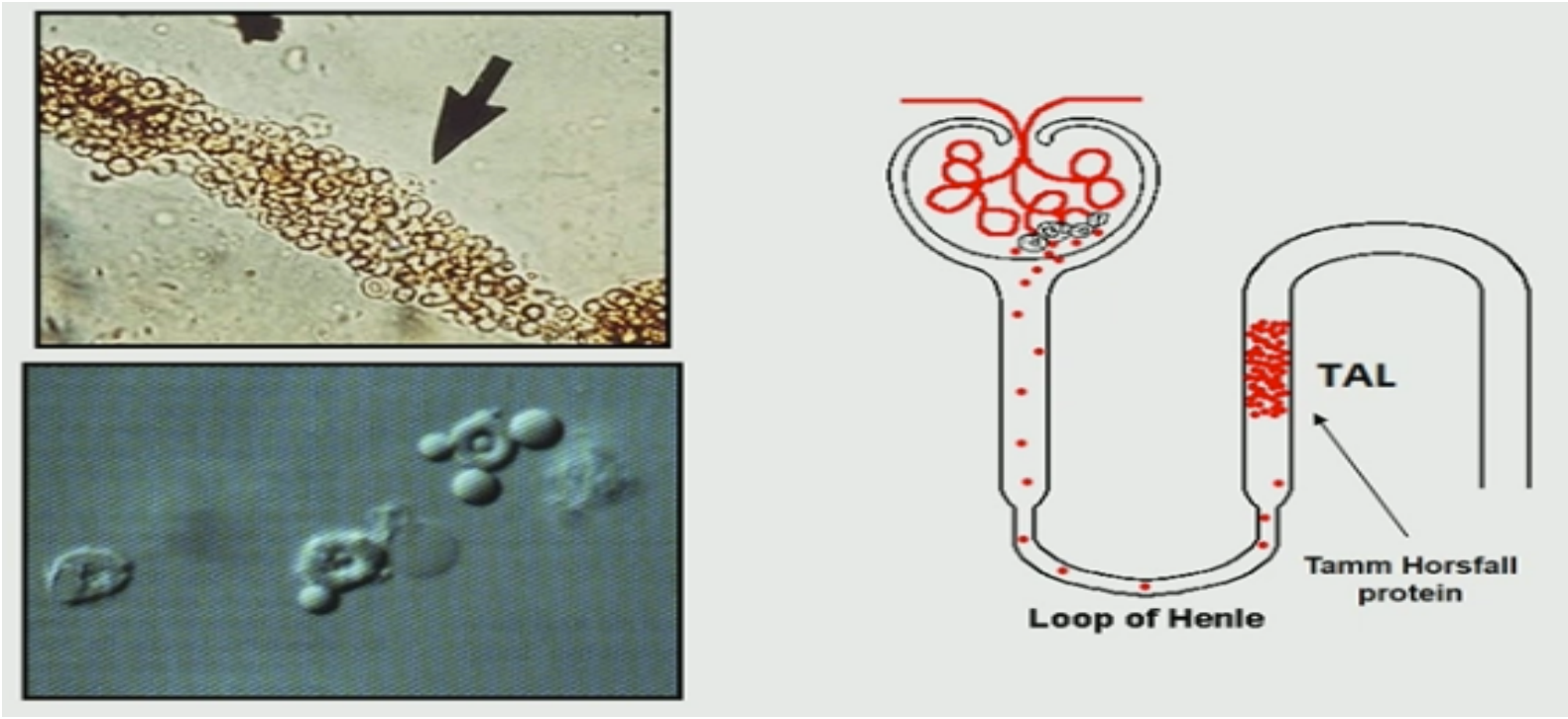
Fe Na 1%

Urine sediment: dysmorphic RBCs

Creatinine subsequently climbed daily:

1.5 → 1.7 → 2.1 → 2.3 → 2.6 → 2.9

DYSMORPHIC RBCS



INFECTION-RELATED GLOMERULONEPHRITIS

- Nearly always associated with CONCURRENT staph infection
- Distinct from post-streptococcal GN
  - Post-strep GN occurs AFTER infection
- Can be accompanied by vasculitis skin rash
- Serum complements low
  - Low C3 more common than low C4
- No serologic test available; definitive diagnosis requires kidney biopsy

GLOMERULONEPHRITIS/RPGN

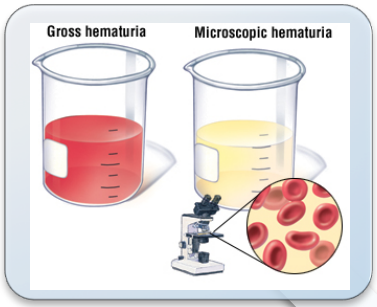
Primary Glomerular Disease	Mechanism	Disease
	Immune complex	Ig A nephropathy MPGN (HCV) Infection-related GN

Systemic Disease	Mechanism	Disease
	Antibody-mediated	Anti-GBM disease
	Pauci-immune	Small vessel vasculitis (GPA, MPA, Churg-Strauss)
	Immune complex	Lupus nephritis Cryoglobulinemia

Laboratory evaluation: Complement levels, ANCA group, anti GBM, ANA with reflexive panel

Definitive diagnosis: Kidney biopsy

Clinical clues that should prompt nephrology consultation



Concern for pulmonary-renal syndromes

Concern for AIN

Nephrotic syndrome

Renal Consult

Persistent oligoanuria with AKI

Take-home points

- Urine microscopy is a simple and useful tool
  - Granular casts → if >6/hpf, likely to be ATN
  - Dysmorphic RBCS → think about glomerular pathology

- >90% of AKI in hospitalized patients is low EABV (including pre-renal, cardiorenal, hepatorenal) or ATN

- AKI in the contemporary hospitalized patient can be multifactorial with overlapping causes

Questions?

KIDNEY RESEARCH INSTITUTE

A collaboration between
Northwest Kidney Centers and UW Medicine