Diagnosis and Management of Acute Kidney Injury

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BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

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Disclosures

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- Sidereal Therapeutics
- Casma Therapeutics
- MexBrain
- Entrada
- CardioRenal Systems, Inc.
- Alexion Pharmaceuticals

Clinical Research in AKI

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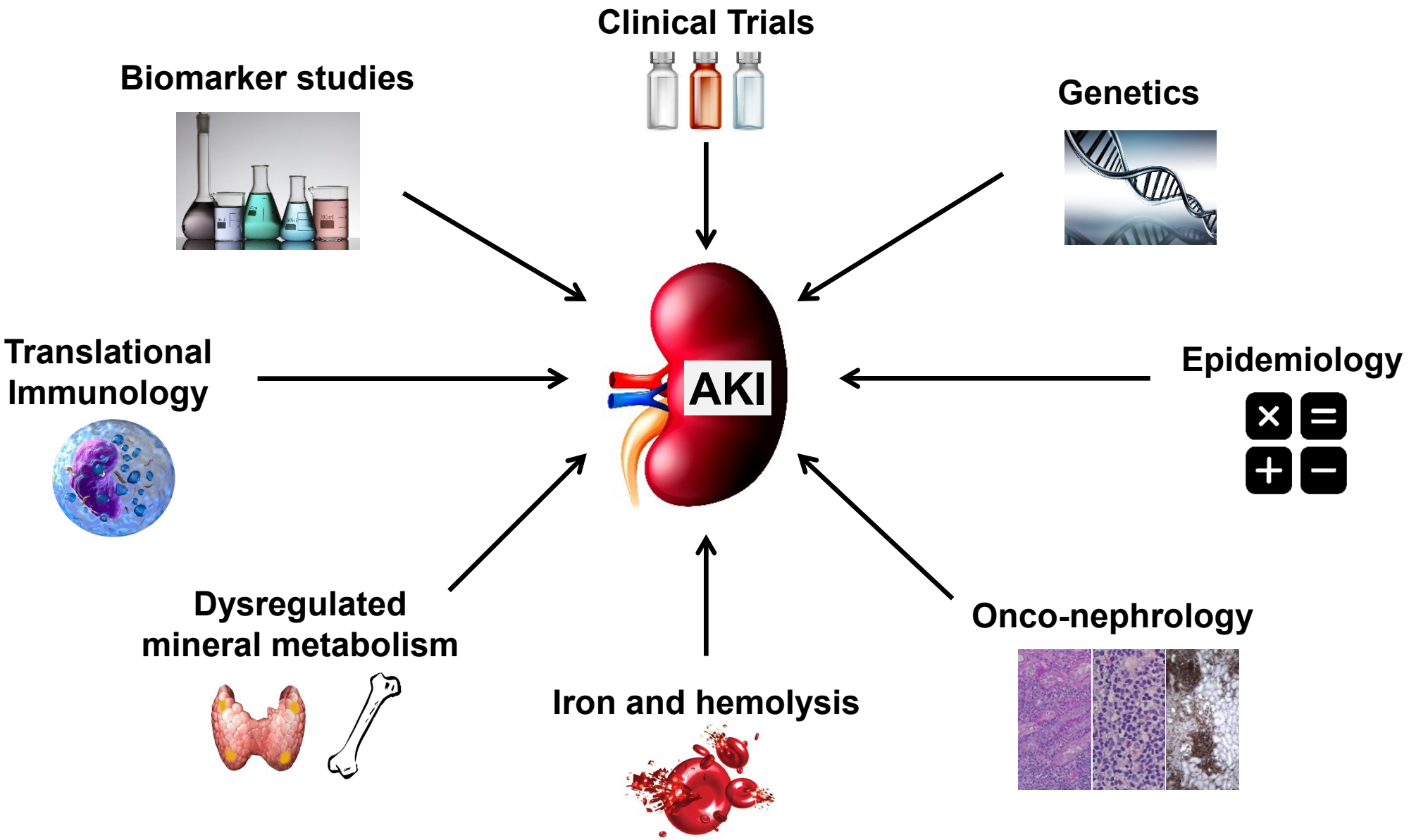
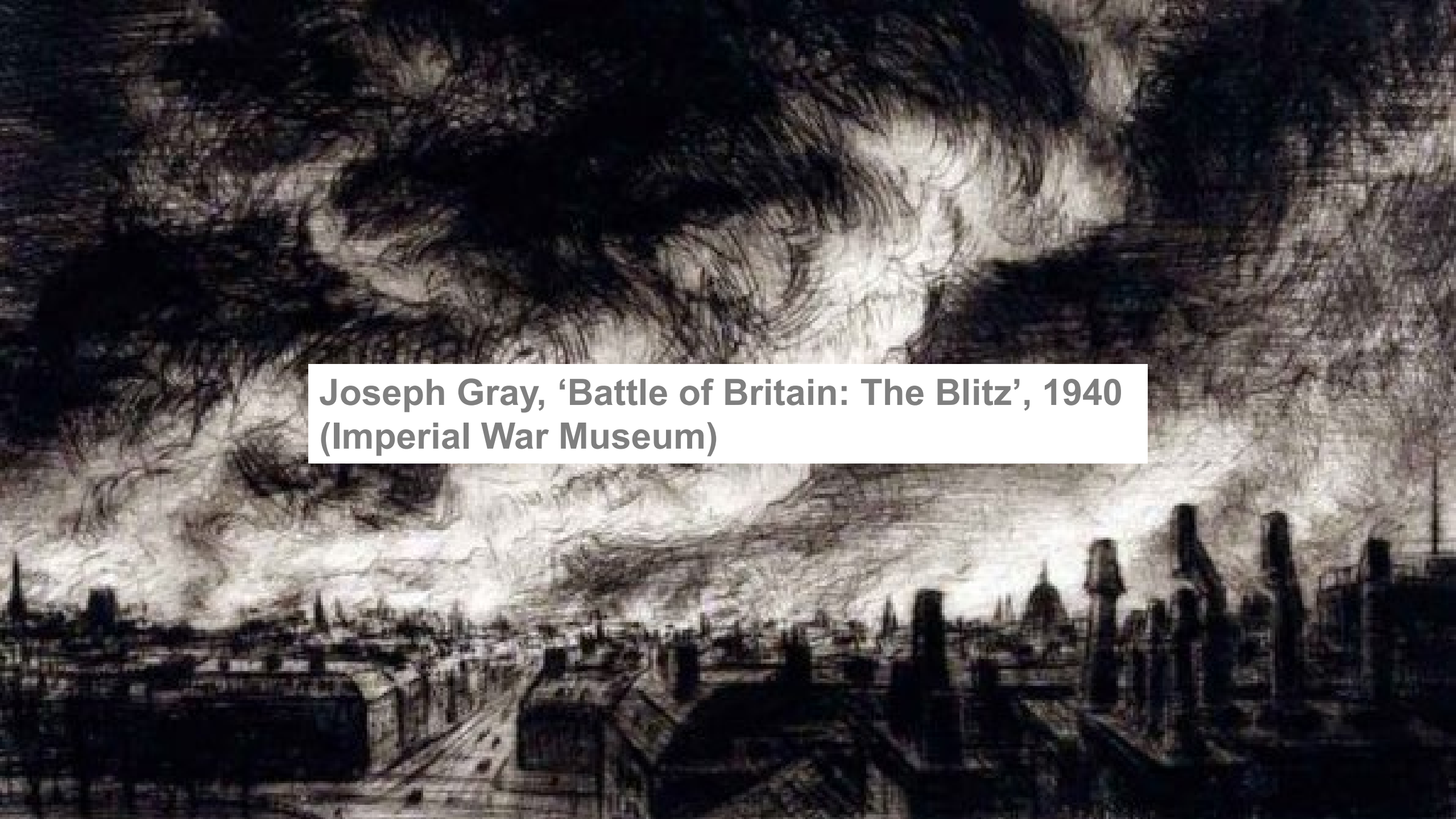




Joseph Gray, ‘Battle of Britain: The Blitz’, 1940 (Imperial War Museum)

Original Description of AKI

BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 22 1941

CRUSH INJURIES WITH IMPAIRMENT OF RENAL FUNCTION

BY

E. G. L. BYWATERS, M.B., B.S., M.R.C.P.

Beit Memorial Fellow

AND

D. BEALL, Ph.D.Toronto

(From the Departments of Medicine and Pathology, British Postgraduate Medical School)

[WITH SPECIAL PLATE]

Amongst air-raid casualties seen at this hospital have been four cases of crush injury of the limbs which, because of the general similarity of their clinical course, were thought to represent a specific and hitherto unreported syndrome, and one which has been and will be seen elsewhere during the war. Such a condition may have been observed in civil practice, but we have been unable to find any account of it in the literature. The cases are of interest on account of the problem propounded by both pathogenesis and treatment. The picture presented by these four cases, and substantiated by others, is briefly as follows:

The patient has been buried for several hours with pressure on a limb. On admission he looks in good condition except for swelling of the limb, some local anaesthesia, and wheals. The haemoglobin, however, is raised, and a few hours later, despite vasoconstriction, made manifest by pallor, coldness, and sweating, the blood pressure falls. This is restored to pre-shock level by (often multiple) transfusions of serum, plasma, or, occasionally, blood. Anxiety may now arise concerning the circulation in the injured limb, which may show diminution of arterial pulsation distally, accompanied by all the changes of incipient gangrene. Signs of renal damage soon appear, and progress even though the crushed limb be amputated. The urinary output, initially small, owing perhaps to the severity of the shock, diminishes further. The urine contains albumin and many dark brown or black granular casts. These later decrease in number. The patient is alternately drowsy and anxiously aware of the severity of his illness. Slight generalized oedema, thirst, and incessant vomiting develop, and the blood pressure often remains slightly raised. The blood urea and potassium, raised at an early stage, become progressively higher, and death occurs comparatively suddenly, frequently within a week. Necropsy reveals necrosis of muscle and, in the renal tubules, degenerative changes and casts containing brown pigment.

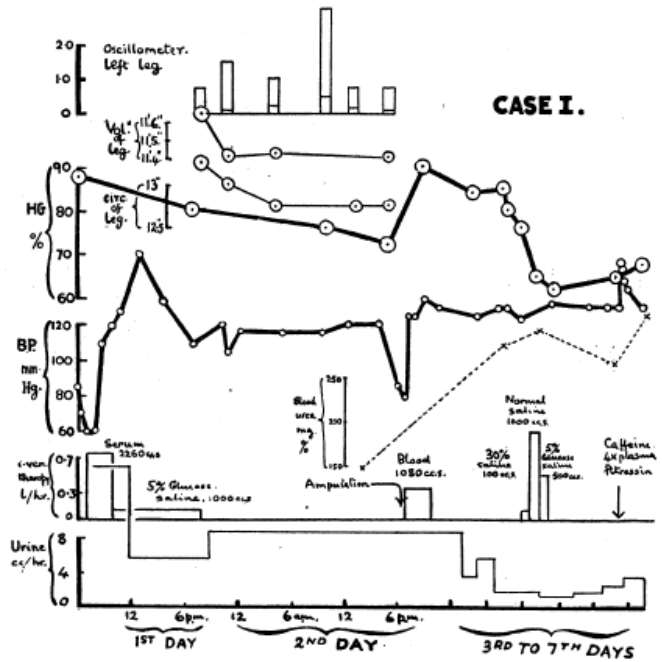


CHART I.—Case I.

Case I

A female aged 17 had been buried for nine hours with heavy masonry lying across the left leg. On admission she showed slight bruises generally, and multiple superficial abrasions below the left knee. The leg was swollen and sensation was impaired at the ankle, where all power and movement were lost. Other limbs appeared undamaged. The skin was pallid and clammy; the blood pressure was 85/70 mm. Hg. The clinical course is shown on Chart I. Recalcified plasma-saline (Clegg and Dible, 1940) (subsequently referred to as "serum"), followed by 5% glucose-saline,

Eric Bywaters, MB BS

Jan 6, 1910 – Feb 4, 2003

Hammersmith Hospital, London

Pigmented cast in a renal collecting tubule

Case #1

- 67yoF prisoner sent to ED for AMS
- PMHx: Not available
- Meds: None
- Soc Hx: Institutionalized
- Exam: **T 102.6, BP 88/50, HR 112, RR 24, SpO2 92%RA**
- HEENT: Icteric sclerae
- CV: Tachycardic, **?pericardial friction rub**
- Lungs: **Crackles ½ up bilaterally**
- Abd: Soft, non-distended, tender in RUQ
- Ext: Skin jaundiced, **3+ lower extremity edema**
- Neuro: **Obtunded; responsive to sternal rub only**

Case #1

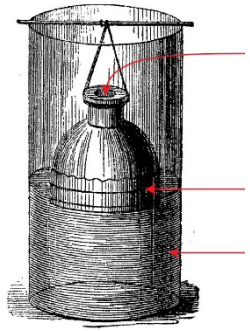
What lab studies do you want?

K 14.1 mEq/L BUN 396 mg/dL

September 11, 1945: first life-saving hemodialysis procedure

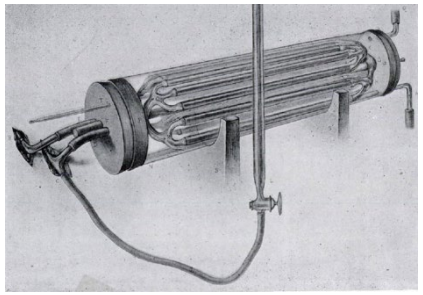
Early days of hemodialysis

1854



Thomas Graham
Ox bladder in distilled water

1912

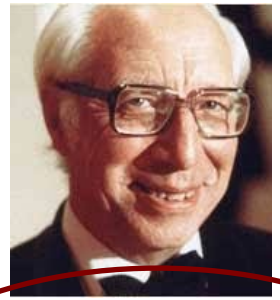


Abel, Rowntree, Turner
"Vividiffusion"
2 hour procedure on a rabbit

1924

Georg Haas
First ever HD session (15 min)

September 11, 1945

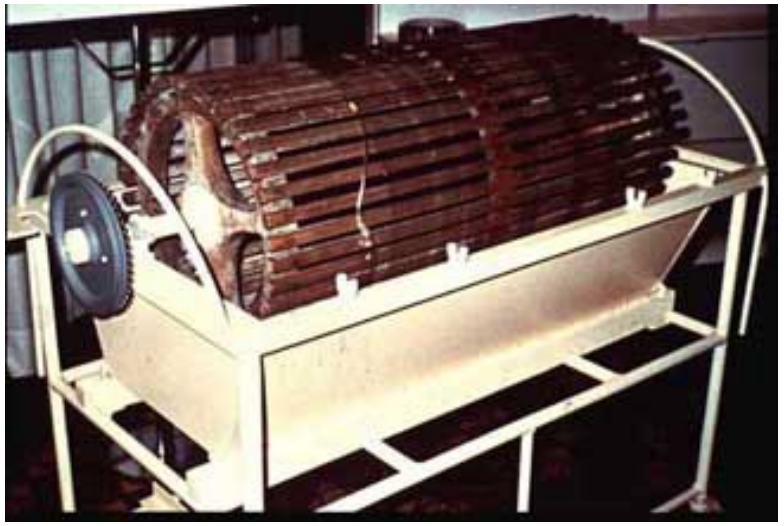


Willem Kolff
First life saved using hemodialysis

Slide courtesy of Dr. Sus Waikar

Early days of hemodialysis

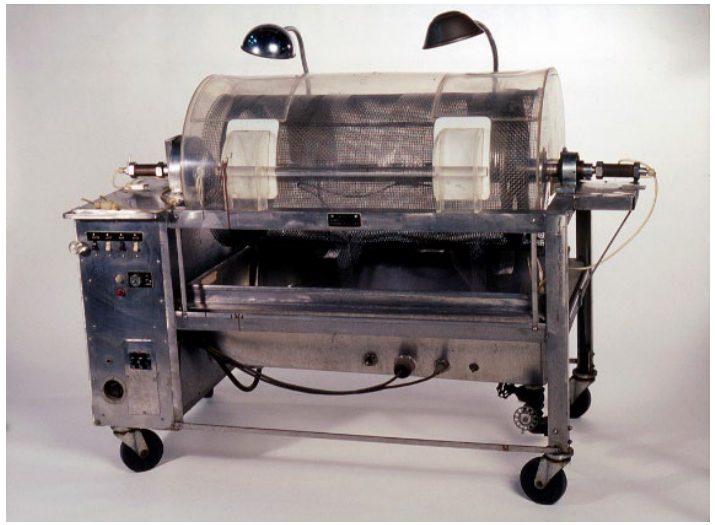
1945



Kolff Rotating Drum artificial kidney

Built out of scraps of metal and wood; 20-meter long cellophane sausage casing used as a semi-permeable membrane

1950



Kolff-Brigham Artificial Kidney

George Thorn invited Kolff to PBBH; Kolff worked with Carl Walters and John Merrill to redesign the rotating drum machine

December 23, 1954:

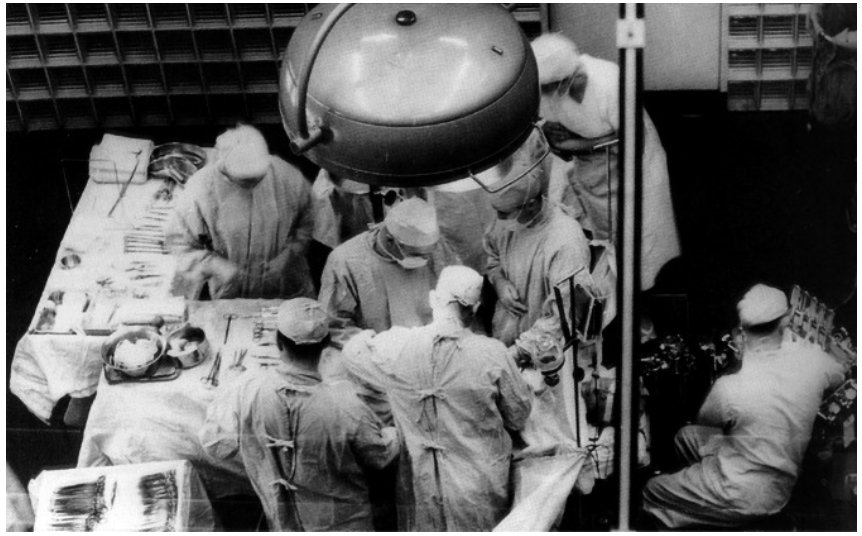
First Successful Kidney Transplant

“Never before has such a feat of organ transplanting in man been accomplished. In no other case in the history of medicine has a human kidney transplant ‘taken’ and lasted so long. Attempts at transplanting other organs have not succeeded either.”

-Robert K. Plumb, New York Times

MAN'S LIFE SAVED BY TWIN'S KIDNEY

Identical Brother Furnishes Organ in First Successful Transplanting Surgery



2 American Transplant Pioneers Win Nobel Prize in Medicine

Tens of thousands of lives have been saved through their work.

1990: Dr. Joseph Murray awarded the Nobel Prize in Physiology or Medicine

Acute Kidney Injury (AKI) Today: A Major Public Health Burden

AKI occurs in ~10% of hospitalized patients and up to 50% of ICU patients

Costs >$10B annually in the U.S. alone

Patients who develop AKI are at ↑↑risk of in-hospital death

Those who survive have an increased risk of CKD, ESKD, and CV events

No therapy reliably prevents or treats AKI

Outline

AKI Definitions

Epidemiology of AKI

Diagnostic Approach

Management

Why AKI is the most interesting topic in internal medicine

Acute Kidney Injury (AKI) Nomenclature

or the syndrome formerly known as “Acute Renal Failure”

“Acute”

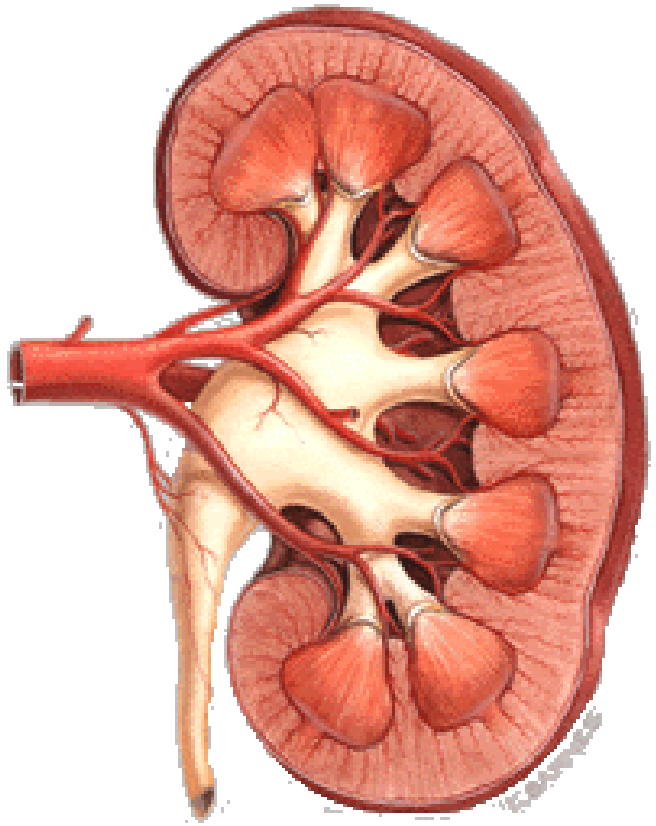
Happens within hours to days

“Kidney”

More familiar to patients than “Renal”

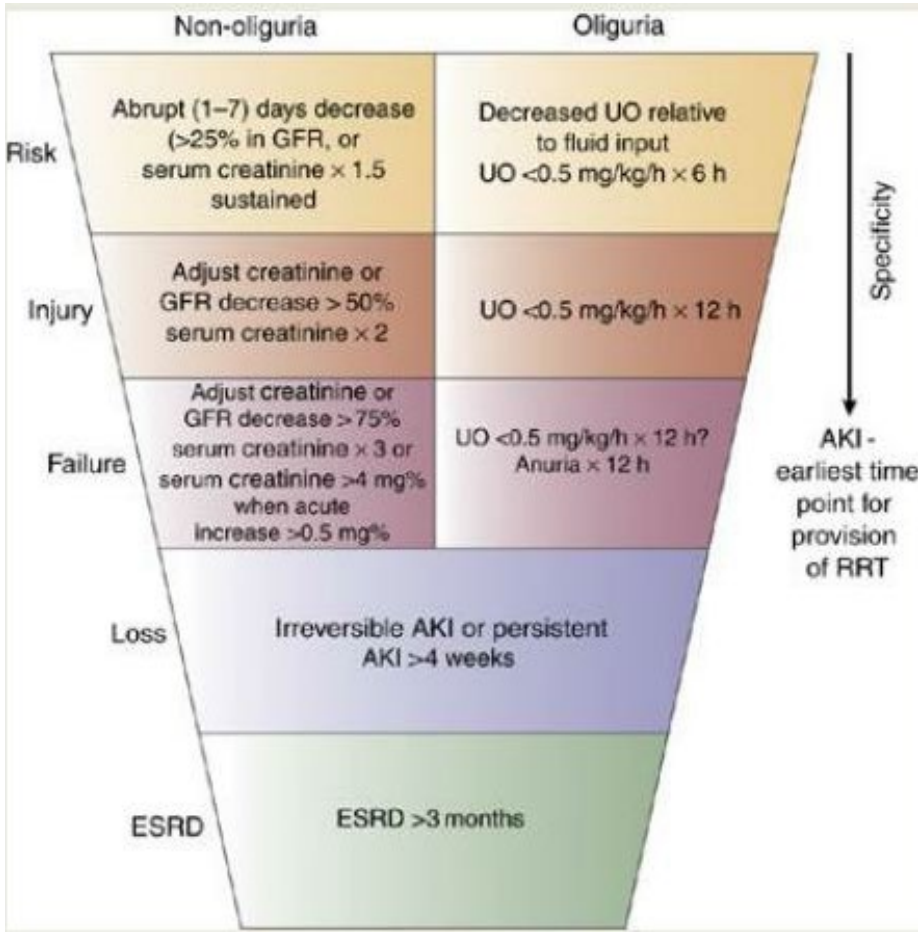
“Injury”

Refers to organ damage (“Failure” implies need for dialysis)



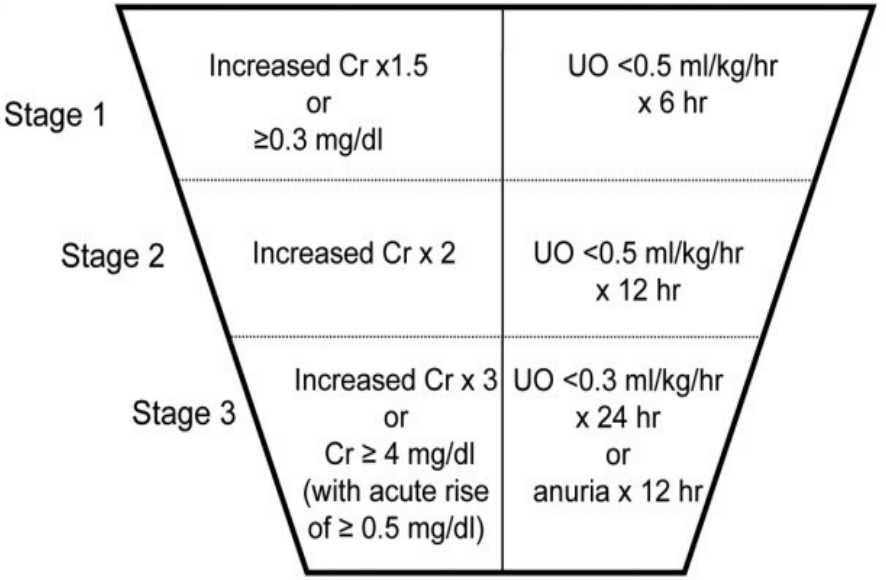
Historical Consensus Definitions of AKI

RIFLE Criteria



Crit Care, 2004

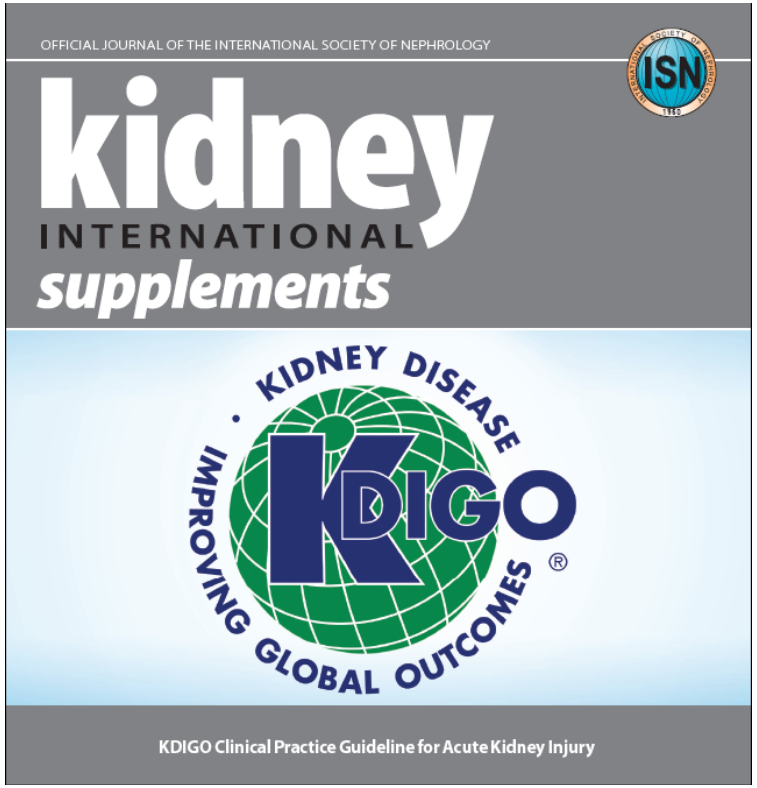
AKIN Criteria



Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT.

Crit Care, 2007

Current Consensus Definition of AKI



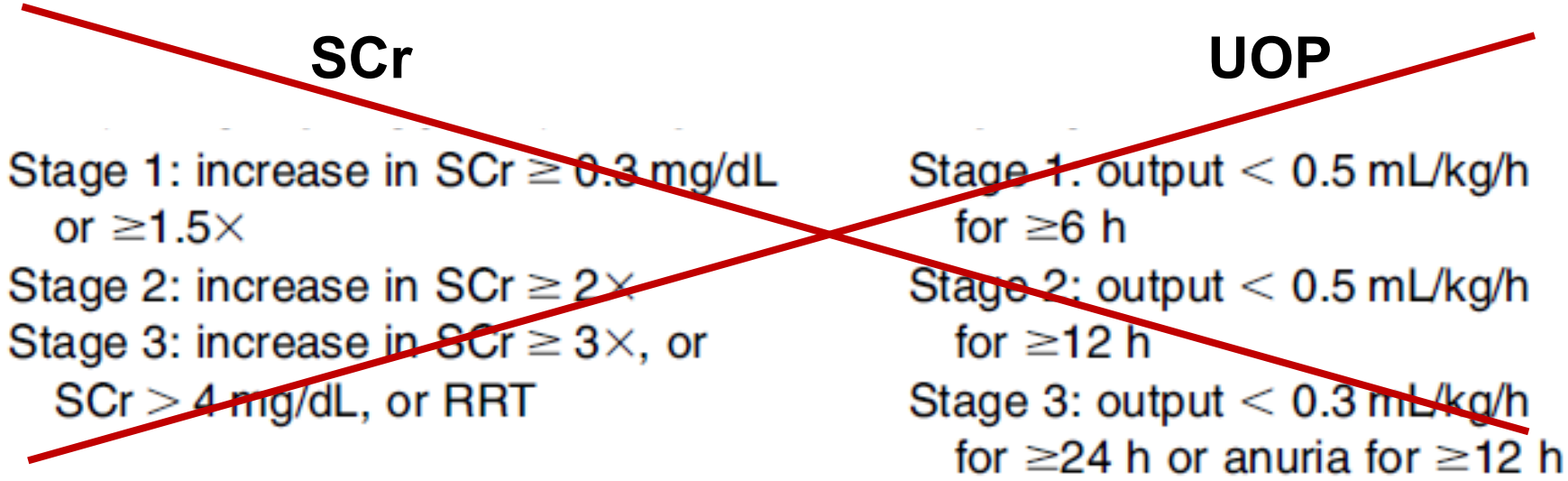
***Kidney Int*, 2012**

"KDIGO" Definition of AKI

Any of the following:

- ↑SCr ≥0.3 mg/dL in 48h or ≥50% in 7d
- Oliguria (UOP <0.5 ml/kg/h x 6h)
- Dialysis

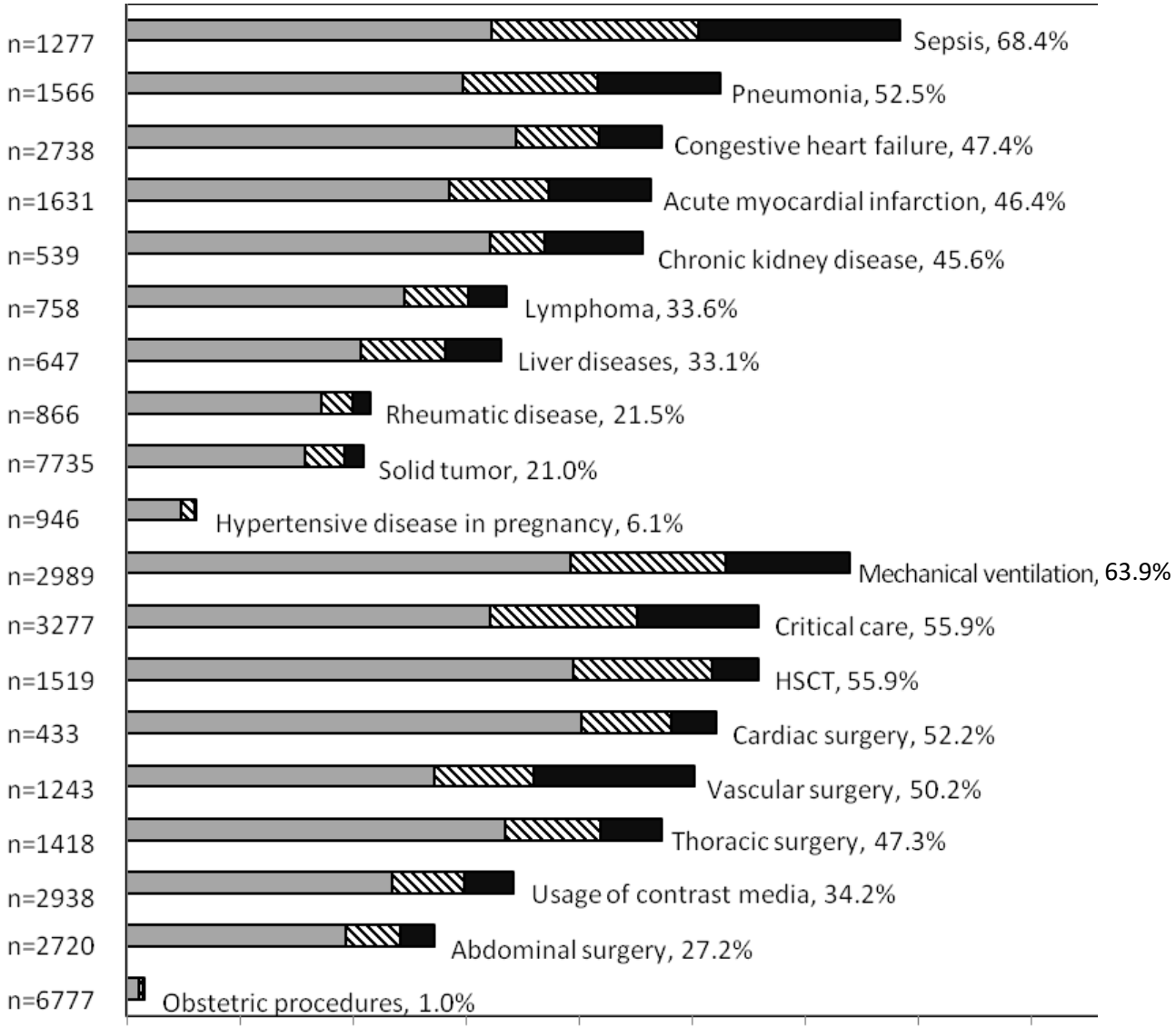
Staging of AKI severity

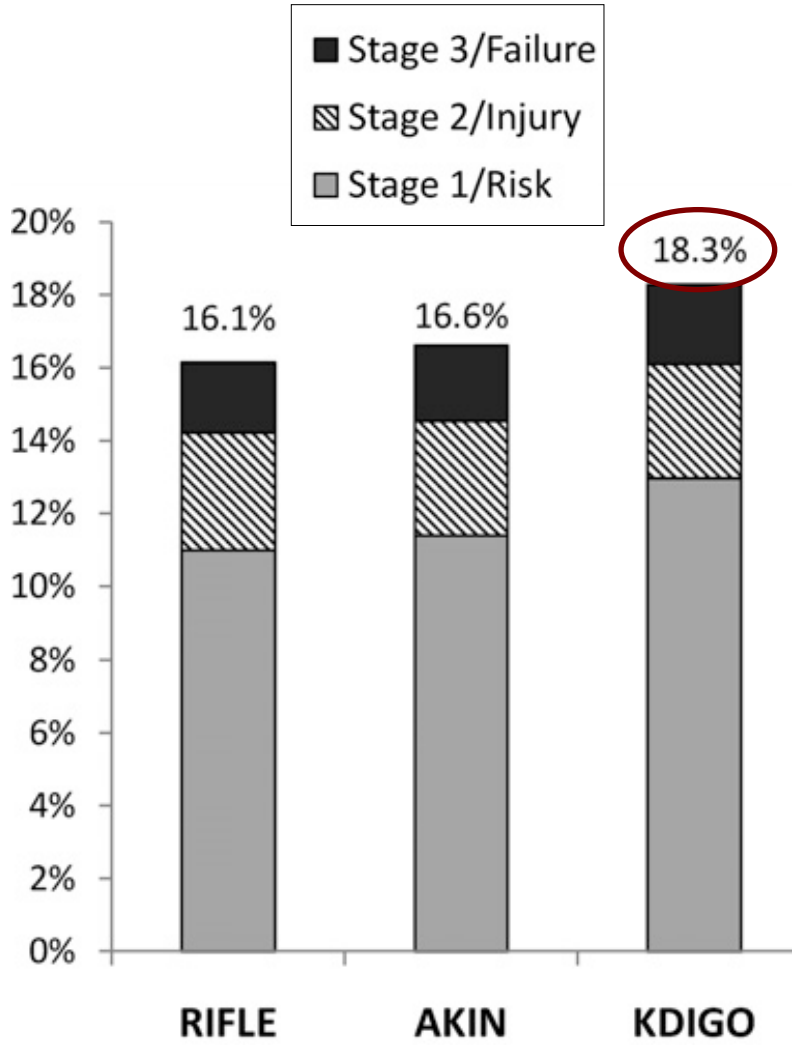


"On rounds, when a medical student presents a case of AKI, the focus may turn to the KDIGO-sanctioned stage: is it 1a or is it 1b, or could it even be stage 2? **We then have less time to argue over why the creatinine is increased in the first place…**"

–Sushrut Waikar, *Kidney Int*, 2019

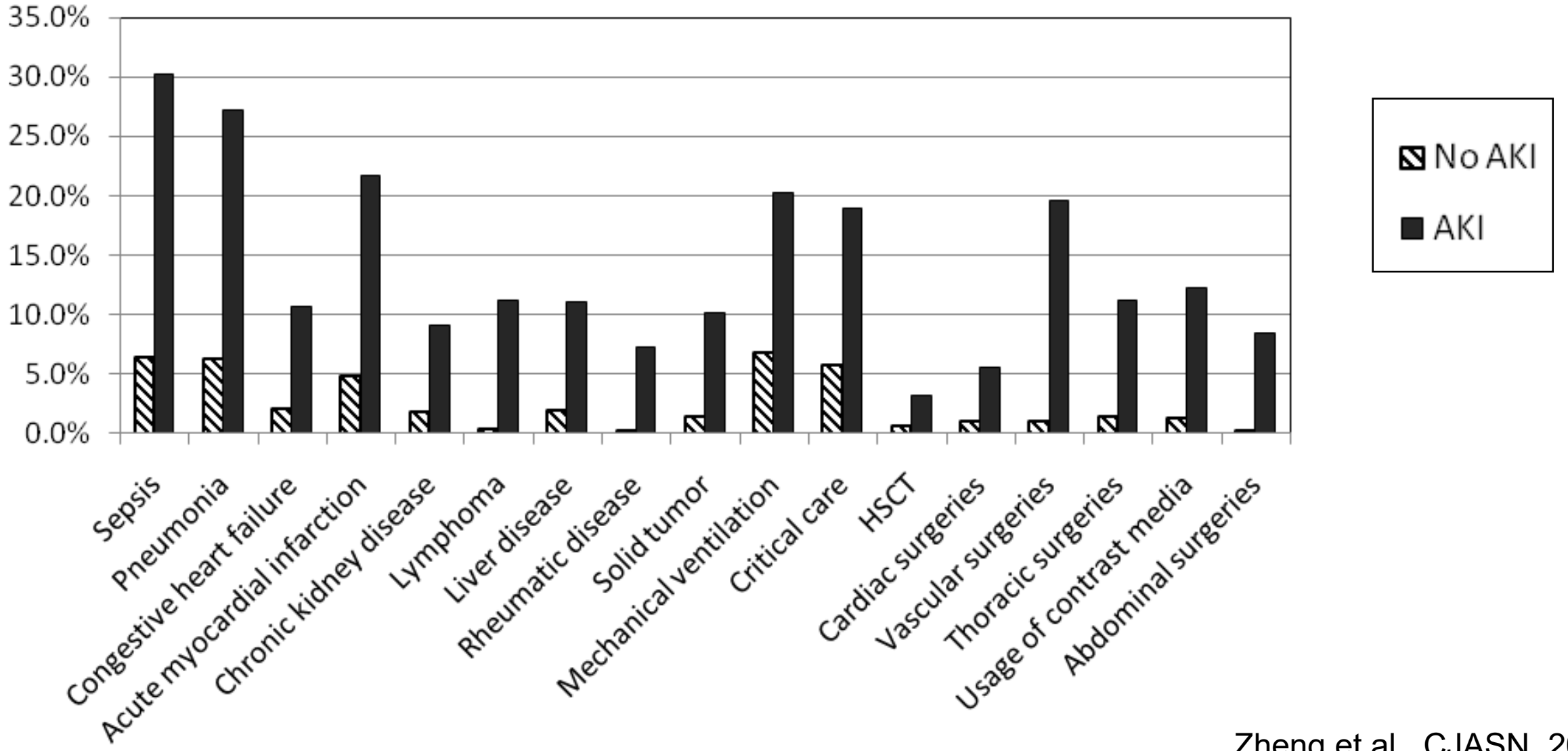
Incidence of AKI among hospitalized patients at BWH (*n*=31,971) in 2010





Zheng et al., CJASN, 2013

Mortality associated with AKI



Zheng et al., CJASN, 2013

Case #2: History, Vitals, Exam, Labs

37M with Crohn's disease s/p subtotal colectomy admitted with cough, fatigue → **LLL PNA**

Vitals

T: 101.5
BP: 115/ 71
HR: 148
RR: 20
SpO2: 98% RA

Exam

Gen: NAD
Lungs: Clear
CV: Tachycardia
Abd: Non-tender

Labs

129	90	6
4.8	20	0.85

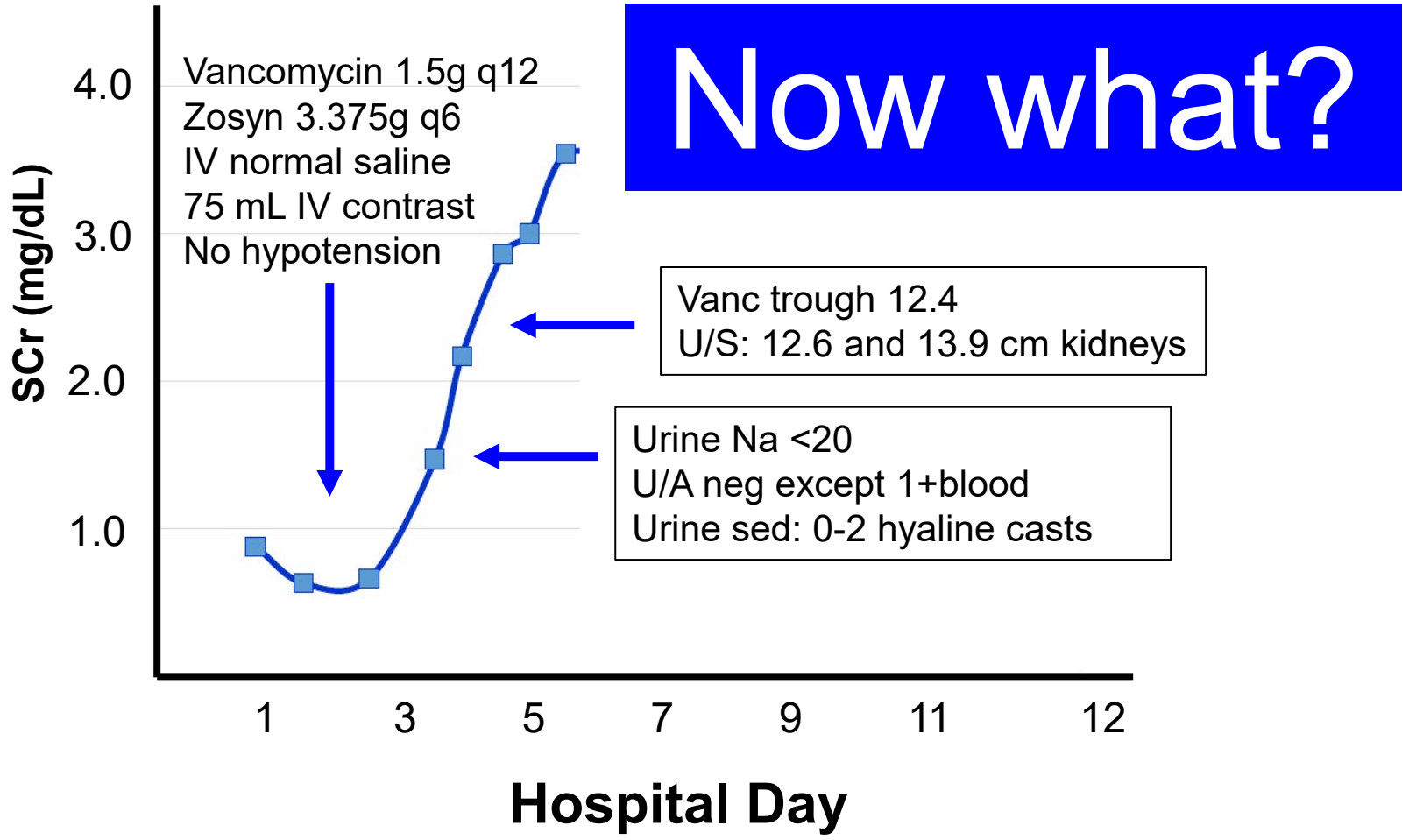
WBC 25.8 (87% N)
Hgb 14.3; Plts 501

AST 11, ALT 11, ALK-P 111
T.Bili 0.4, Alb 3.0

BCx, flu, legionella: all neg
CTAP w/ IV contrast: neg

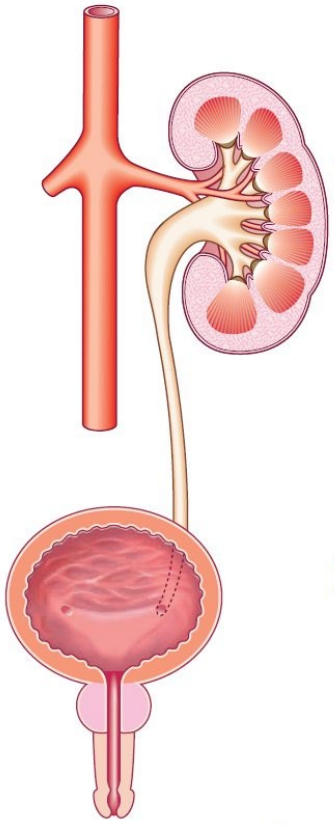
Case 2: Hospital Course

Case 2: Hospital Course



Classification and Common Etiologies of AKI

Physiologic Classification



PRE-RENAL

Impaired perfusion:
- Cardiac failure
- Sepsis
- Blood loss
- Dehydration
- Vascular occlusion

RENAL

Glomerulonephritis
Small-vessel vasculitis
Acute tubular necrosis
- Drugs
- Toxins
- Prolonged hypotension

Interstitial nephritis
- Drugs
- Toxins
- Inflammatory disease
- Infection

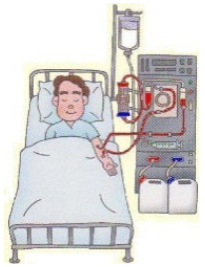
POST-RENAL

Urinary calculi
Retroperitoneal fibrosis
Benign prostatic enlargement
Prostate cancer
Cervical cancer
Urethral stricture/valves
Meatal stenosis/phimosis

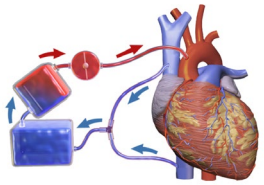
Davidsons Essentials of Medicine, 2nd edition

Common clinical settings where AKI occurs

Sepsis



Cardiac surgery



Nephrotoxins

Exogenous

- Chemotherapy
- Antibiotics
- NSAIDs
- IV contrast

Endogenous

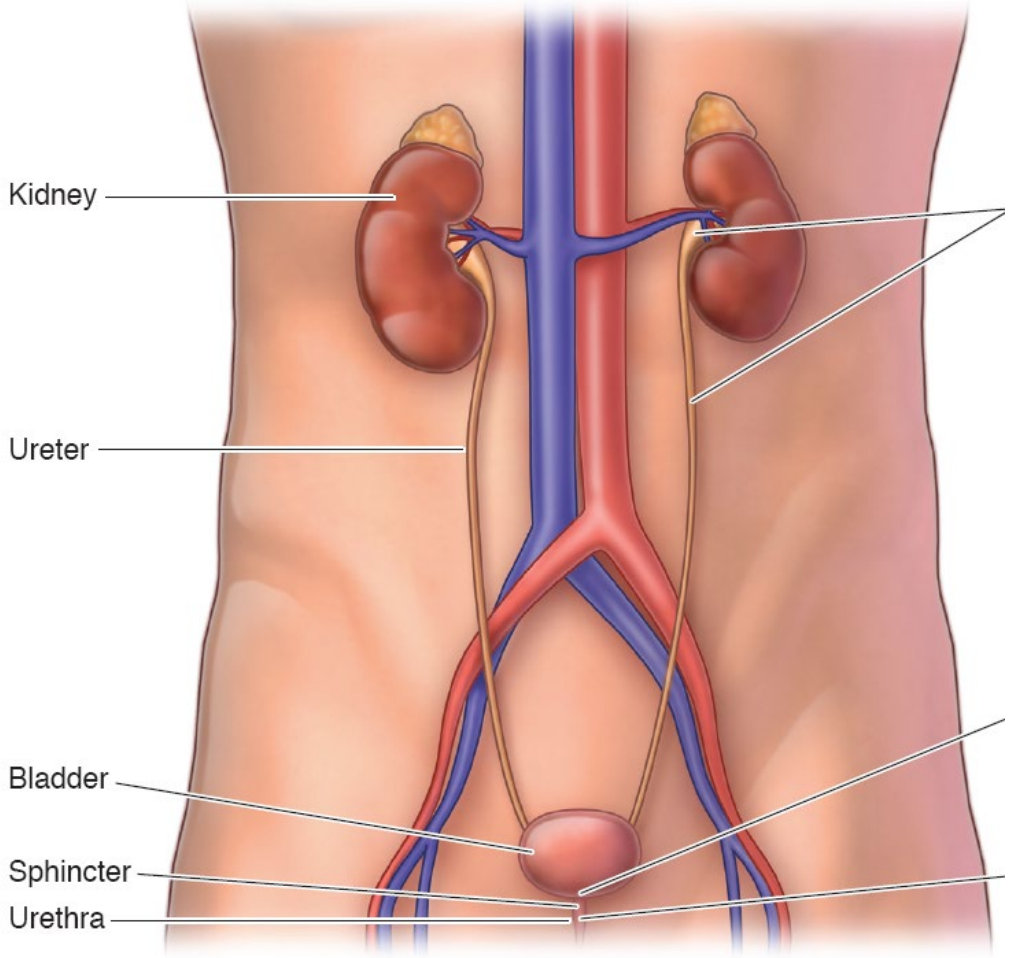
- Myoglobin (rhabdo)
- Hemoglobin (MAHA)
- Uric acid (TLS)

Approach to the Patient with AKI

Pre-Renal

Intrinsic Renal

Post-Renal



Waikar & Bonventre, AKI chapter in Harrison's Principles of Internal Medicine, 18th ed.

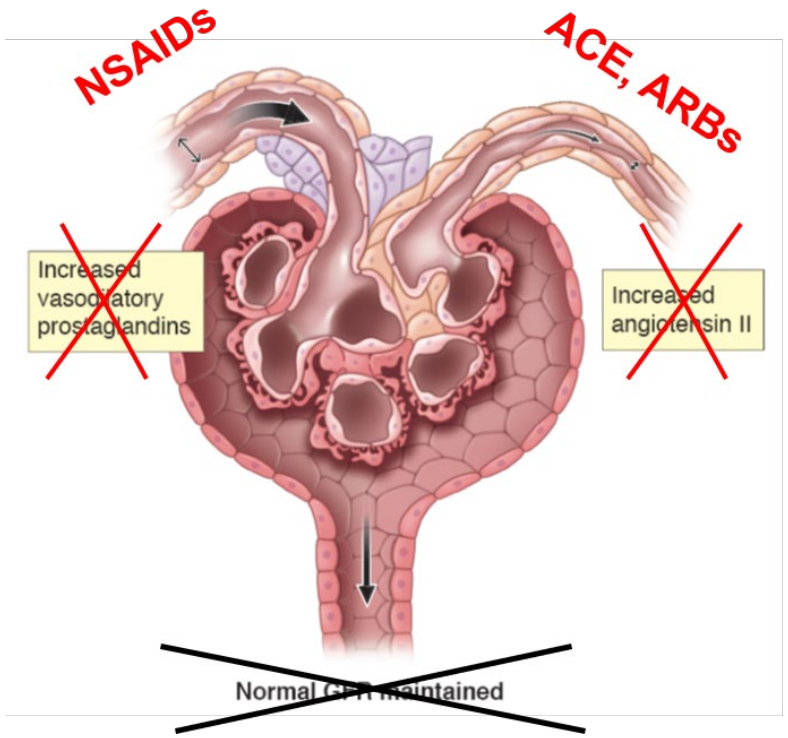
Pre-renal ~~AKI~~ azotemia

Overview

- **No structural injury to kidney**
- SCr increases due to renal hypoperfusion
- Restoration of hemodynamics -> rapid recovery

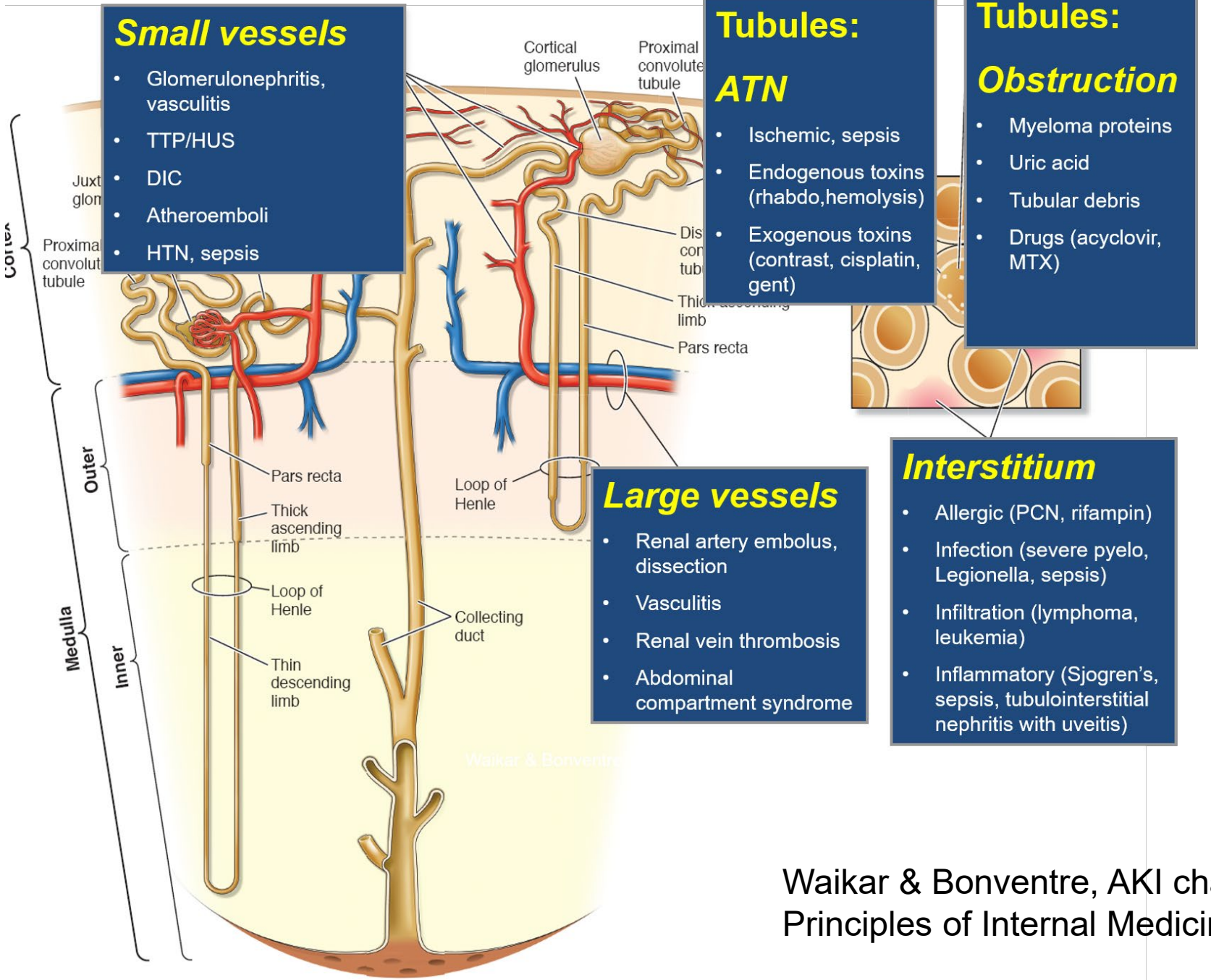
Causes

- "True" Volume depletion
  - GI losses, hemorrhage
- ↓Effective arterial blood volume
  - CHF, HRS
- Impaired renal hemodynamics
  - NSAIDs (afferent vasoconstriction)
  - ACE-I/ARBs (efferent vasodilation)



Waikar & Bonventre, AKI chapter in Harrison's Principles of Internal Medicine, 18th ed.

Intrinsic renal disease



Small vessels

- Glomerulonephritis, vasculitis
- TTP/HUS
- DIC
- Atheroemboli
- HTN, sepsis

Tubules: ATN

- Ischemic, sepsis
- Endogenous toxins (rhabdo,hemolysis)
- Exogenous toxins (contrast, cisplatin, gent)

Tubules: Obstruction

- Myeloma proteins
- Uric acid
- Tubular debris
- Drugs (acyclovir, MTX)

Large vessels

- Renal artery embolus, dissection
- Vasculitis
- Renal vein thrombosis
- Abdominal compartment syndrome

Interstitium

- Allergic (PCN, rifampin)
- Infection (severe pyelo, Legionella, sepsis)
- Infiltration (lymphoma, leukemia)
- Inflammatory (Sjogren's, sepsis, tubulointerstitial nephritis with uveitis)

Waikar & Bonventre, AKI chapter in Harrison's Principles of Internal Medicine, 18th ed.

Post-renal: A plumbing problem

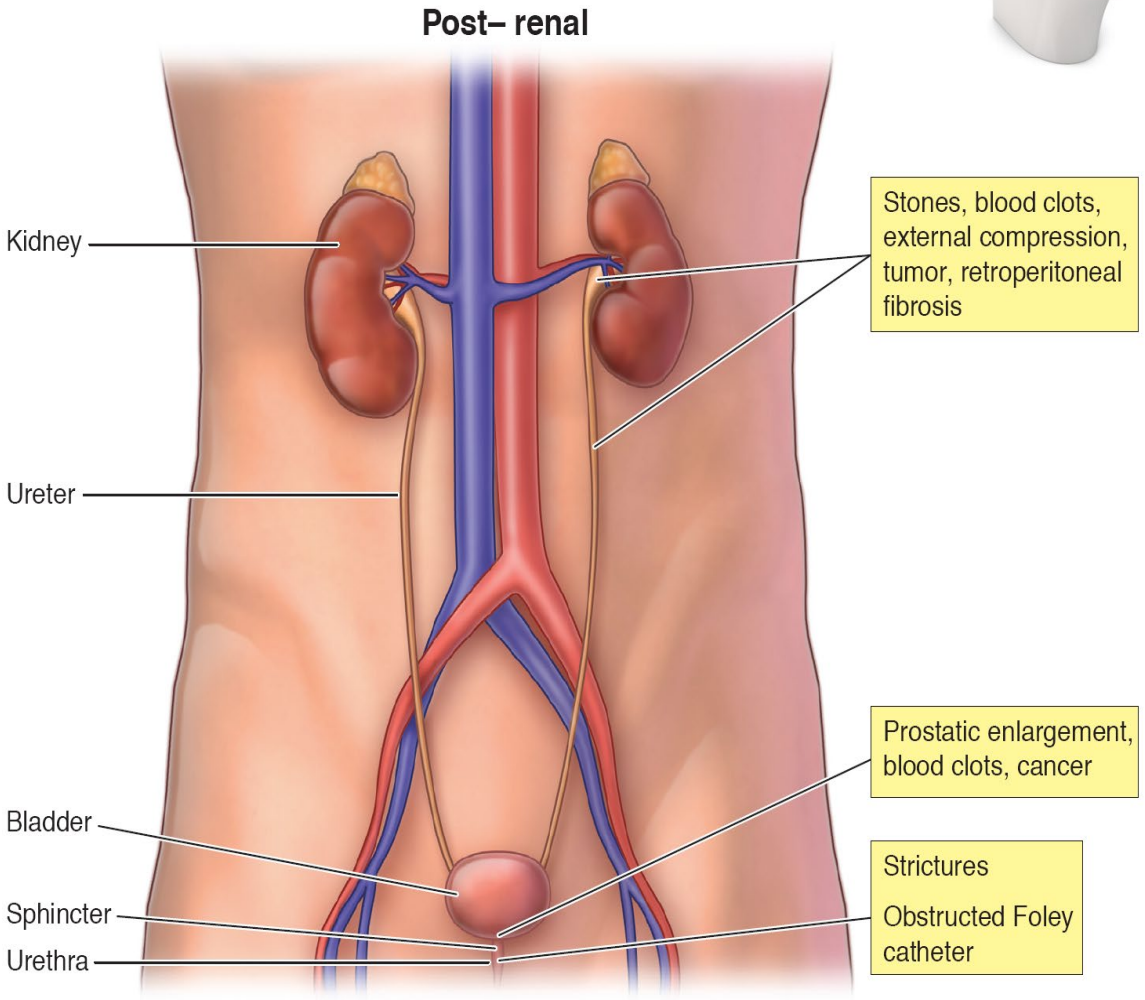
Diagnostic/imaging workup:

- Bladder scan or insert Foley
- Renal U/S or CTAP

However, not every patient with AKI needs a renal U/S! (utility heavily dependent on pre-test probability)

Pearl

- Early in the course of obstruction, beware of false negatives on imaging



Waikar & Bonventre, AKI chapter in Harrison's Principles of Internal Medicine, 18th ed.

Studies to consider ordering (depending on clinical context!)

Urine Tests

- UA, Sediment, Sodium (FeNa)

Blood Tests

- GN: ANCA, anti-GBM, ANA, C3, C4, HCV, cryo
- TLS: Uric acid, Ca, PO4, LDH
- Hemolysis: LDH, haptoglobin, smear
- Rhabdo: CPK
- Paraprotein disorder: SPEP, SFLCs

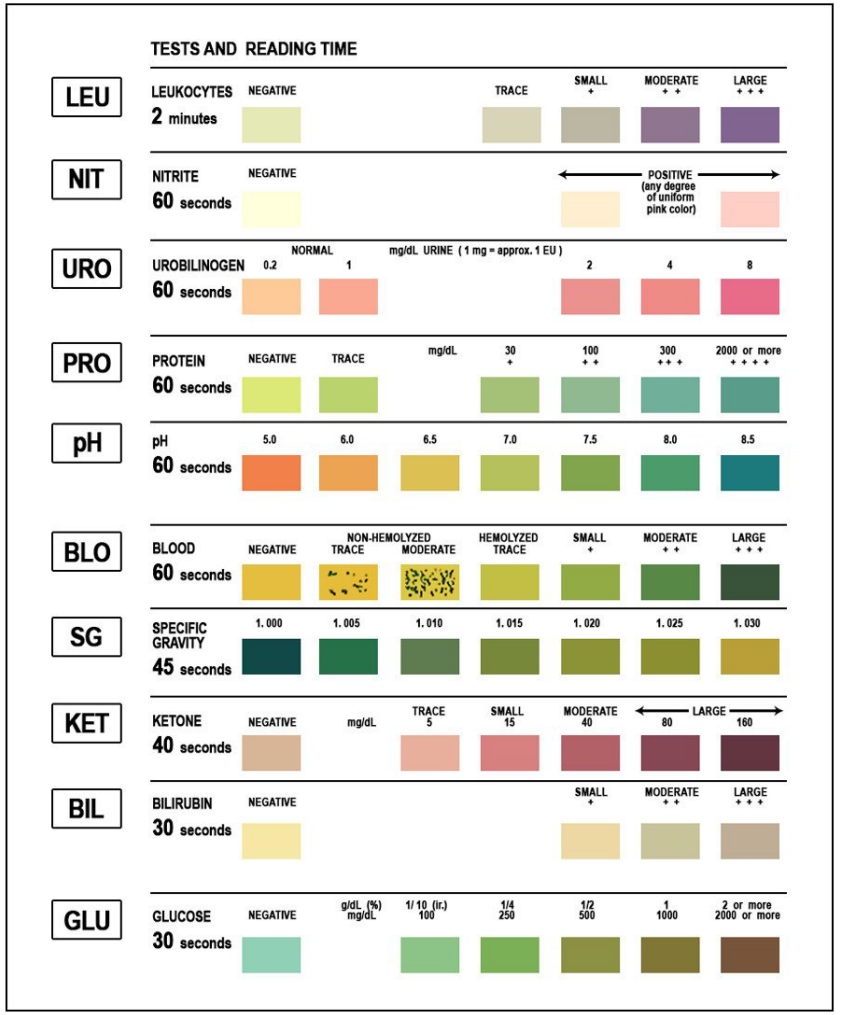
Radiographic Tests

- Renal U/S or CTAP

Pearls re Urinalysis and AKI

- "Blood" (heme) on UA but no RBCs in urine sediment: think **rhabdo** or **hemolysis**
- "Protein" on UA only detects albumin (can miss other causes of proteinuria, like MM)
- Normoglycemic glucosuria: think **proximal tubular dysfunction** (aka Fanconi's syndrome)

  Tenofovir
  Ifosphamide
  Cisplatin
  Myeloma



Urinalysis/Urine Sediment and AKI

UA/urine sediment finding	Diagnosis
3+Blood on dipstick, no RBCs on sediment	
3+hematuria, 3+proteinuria, RBCs, WBCs	
Completely bland (no protein, no LE/nit/heme, no WBC/RBC)	
Granular casts	
Sterile pyuria	
Oxalate crystals	

Fractional Excretion of Sodium (FeNa)

Percentage of **filtered** sodium that is **excreted**

$$FENa = \frac{\text{Urine Na x Serum Cr}}{\text{Serum Na x UrCr}}$$

Traditional teaching: <1% = pre-renal; >2% = ATN

Low FeNa does not necessarily mean give IVF!

Causes of low FeNa:

- GN
- Rhabdo
- IV Contrast

Causes of high FeNa:

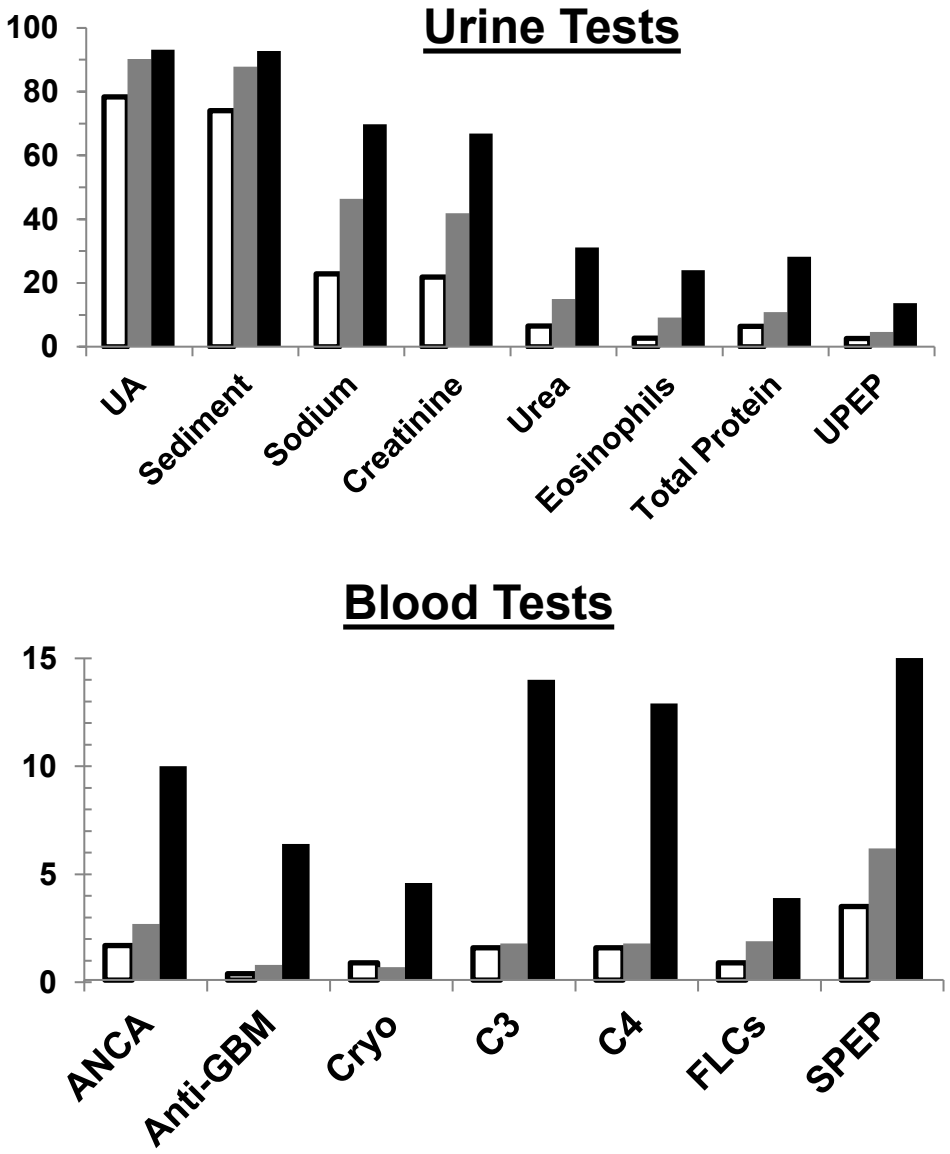
- Diuretics
- CKD

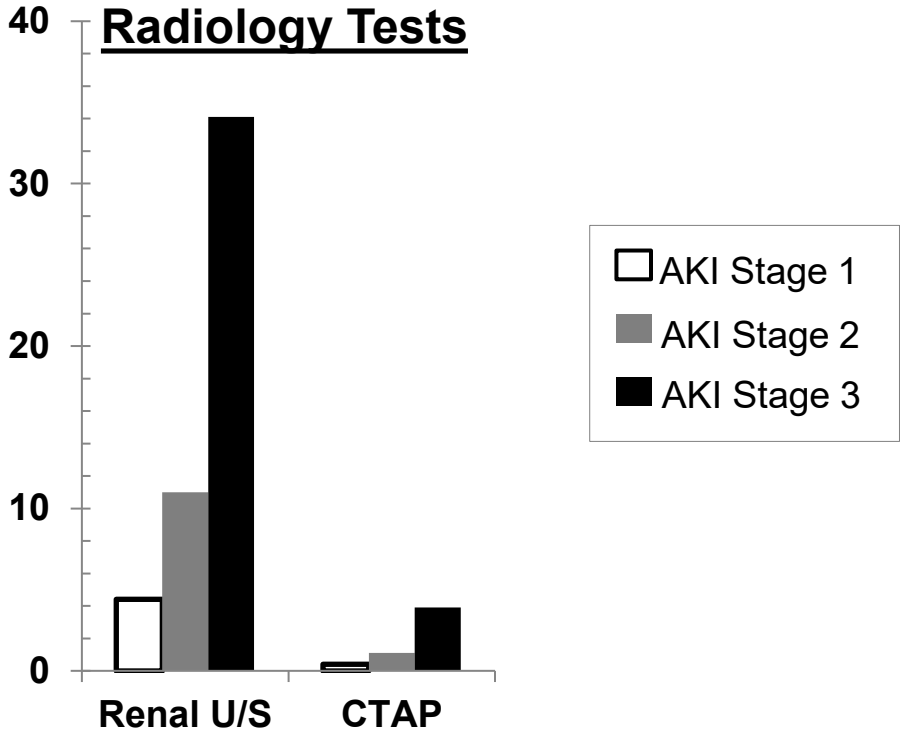
Frequency and Utility of Diagnostic Testing in AKI

- N~32,000 admissions to BWH in 2010
  n=4903 patients with AKI (5,731 AKI episodes)
- Reviewed all diagnostic tests ordered by clinicians
- Assessed frequency of abnormal results, and how often test results influenced diagnosis or management

Leaf et al., BMC Nephrol, 2016

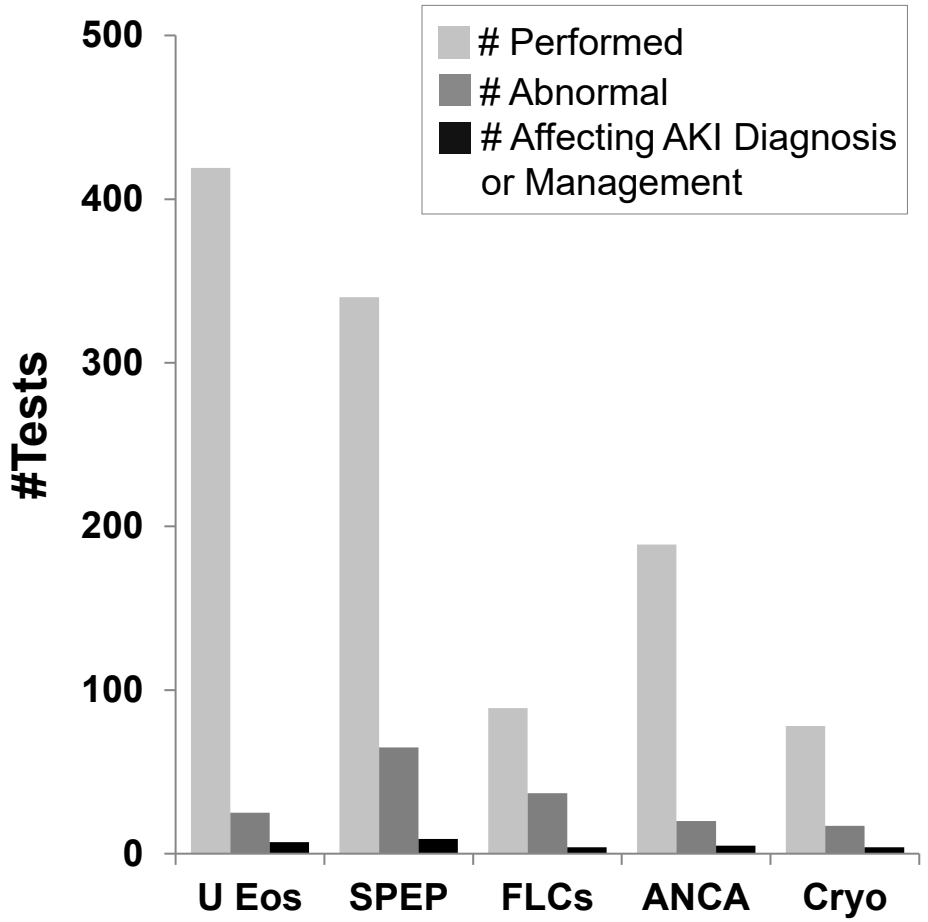
Frequency and Utility of Diagnostic Testing in AKI

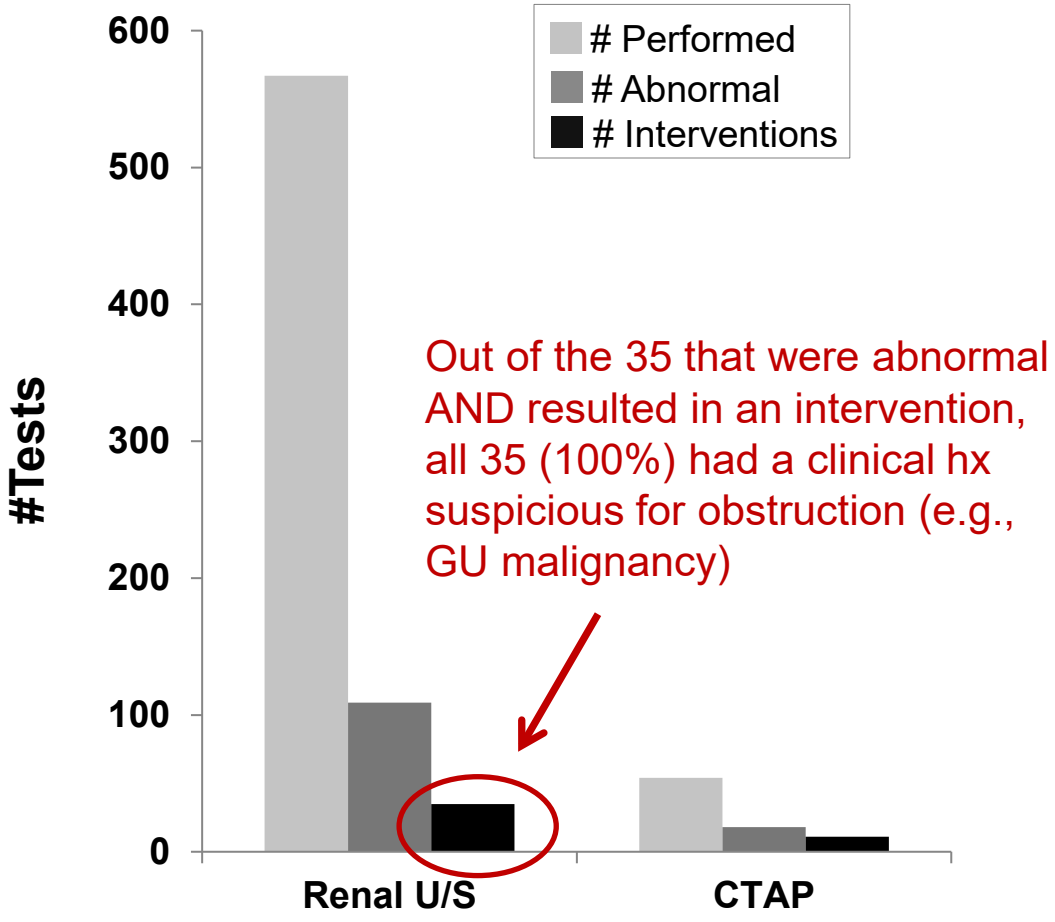




Leaf et al., BMC Nephrol, 2016

Utility of Diagnostic Testing in AKI



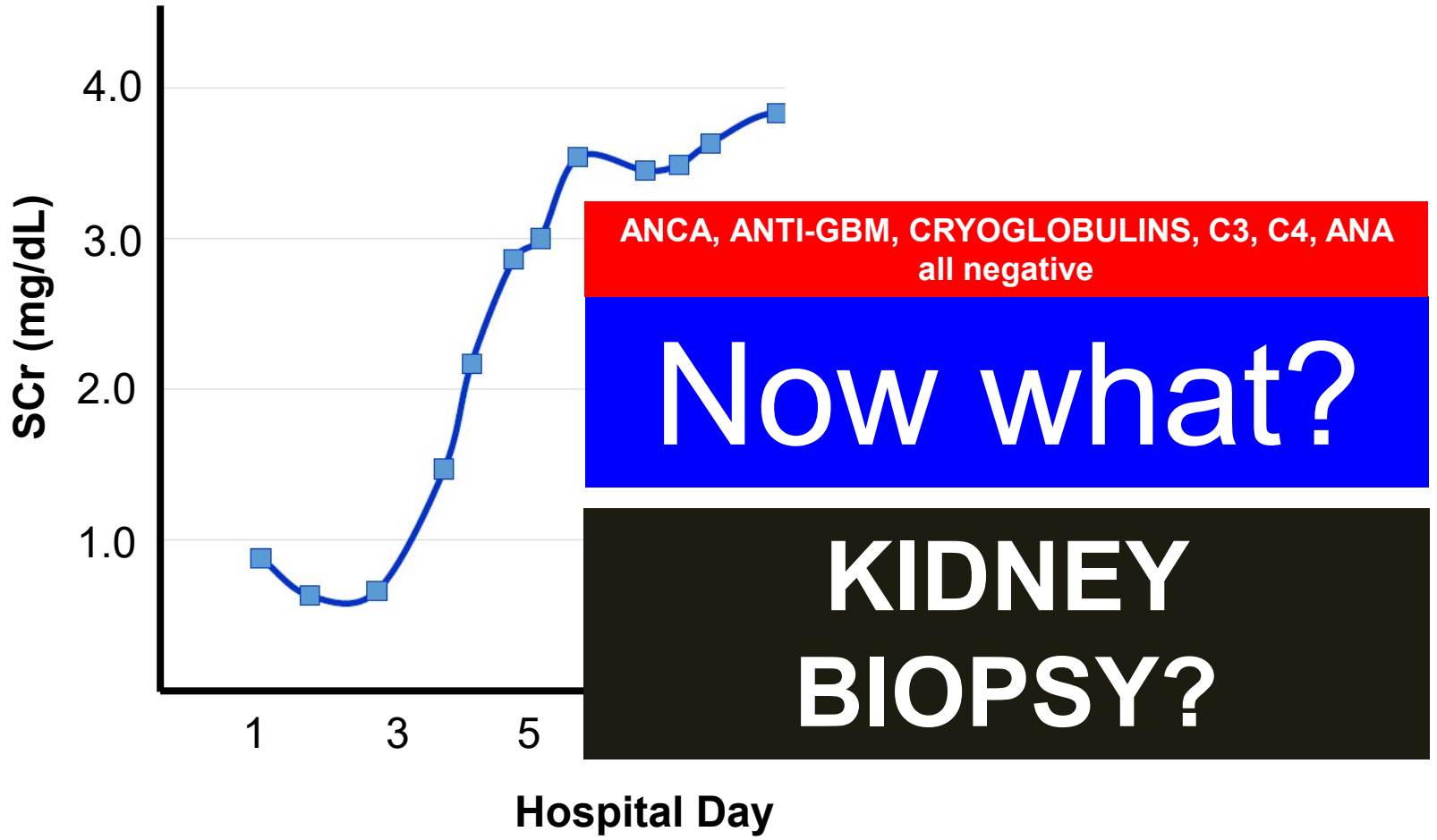


Leaf et al., BMC Nephrol, 2016

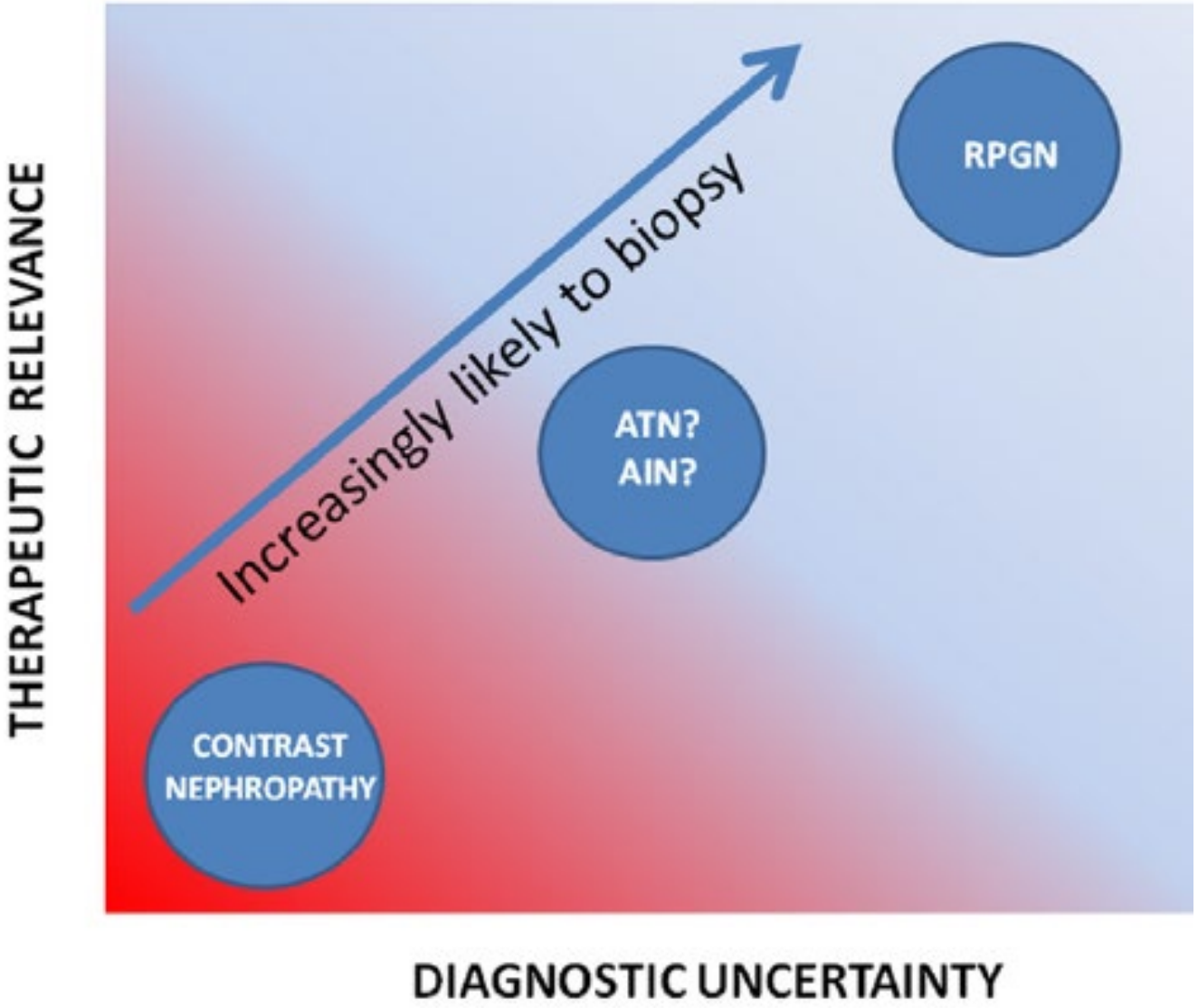
Utility of Diagnostic Testing in AKI: Take-home Points

- We have a limited spectrum of tests available in AKI
- Yield of “serologic” testing (e.g., ANCA, anti-GBM, and SPEP) in unselected AKI is very low
- Renal ultrasound has reasonably high yield **when suspicion for obstruction is high**

Hospital Course (continued)



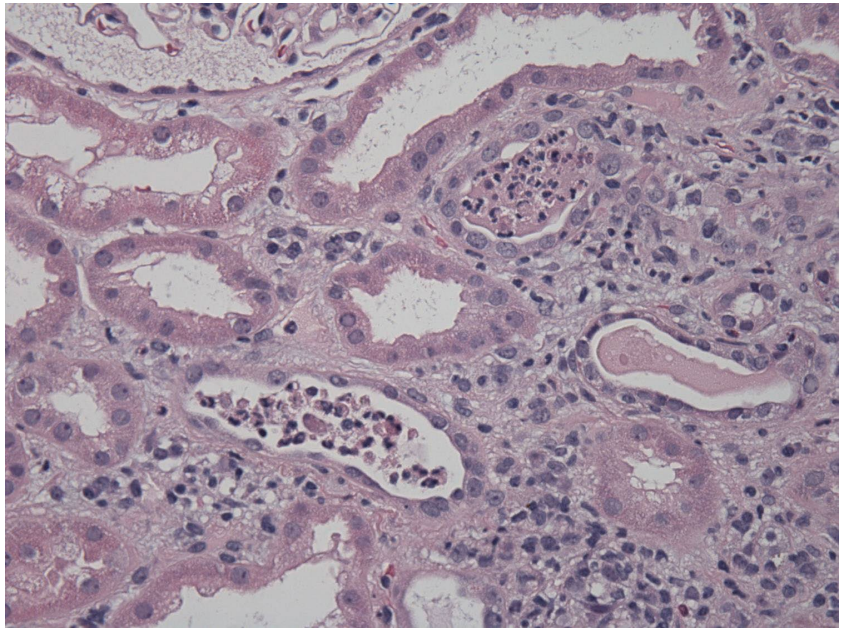
When to biopsy for AKI

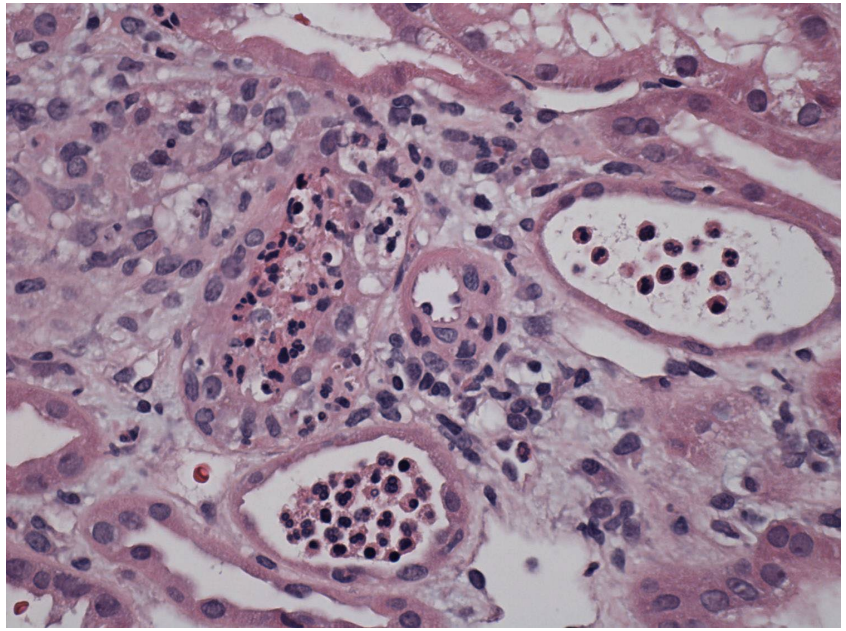


Safety!
Mechanical ventilation?
Uncontrolled HTN?
ASA/Anticoagulation?

Waikar and McMahon, Semin Nephrol, 2017

Renal Biopsy Findings



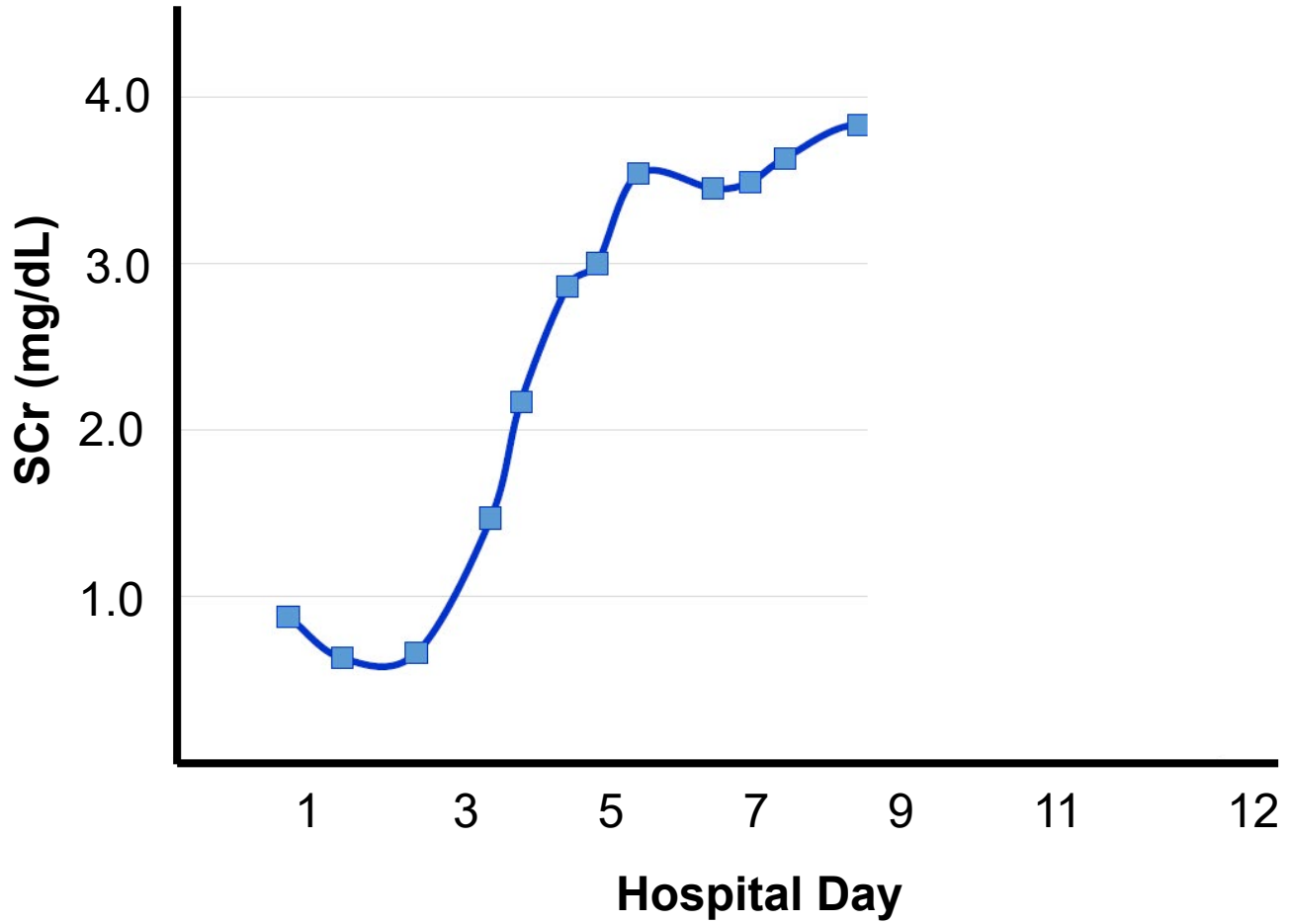


Acute interstitial nephritis – severe

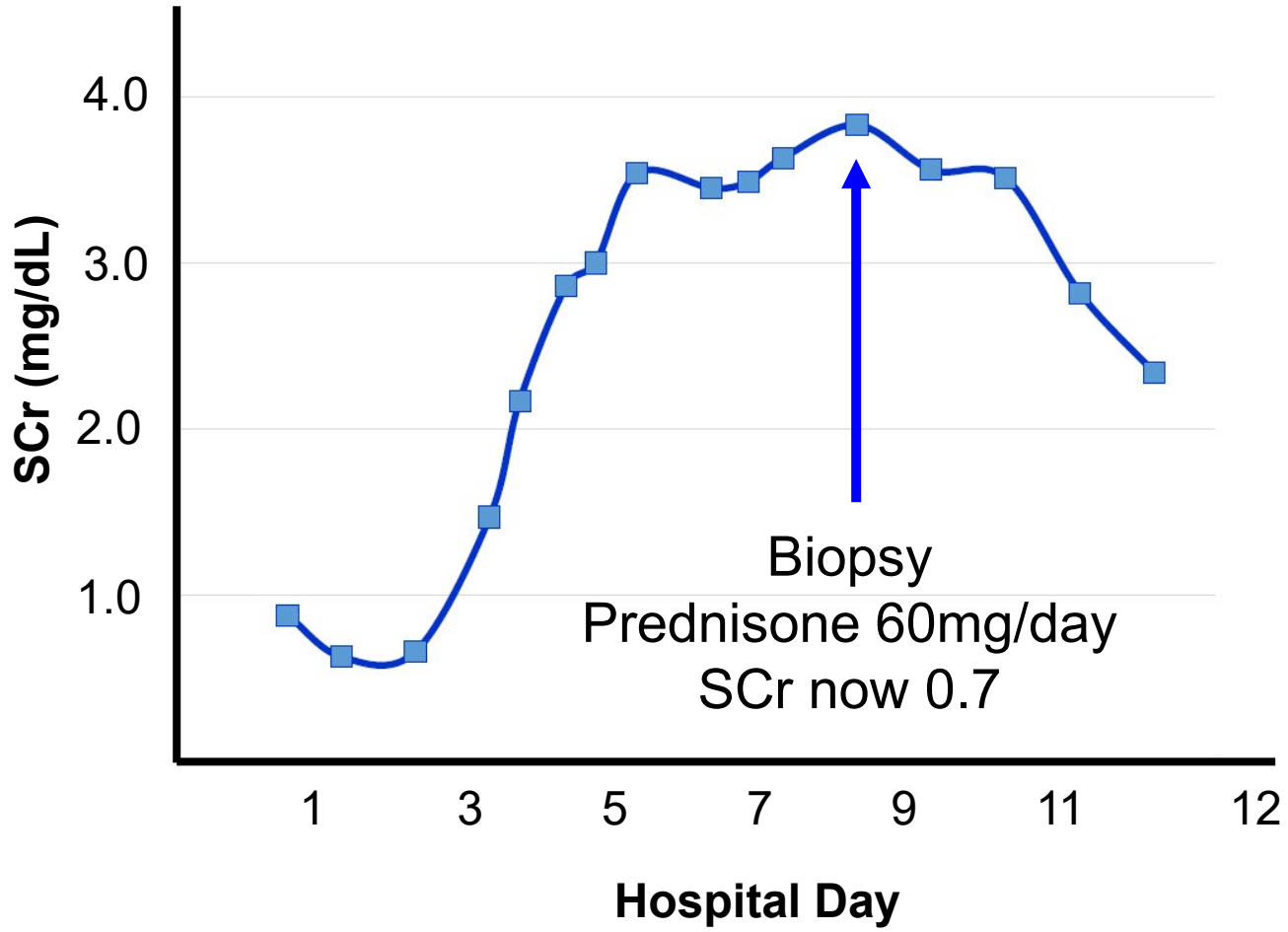
Acute tubular necrosis

Courtesy, H. Rennke

Hospital Course (continued)



Hospital Course (continued)



Summary of his AKI

- Non-oliguric AKI with SCr from <1 to >4 in one week
  - AIN from Abx (Zosyn)
  - ATN (?contrast vs. from AIN)
  - Diagnosis through biopsy guided therapy

- Traditional diagnostic tests of limited value
  - FeNa was < 1%
  - Urine sediment was bland
  - No eosinophilia

Can we do better?

Acute Interstitial Nephritis (AIN)

- Variable timing of onset
  - Several weeks with 1st exposure to drug, 3-5 days after 2nd exposure
- Classic triad: fever, rash, eosinophilia seen in only 10%
- Can see:
  - Urinary WBCs, WBC casts; sometimes RBCs
  - Subnephrotic proteinuria (“tubular” proteinuria”)
  - Fanconi’s (glucosuria, aminoaciduria, PO4 wasting, type 2 RTA)
- Gallium scan: old mini-literature from 1980s; ?utility
- Kidney biopsy: interstitial edema, infiltrate with T cells, monocytes; also eosinophils, plasma cells, neutrophils

Acute Interstitial Nephritis (AIN) – Utility of Clinical Features

AJKD
Original Investigation

Biopsy-Proven Acute Interstitial Nephritis, 1993-2011: A Case Series

Angela K. Muriithi, MBChB, MPH,[1] Nelson Leung, MD,[1] Anthony M. Valeri, MD,[2] Lynn D. Cornell, MD,[3] Sanjeev Sethi, MD, PhD,[3] Mary E. Fidler, MD,[3] and Samih H. Nasr, MD[3]

133 patients with biopsy-proven AIN

Characteristic	All Patients (N = 133)
Age (y)	58 (43-70.5)
Male sex	64 (48)
White race	121/126 (96)
Inpatient	77 (58)
Rash	22 (17)
Fever	22 (17)
Oliguria	19 (14)
Leukocytosis	38 (29)
Eosinophilia	22 (18)
Triad of fever + rash + eosinophilia	9 (7)
Pyuria	61 (47)
Hematuria	39 (30)
Eosinophiluria	28/82 (34)
Proteinuria	122 (92)

Acute Interstitial Nephritis (AIN) – Treatment

- Treatment approach
  - Careful review of medications
  - Discontinuation of offending agent
  - +/- steroids

    - No RCT has ever been (perhaps never will be) performed
    - Early steroid therapy may speed recovery (observational data only)

AKI Management in Specific Clinical Settings

AKI Etiology	Therapy	Clinical Pearl
Rhabdo		
TLS		
CHF/ADHF		
AIN		
Anti-GBM		

Indications for Dialysis in AKI

A	**Acidosis**
E	**Electrolytes (K+)**
I	**Ingestion (lithium, metformin, salicylates)**
O	**Overload (refractory to diuretics)**
U	**Uremia (AMS, pericarditis)**

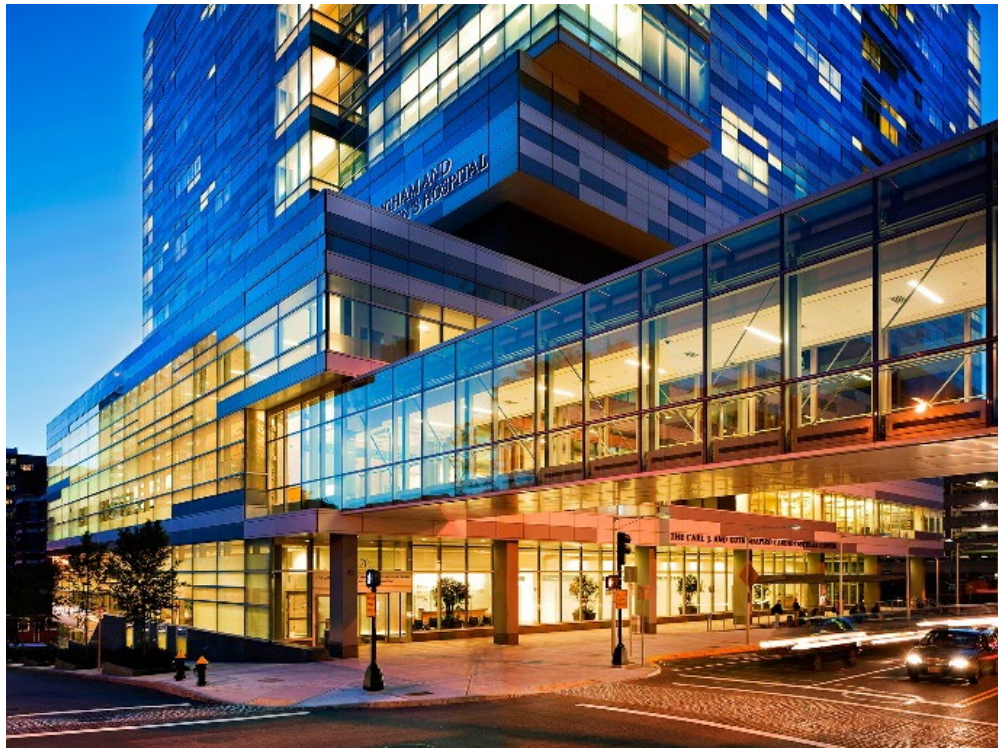
Dialysis Modality in AKI: Indications for CRRT over iHD

Hemodynamic instability (e.g., multi-pressor shock)

Large daily obligate fluid intake

Traumatic brain injury / concern for herniation

Fulminant hepatic failure



Thank you!

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LEAF LAB
www.leaflab.org

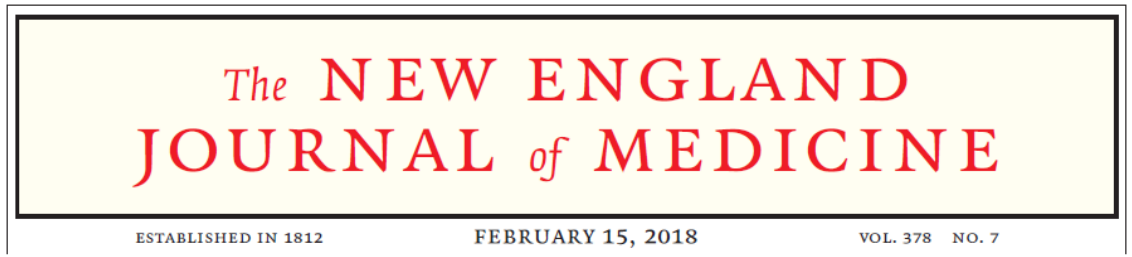
Brigham and Women's Hospital
Founding Member, Mass General Brigham

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Extra Slides

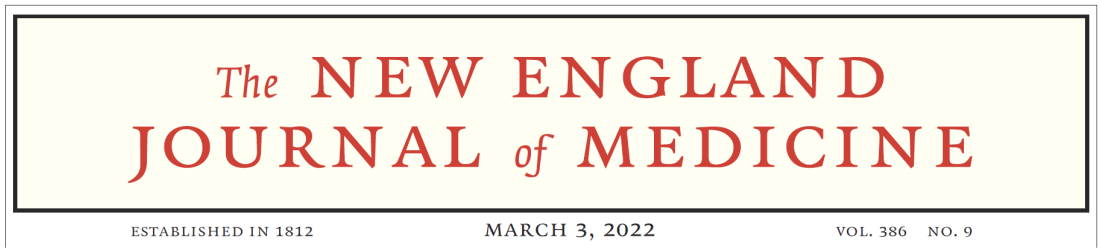
4 Important Recent RCTs in AKI

PRESERVE



Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine

PLUS



Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults

STARRT-AKI

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

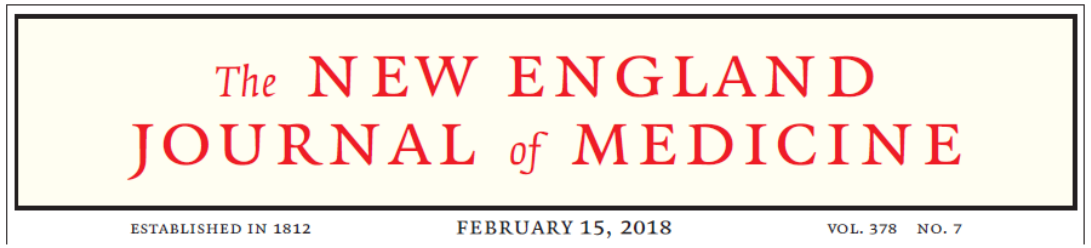
CONFIRM

Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome

PRESERVE Trial

5177 patients undergoing coronary or non-coronary angiography

Randomized (2x2 factorial design):
- **IV bicarb vs. IV saline**
- **NAC vs. placebo**



<u>Primary end point</u>: composite of death, dialysis, or persistent renal function decline (↑SCr ≥50% at 90 days)

No effect of either intervention on the primary outcome

Weisbord et al., *N Engl J Med*, 2018

PLUS Trial

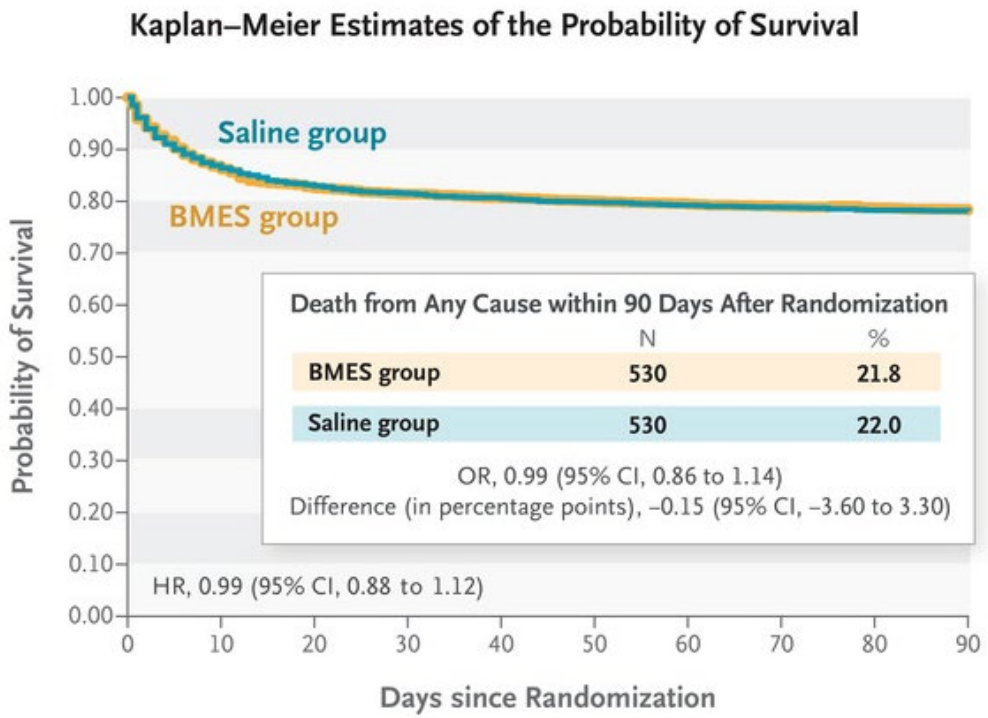
5037 critically ill adults randomized to normal saline vs. balanced solution (Plasma-Lyte 148)

<u>Primary endpoint</u>: 90-day mortality

Secondary endpoints:
-Max SCr
-AKI-RRT

No effect on the primary outcome

Finfer et al., *N Engl J Med*, 2022



Secondary Outcomes

	BMES	Saline
Maximum creatinine level in the ICU during days 1 to 7, mg/dl Absolute difference, 0.01 (−0.04 to 0.06)	1.76±1.44	1.75±1.43
Maximum increase in creatinine level in the ICU, mg/dl Absolute difference, 0.01 (−0.05 to 0.06)	0.41±1.06	0.41±1.02
Receipt of new renal-replacement therapy, no. (%) OR, 0.98 (0.83 to 1.16) Absolute difference, −0.20 (−2.96 to 2.56) percentage points	306 (12.7)	310 (12.9)

NEJM Evidence

Published January 18, 2022

DOI: 10.1056/EVIDoa2100010

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis

13 RCTs
35,884 Critically ill adults

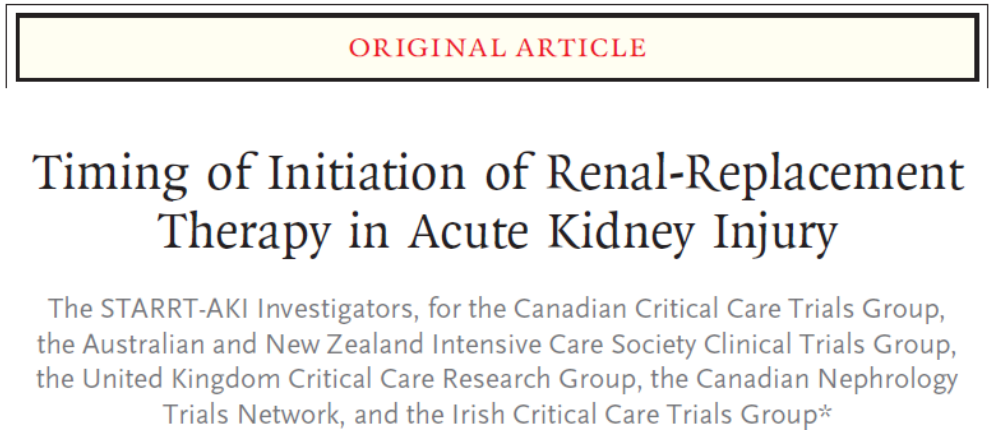
No difference in 90-day mortality or risk of AKI

STARRT-AKI Trial

3019 critically ill patients with AKI

Randomized to accelerated RRT (initiated within 12h of meeting criteria) vs. standard strategy

<u>Primary end point</u>: 90-day mortality


ORIGINAL ARTICLE

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

The STARRT-AKI Investigators, for the Canadian Critical Care Trials Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group, the United Kingdom Critical Care Research Group, the Canadian Nephrology Trials Network, and the Irish Critical Care Trials Group*

No effect of accelerated RRT on mortality

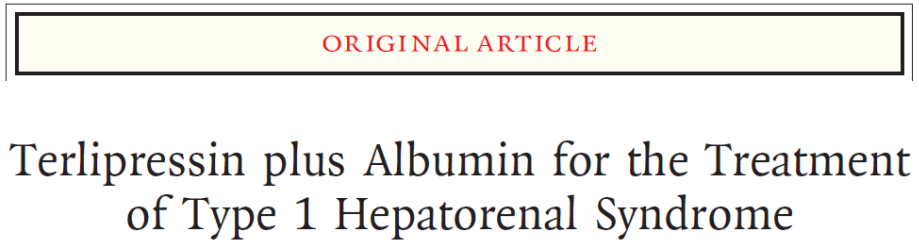
STARRT-AKI, *N Engl J Med*, 2020

CONFIRM Trial

300 patients with HRS

Randomized 2:1 to terlipressin vs. placebo

Concomitant use of albumin strongly recommended in both groups


ORIGINAL ARTICLE

Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome

<u>Primary end point:</u> Reversal of HRS (≥2 consecutive SCr values ≤1.5 mg/dl AND survival without dialysis for ≥10 days after completion of treatment)

HRS reversal occurred in 32% in the terlipressin group and 17% in placebo (P=0.006)

Wong et al., *N Engl J Med*, 2021

Summary of key findings from recent RCTs

PRESERVE Trial found no benefit with IV $NaHCO_3$ (vs. IV NS) or NAC (vs. placebo) in preventing contrast nephropathy

PLUS Trial found no benefit with balanced crystalloid (vs. NS)

STARRT Trial found no benefit with accelerated (vs. standard) RRT

CONFIRM Trial found a benefit with terlipressin in HRS

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection

The ACORN Randomized Clinical Trial

RESULTS There were 2511 patients included in the primary analysis (median age, 58 years [IQR, 43-69 years]; 42.7% were female; 16.3% were Non-Hispanic Black; 5.4% were Hispanic; 94.7% were enrolled in the emergency department; and 77.2% were receiving vancomycin at enrollment). The highest stage of acute kidney injury or death was not significantly different between the cefepime group and the piperacillin-tazobactam group; there were 85 patients (n = 1214; 7.0%) in the cefepime group with stage 3 acute kidney injury and 92 (7.6%) who died vs 97 patients (n = 1297; 7.5%) in the piperacillin-tazobactam group with stage 3 acute kidney injury and 78 (6.0%) who died (odds ratio, 0.95 [95% CI, 0.80 to 1.13], *P* = .56). The incidence of major adverse kidney events at day 14 did not differ between groups (124 patients [10.2%] in the cefepime group vs 114 patients [8.8%] in the piperacillin-tazobactam group; absolute difference, 1.4% [95% CI, −1.0% to 3.8%]). Patients in the cefepime group experienced fewer days alive and free of delirium and coma within 14 days (mean [SD], 11.9 [4.6] days vs 12.2 [4.3] days in the piperacillin-tazobactam group; odds ratio, 0.79 [95% CI, 0.65 to 0.95]).

CONCLUSIONS AND RELEVANCE Among hospitalized adults in this randomized clinical trial, treatment with piperacillin-tazobactam did not increase the incidence of acute kidney injury or death. Treatment with cefepime resulted in more neurological dysfunction.