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

Acute Kidney Injury

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

David Leaf, MD, MMSc

- Undergrad @UPenn
- Medical School @NYU
- Medicine Residency @Columbia
- Nephrology Fellowship @BWH/MGH
- MMSc (Clinical Investigation) @HMS

- Associate Professor of Medicine @HMS
- Clinical and Research Focus: AKI

Disclosures

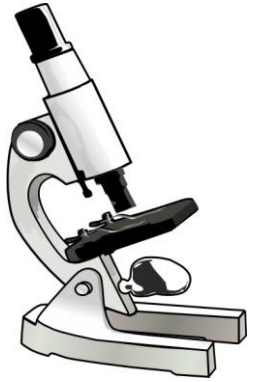
Research Support

- BTG International
- Metro International Biotech LLC
- Renibus Therapeutics, Inc.
- Alexion Pharmaceuticals

Consulting

- Entrada Therapeutics
- CardioRenal Systems, Inc.
- Alexion Pharmaceuticals

Key Learning Objectives



Diagnostic Approach to AKI

- Physiologic classification
- Clinical setting
- Tests to order

Management of AKI

(Including key findings from recent RCTs)

MOC Reflective Statement

In approaching the DDx for AKI, consider pre-renal, intrinsic, and post-renal causes, and order diagnostic tests based on clinical suspicion

Know the diagnoses associated with common UA/sediment findings

Know the treatment for AKI in specific clinical scenarios

Outline

Epidemiology, Nomenclature, and Definitions

Physiologic Classification and Common Clinical Settings

Diagnostic Approach

Management

Recent Updates (large RCTs)

Two Board-style Questions

Epidemiology: AKI is a Major Public Health Burden

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

Costs >$10B annually in the US 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

Therapies that reliably prevent or treat AKI are lacking in most cases

Acute Kidney Injury (AKI) Nomenclature

or the syndrome formerly known as “Acute Renal Failure”

“Acute”

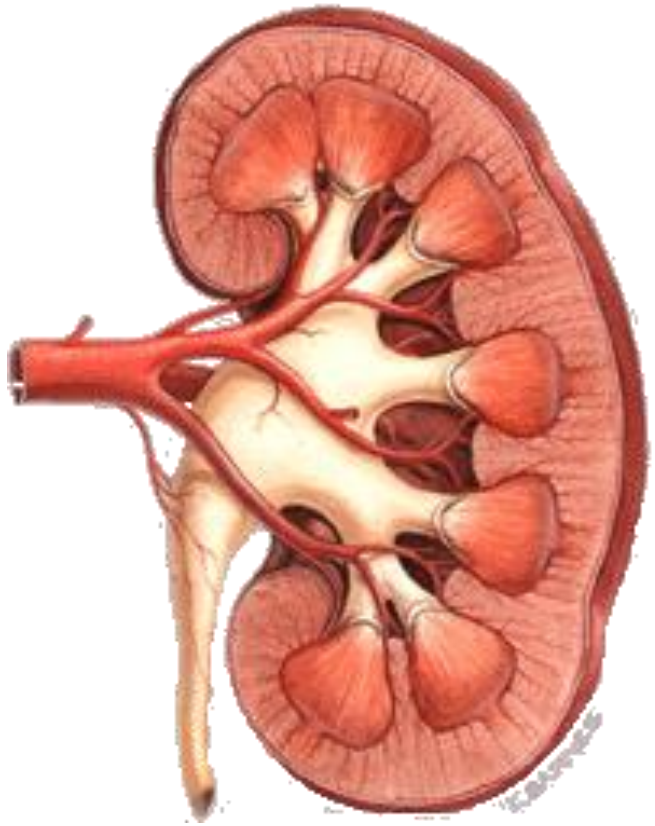
Happens within hours to days

“Kidney”

More familiar to patients than “Renal”

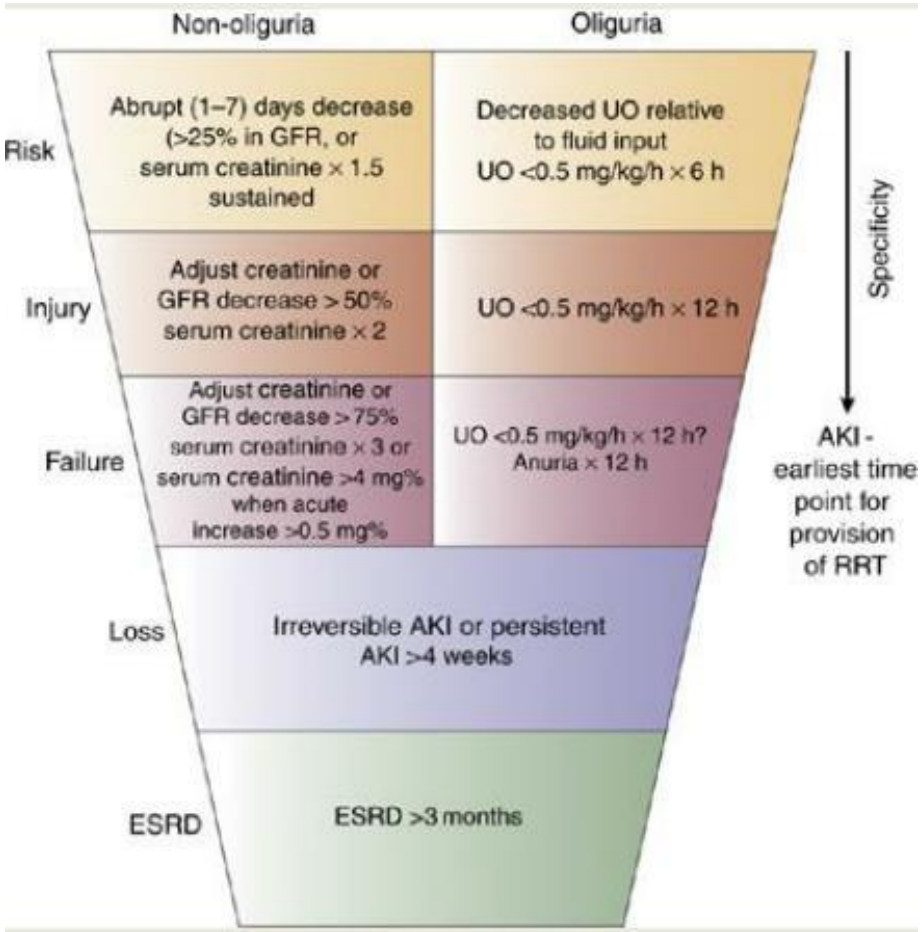
“Injury”

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



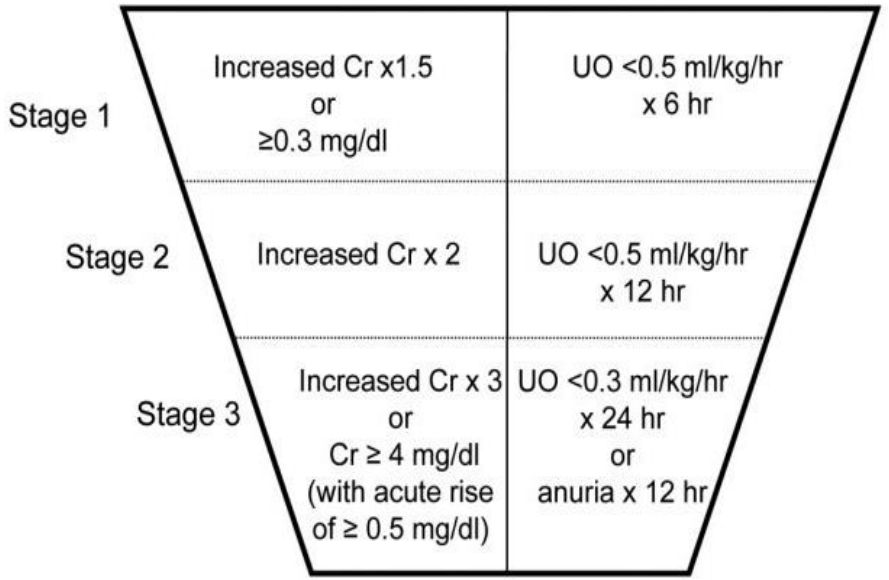
Historical Consensus Definitions of AKI

RIFLE Criteria



Crit Care, 2004

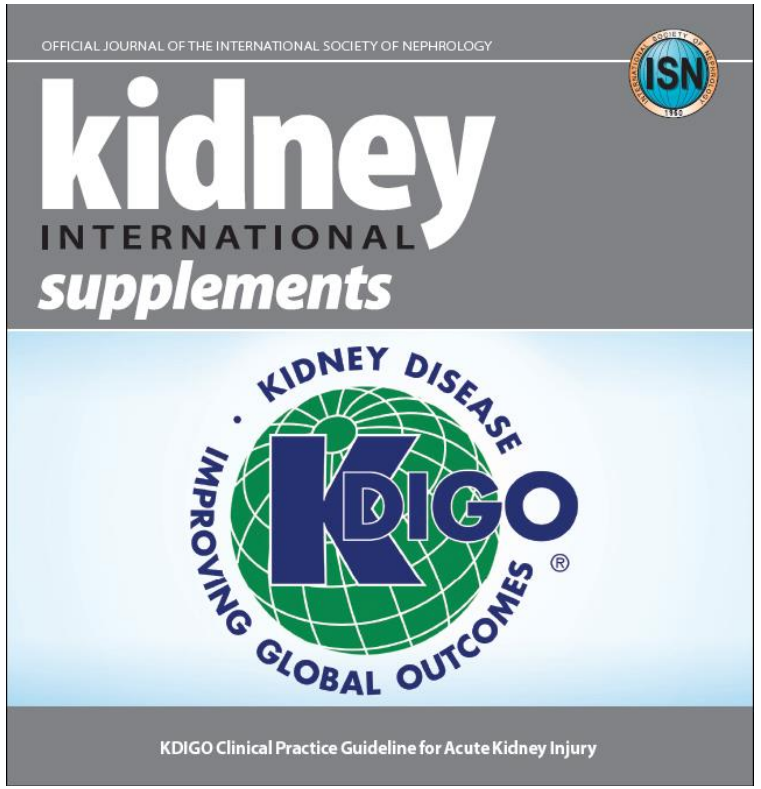
AKIN Criteria



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

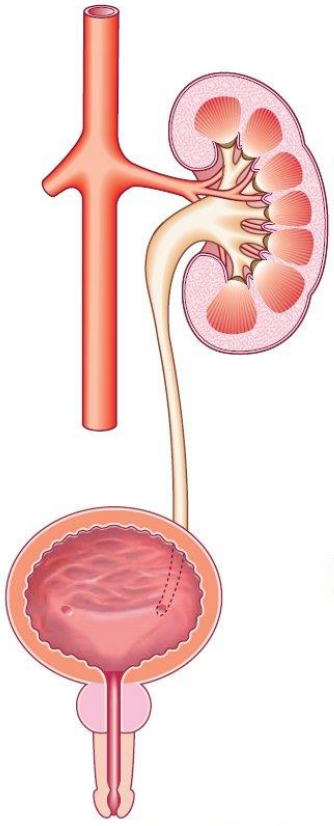
SCr	UOP
Stage 1: increase in SCr ≥ 0.3 mg/dL or ≥1.5×	Stage 1: output < 0.5 mL/kg/h for ≥6 h
Stage 2: increase in SCr ≥ 2×	Stage 2: output < 0.5 mL/kg/h for ≥12 h
Stage 3: increase in SCr ≥ 3×, or SCr > 4 mg/dL, or RRT	Stage 3: output < 0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

"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

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

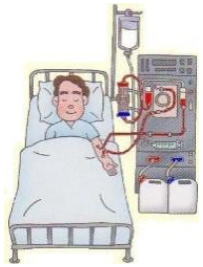
POST-RENAL

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

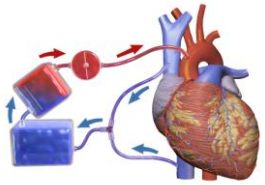
Davidsons Essentials of Medicine, 2nd edition

Common clinical settings where AKI occurs

Sepsis



Cardiac surgery



Nephrotoxins

Exogenous

- Chemotherapy
- Antibiotics
- NSAIDs
- IV contrast

Endogenous

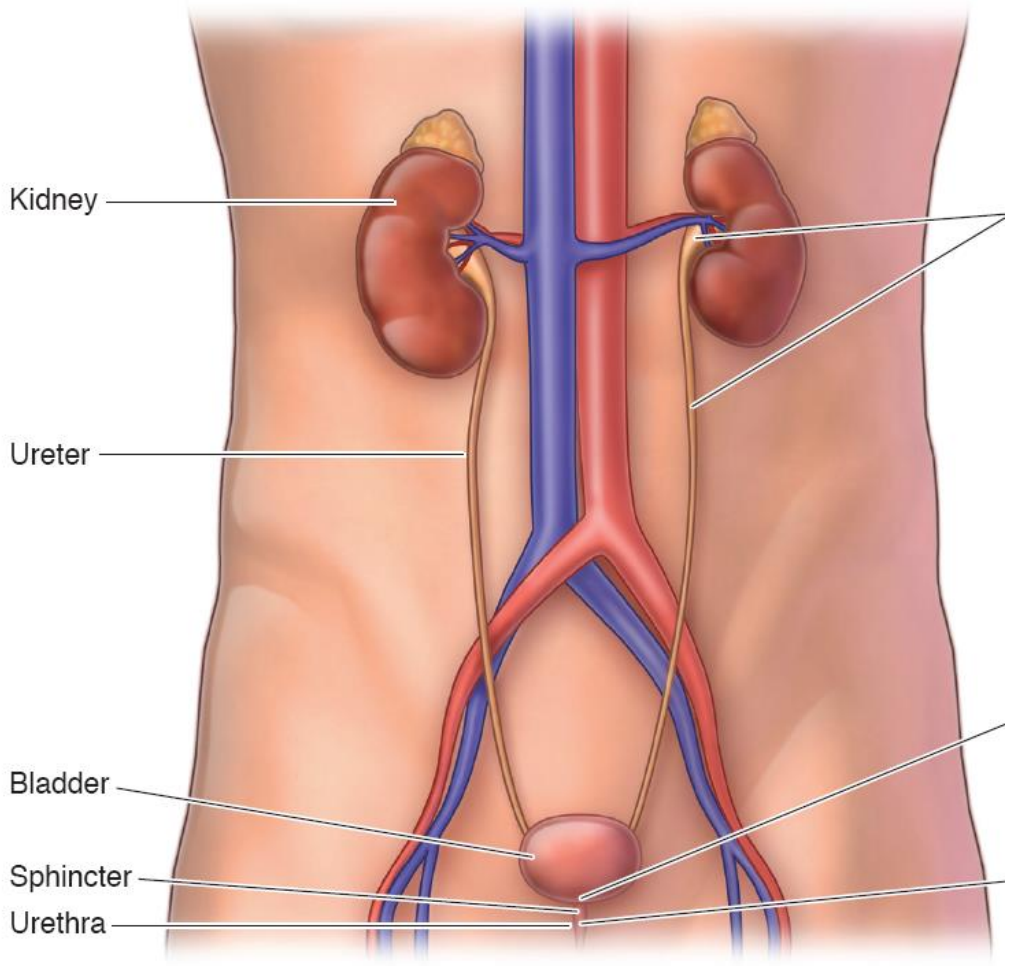
- Myoglobin (rhabdo)
- Hemoglobin (MAHA)
- Uric acid (TLS)

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.

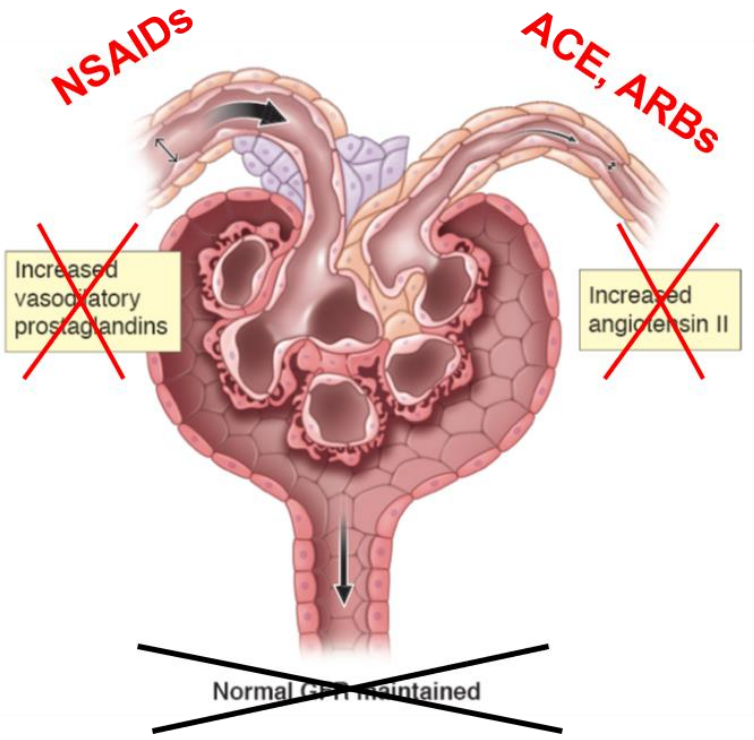
Pre-renal ~~AKI~~ azotemia

Overview

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

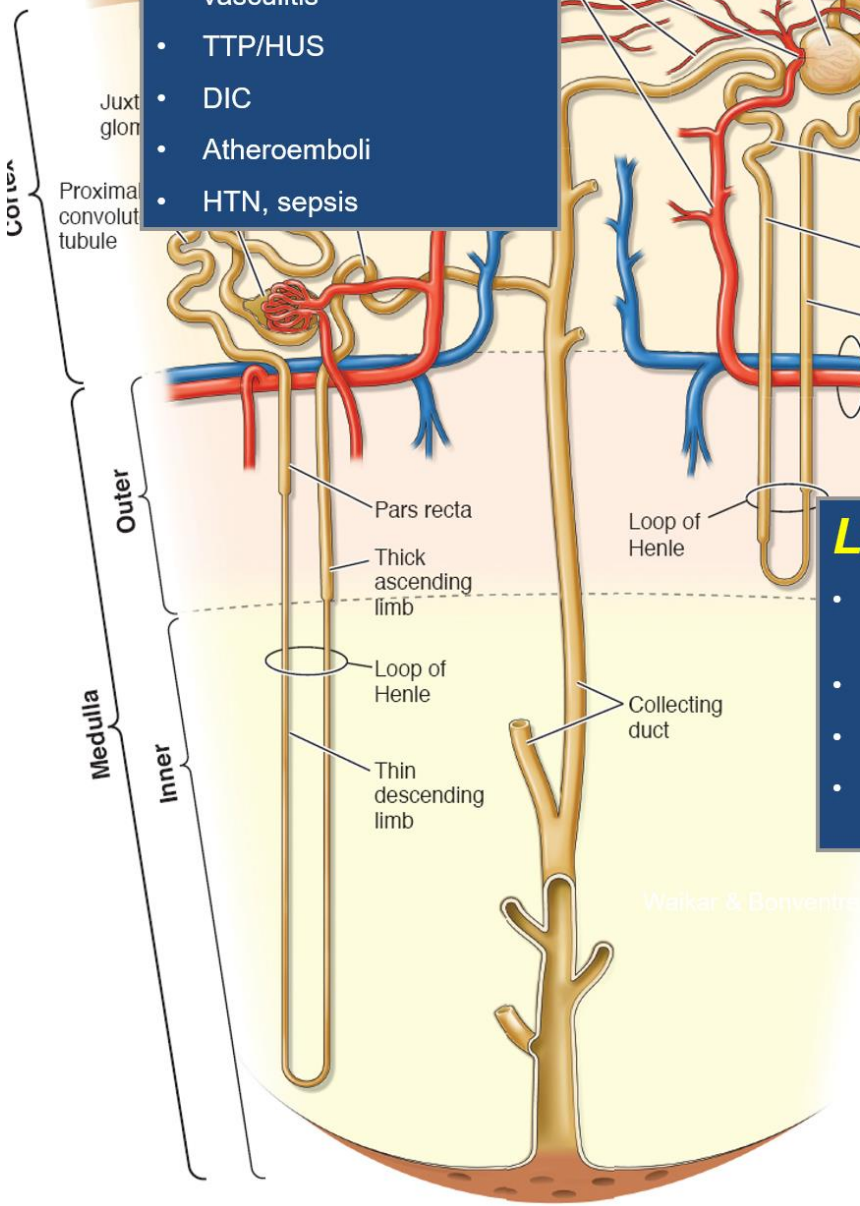
Causes

- "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

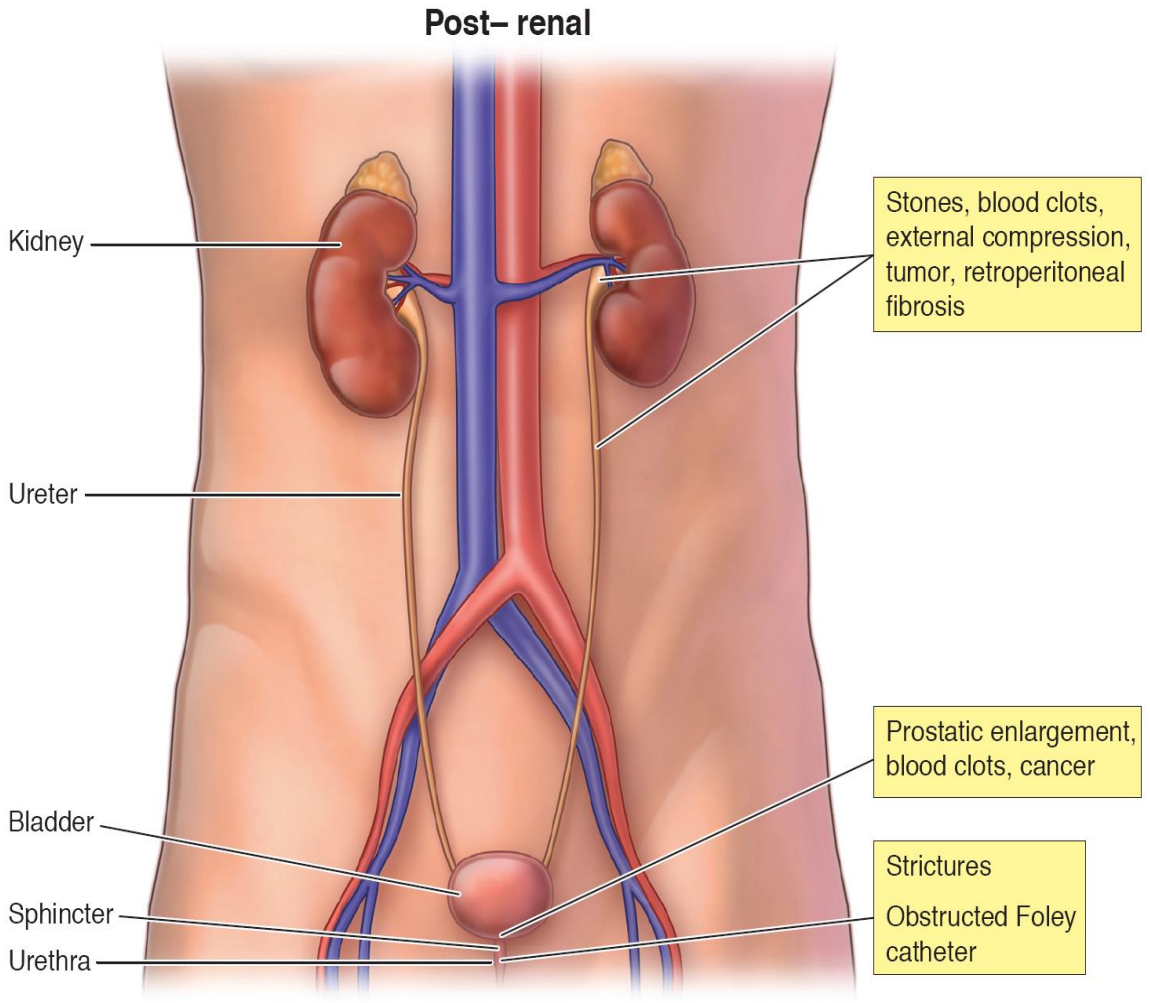
Diagnostic/imaging workup:

- 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
- Hemolysis: LDH, haptoglobin, smear
- Rhabdo: CPK
- Paraprotein disorder: SPEP, SFLCs

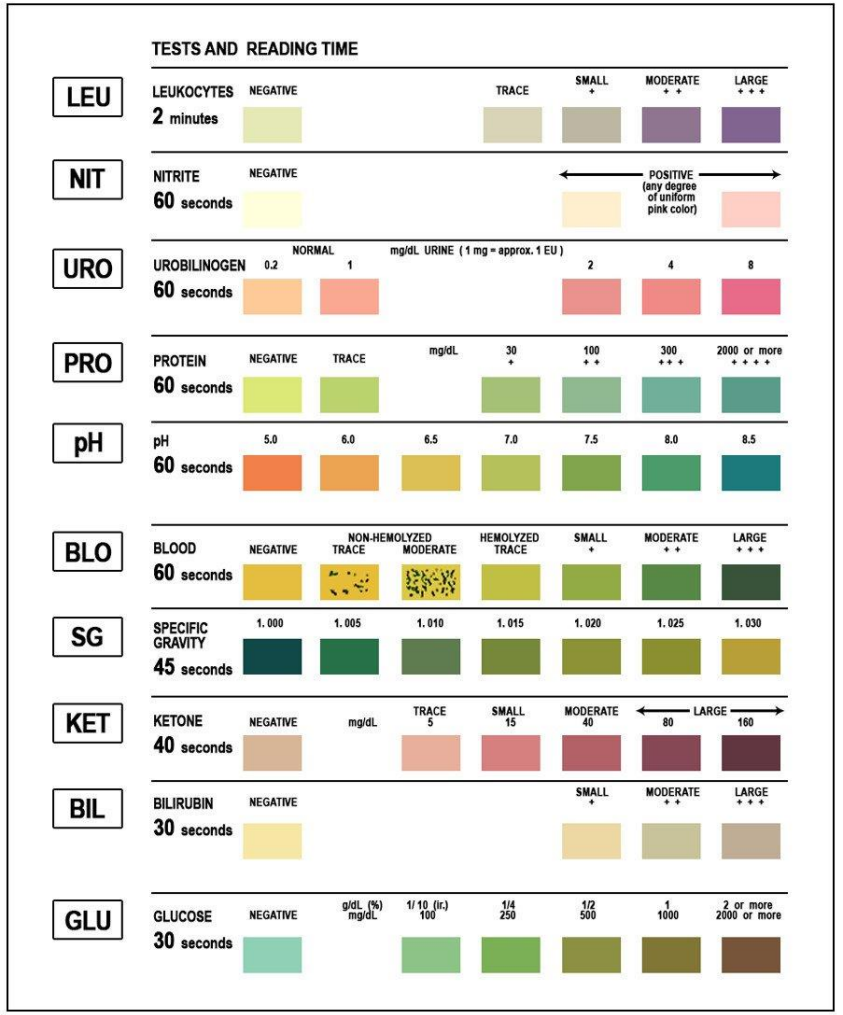
Radiographic Tests

- 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+hematuria (on UA) but negative/trace RBCs on sediment	Rhabdo or intravascular hemolysis
3+proteinuria on UA, lots of RBCs and WBCs on sediment	Glomerulonephritis
Muddy brown casts	ATN (however, nonspecific)
Sterile pyuria	AIN
Oxalate crystals	Ethylene glycol toxicity (however, nonspecific)
Bland	Pre-renal azotemia, cardiorenal, HRS, contrast nephropathy

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

AKI Management in Specific Clinical Settings

AKI Etiology	Treatment	Clinical Pearl
Rhabdo	IVF; ?Urinary alkalinization	$NaHCO_3$ gtt, watch for ↓[iCa] and ↓[K]
TLS	IVF; Rasburicase	AKI itself will raise the serum uric acid level!
CHF	Loop diuretic	Mild ↑SCr doesn't always mean back off diuresing
AIN	Discontinue offending agent; Steroids	<10% have the triad of fever, rash, and eos!
Anti-GBM	Plasmapheresis, Cytoxan, Steroids	Pulmonary involvement rare unless smoker or underlying lung disease
iATN	Supportive	

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)

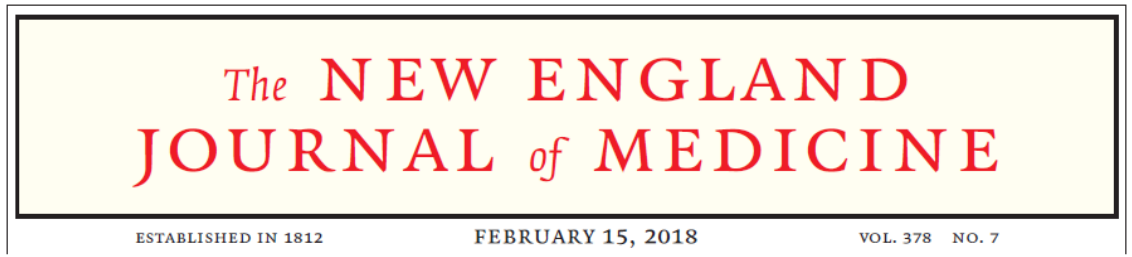
Large daily obligate fluid intake

Traumatic brain injury / concern for herniation

Fulminant hepatic failure

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

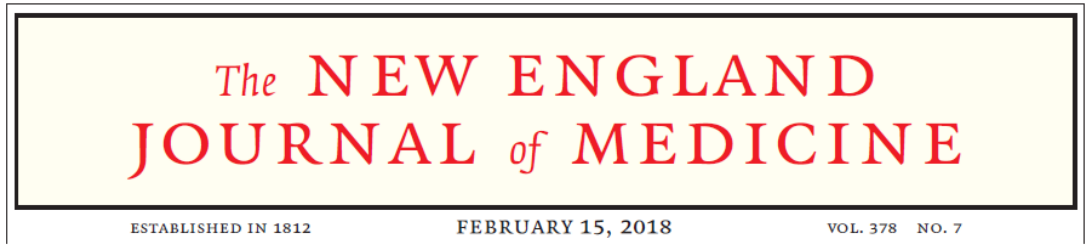
CONFIRM

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

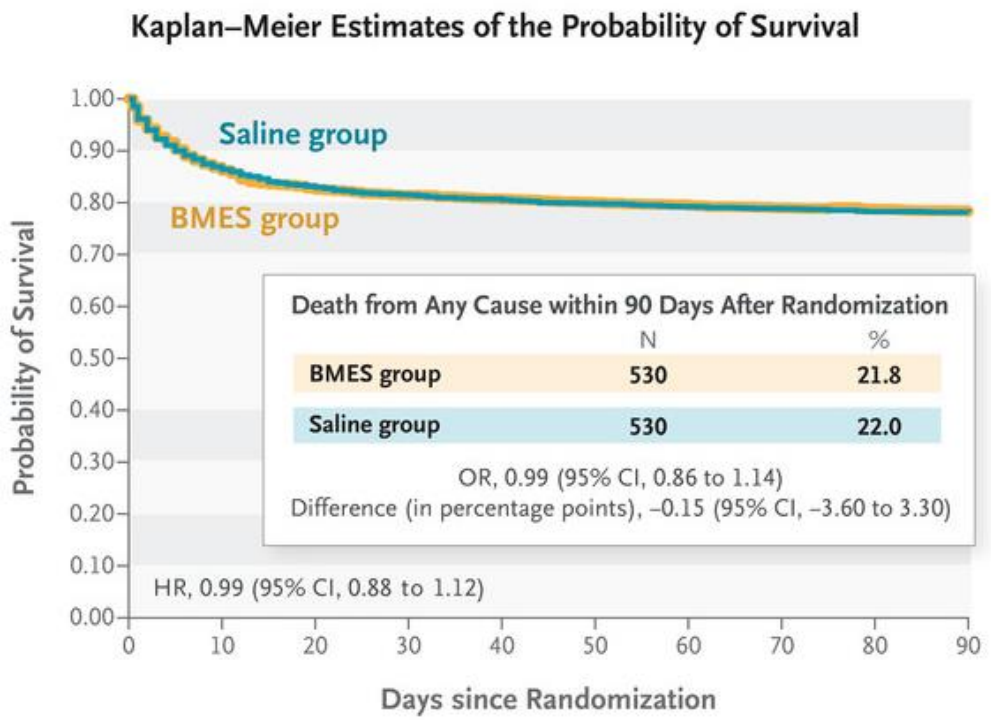
5037 critically ill adults randomized to normal saline vs. balanced solution (Plasma-Lyte 148)

<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

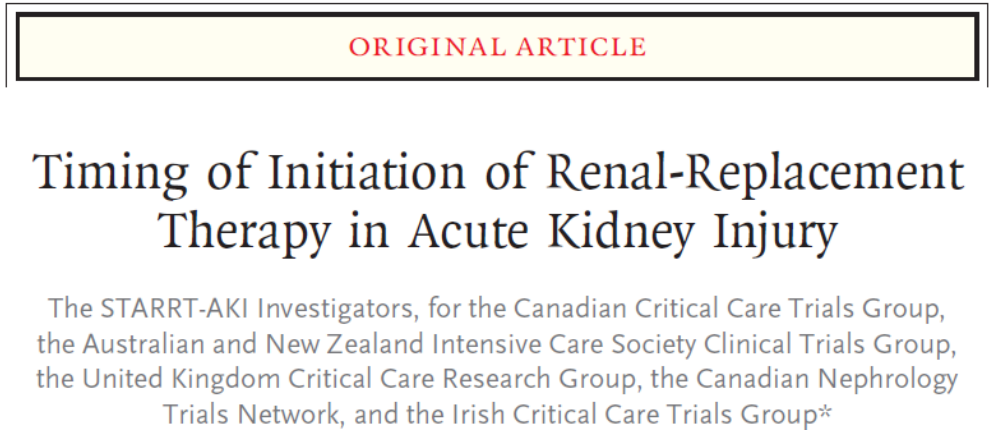
No difference in 90-day mortality or risk of AKI

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

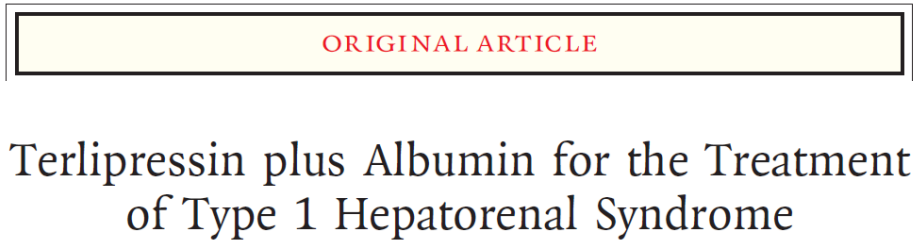
STARRT-AKI, *N Engl J Med*, 2020

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

CONFIRM Trial found a benefit with terlipressin in HRS

Question 1

A 70yoM with metastatic melanoma presents to oncology clinic. He reports several episodes of non-bloody diarrhea during the past 2 weeks. Labs show SCr 6.5 mg/dl (up from his baseline of 1.2 mg/dl). He reports staying well hydrated by drinking Gatorade. He has been receiving treatment with ipilimumab and nivolumab, and his most recent treatment was 3 weeks ago. UPCR is 0.5 g/g. Renal U/S is negative for obstruction. Which of the following is most likely to be seen on kidney biopsy?

A) Collapsing FSGS

B) Thrombotic microangiopathy

C) Acute interstitial nephritis

D) Acute tubular necrosis

E) Glomerulonephritis with crescents

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C) Acute interstitial nephritis

D) Acute tubular necrosis

E) Glomerulonephritis with crescents

Explanation

The answer is C. This patient's presentation is consistent with **acute interstitial nephritis** from immune checkpoint inhibitors.

Immune checkpoint inhibitors

Novel class of monoclonal antibodies that target inhibitory receptors on T cells, other immune cells, and tumor cells

“What we needed to do was to release the brakes of the immune system to fight cancer.”

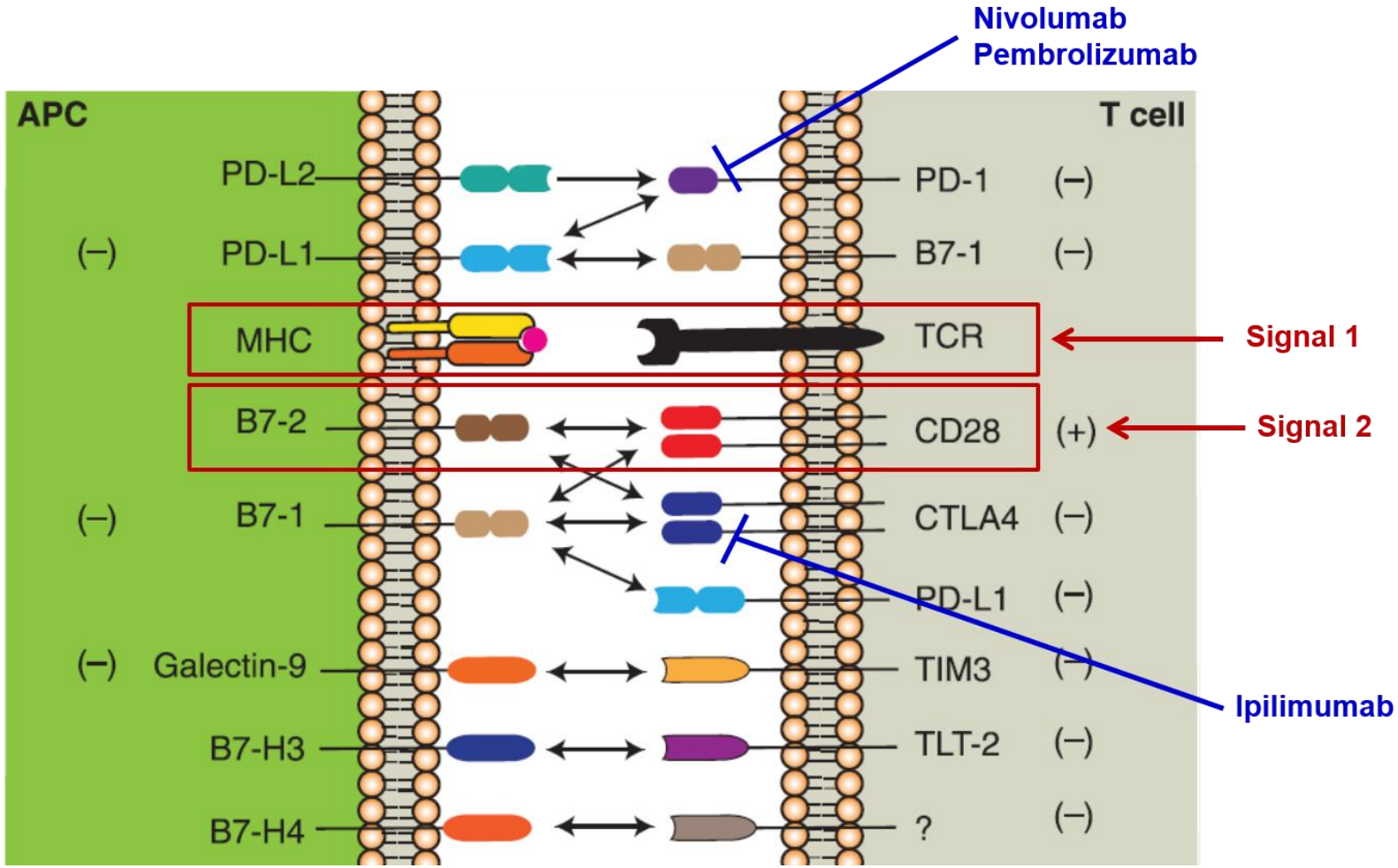
James Allison, Ph.D.
Nobel Prize Laureate, 2018

Immune checkpoint inhibitors

CTLA-4 antagonists
- Ipilimumab

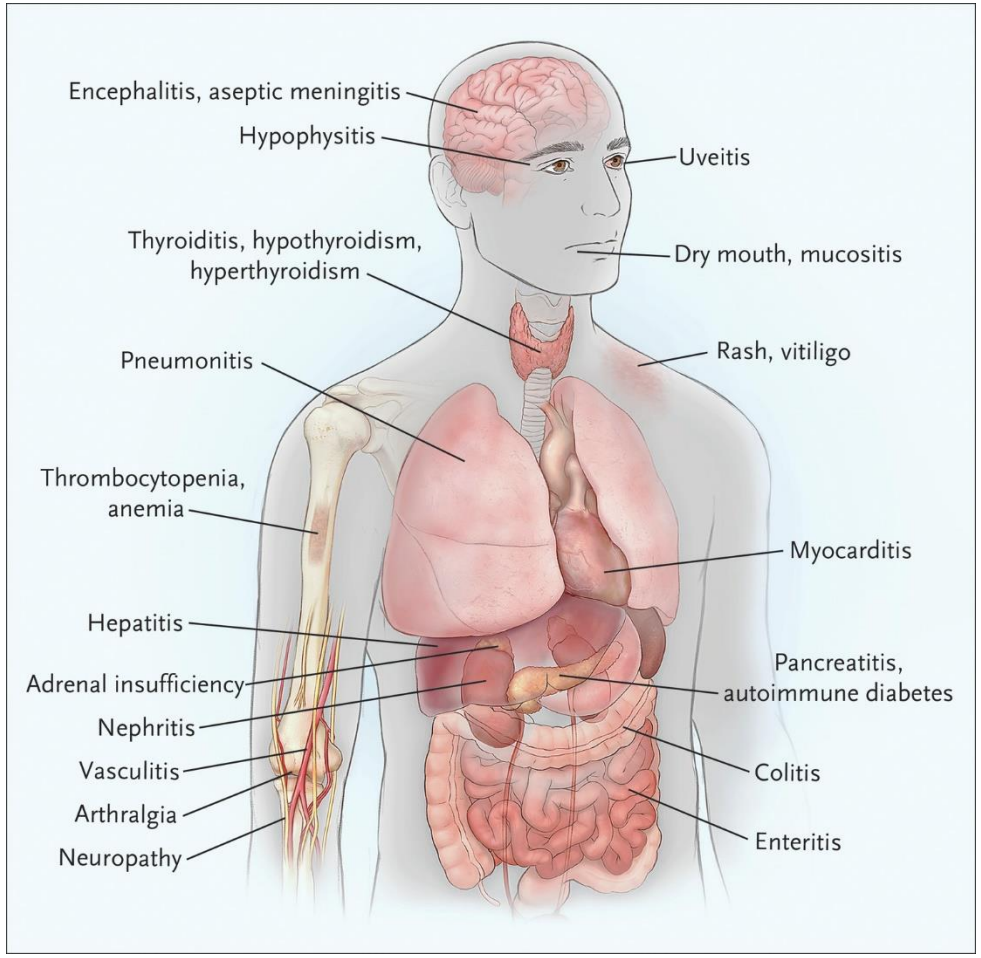
PD-1 antagonists
- Nivolumab
- Pembrolizumab

PD-L1 antagonists
- Atezolizumab
- Avelumab
- Durvalumab



Murakami & Riella, *Transplantation*, 2014

Autoimmune Toxicity ("Immune-Related Adverse Events")



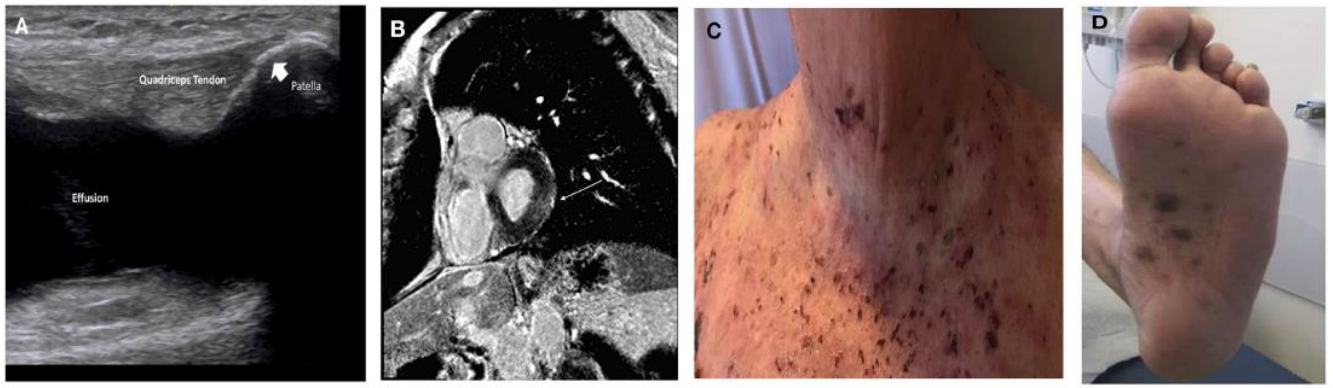
Postow et al., *N Engl J Med*, 2018

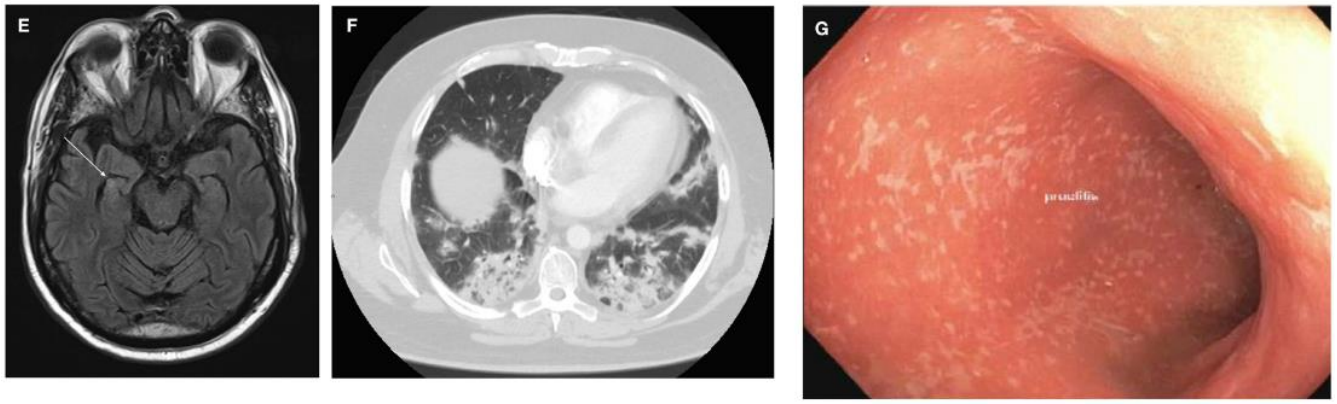
Inflammatory arthritis

Myocarditis

Bullous pemphigoid

Lichenoid dermatitis





Encephalitis

Pneumonitis

Colitis

Connolly et al., *Front Oncol*, 2019

Immune checkpoint inhibitor-associated AKI

Pathophysiology

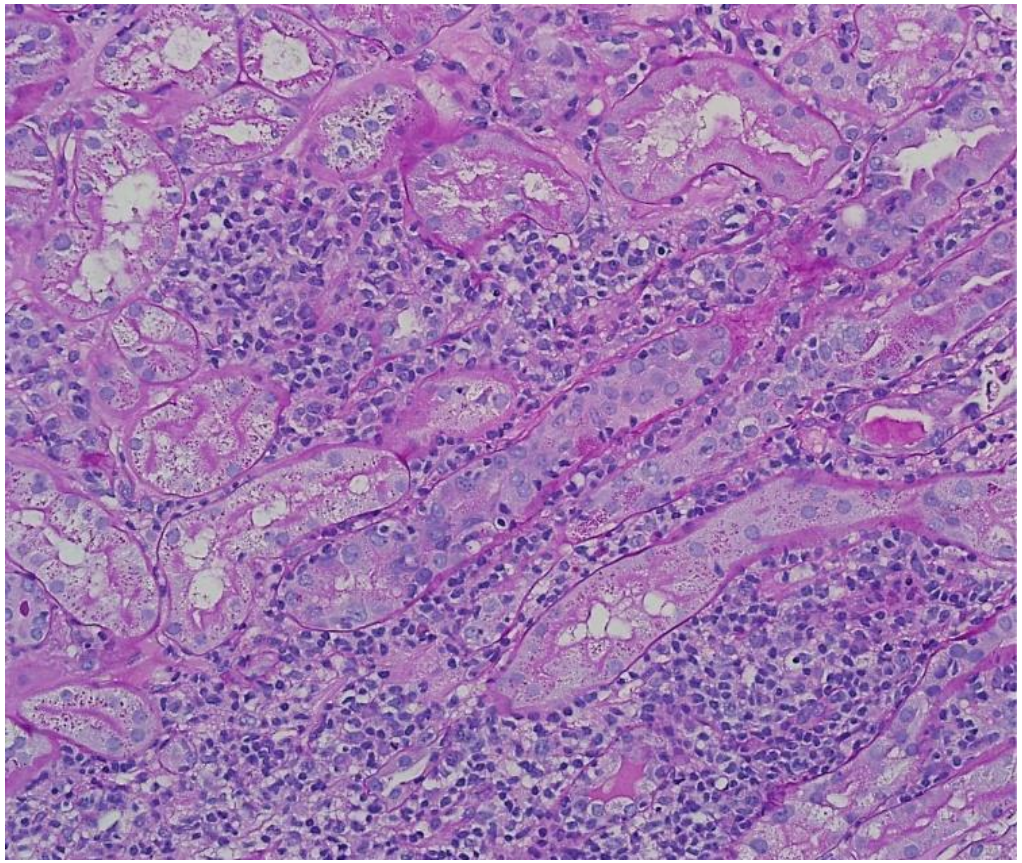
AIN = most common pathological lesion (>90%)

Clinical Presentation

- Similar to other causes of AIN (pyuria, mild-to-moderate proteinuria)
- Extrarenal irAEs are frequent
  -Colitis
  -Rash
  -Thyroiditis
- Delayed onset of AKI (can occur months after ICPi initiation)

Treatment

Glucocorticoids



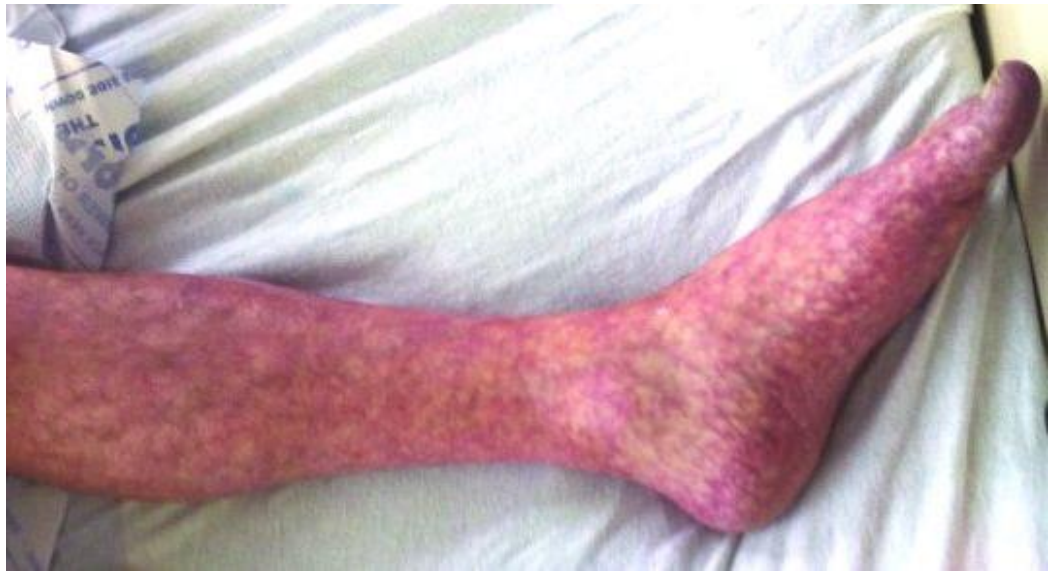
Cortazar…Leaf et al., *Kidney Int*, 2016
Cortazar…Leaf et al., *J Am Soc Nephrol*, 2020
Gupta…Leaf et al., *J Immunother Cancer*, 2021

Question 2

A 66yoM, previously healthy, is admitted to the hospital with chest pain. Vital signs on admission: BP 126/78, HR 102, RR 20. ECG reveals ST-segment elevation in leads II, III, and aVF. He is treated with aspirin, a heparin drip, metoprolol, and nitroglycerin, and taken to the cath lab, where he undergoes successful PCI of an occluded right circumflex artery. During the procedure the BP remained above 120/70, and he remained hemodynamically stable thereafter. SCr was 0.7 mg/dL on admission, rose to 1.4 mg/dL on hospital day 3, and was 7.8 mg/dL by hospital day 9. Physical exam finding is shown in the image.

The part of the kidneys most likely involved in the pathophysiology of his AKI are the:

A) Afferent arterioles and glomeruli
B) Efferent arterioles
C) Tubules
D) Interstitium



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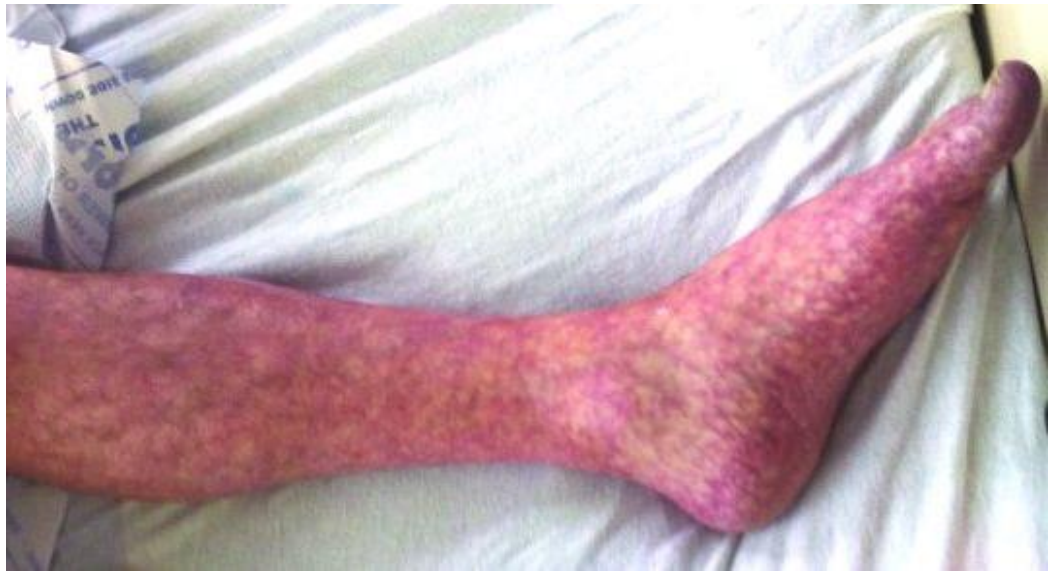
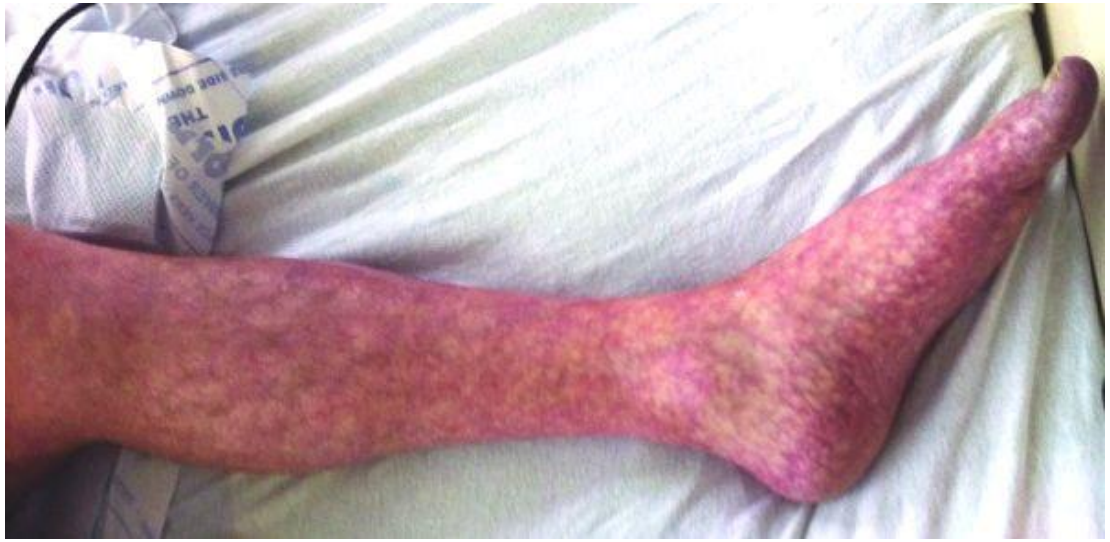


Explanation

The answer is A. This presentation is consistent with **renal atheroemboli**. Angiography is the most common triggering event, and therapeutic anticoagulation is also a risk factor. The clinical course is variable and includes subacute kidney injury (occurring weeks later), but patients can also present with more rapid and severe AKI (as in the current case). Physical exam findings include **livedo reticularis** and **blue toes**. Urinary findings are non-specific. **Eosinophilia** and **hypocomplementemia** may be seen.

Pathophysiology: cholesterol crystals lodged in small arteries, including the afferent arterioles and glomeruli

Treatment: supportive



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Thank you!

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