

Acute Kidney Injury

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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”

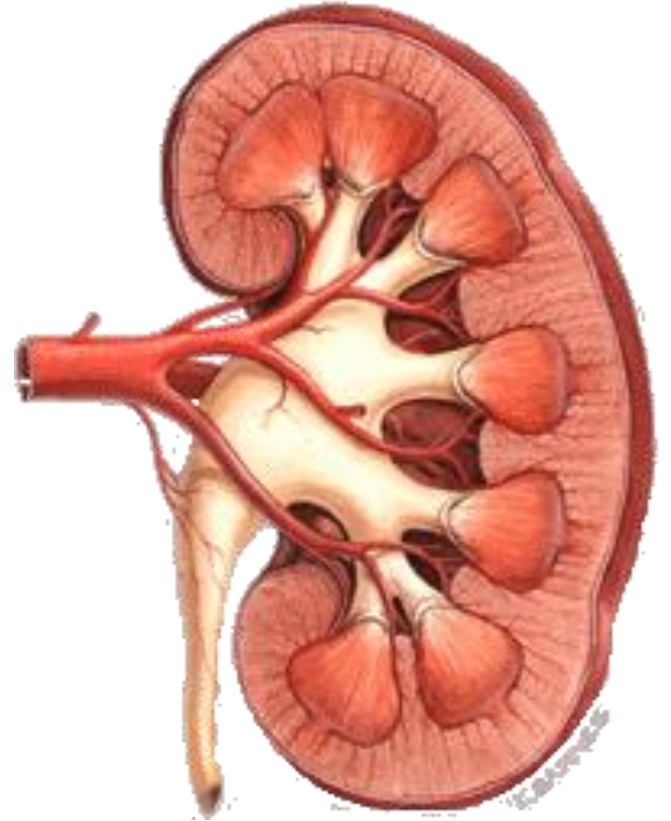
Happens within hours to days

“Kidney”

More familiar to patients than “Renal”

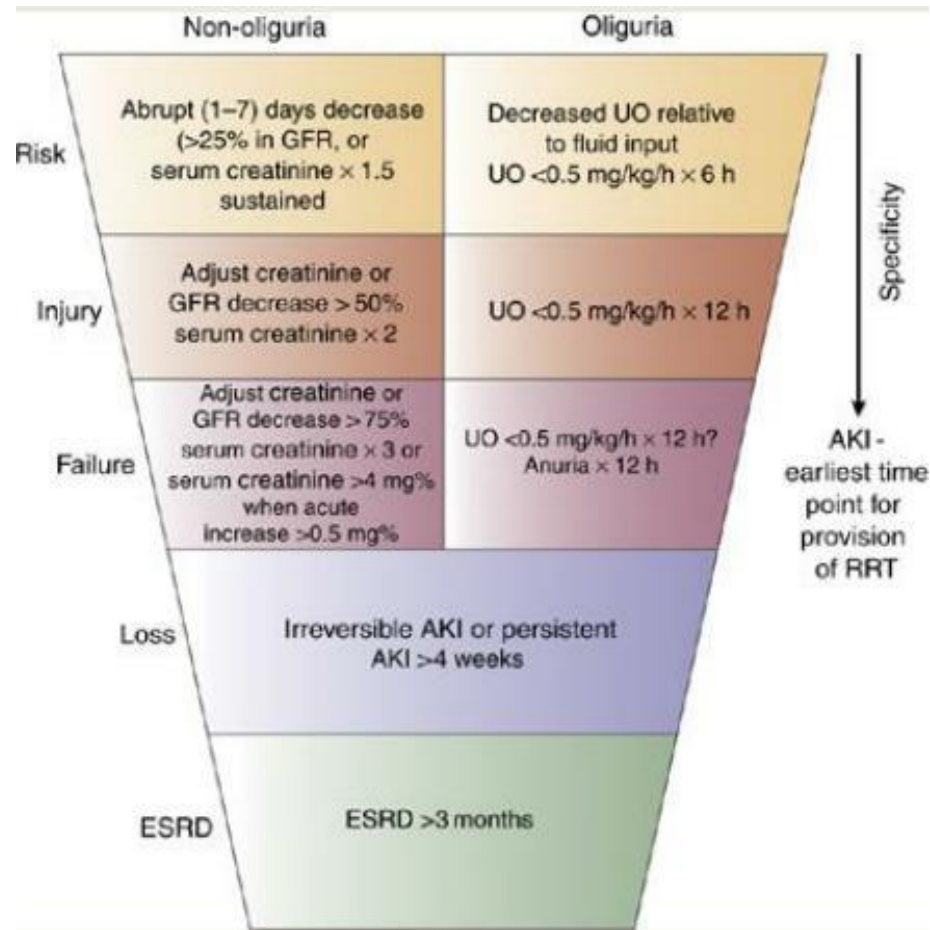
“Injury”

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



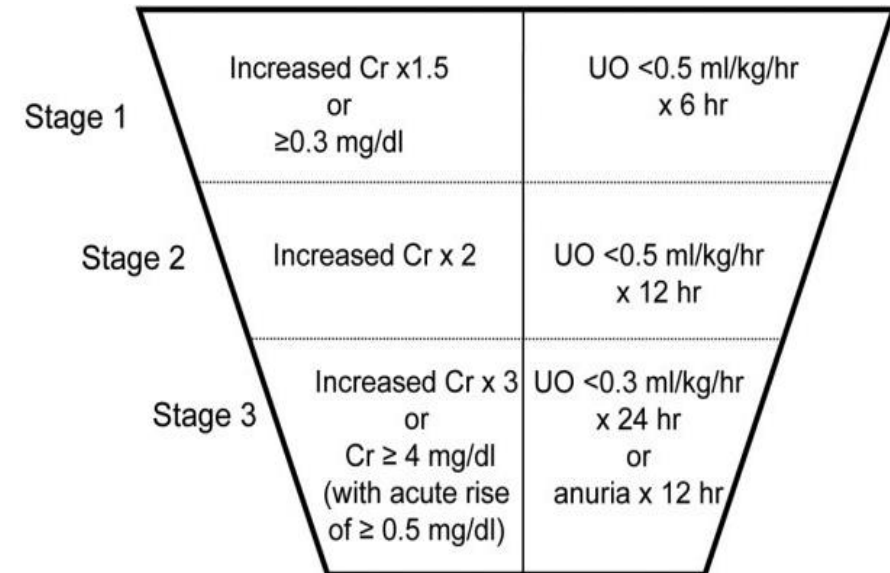
Historical Consensus Definitions of AKI

RIFLE Criteria



Crit Care, 2004

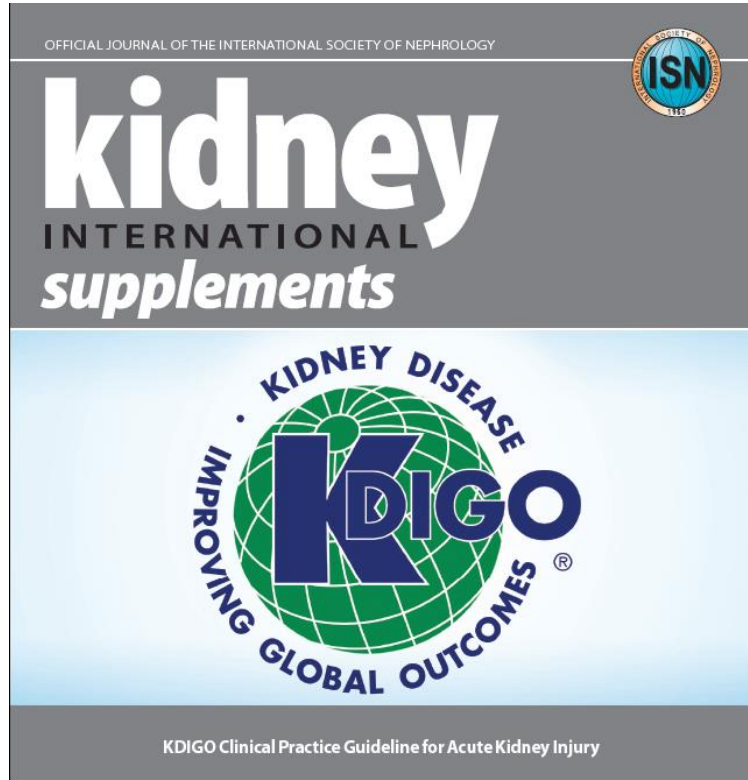
AKIN Criteria



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:

- $\uparrow \text{SCr} \geq 0.3 \text{ mg/dL}$ in 48h or $\geq 50\%$ in 7d
- Oliguria ($\text{UOP} < 0.5 \text{ ml/kg/h} \times 6\text{h}$)
- Dialysis

Staging of AKI severity

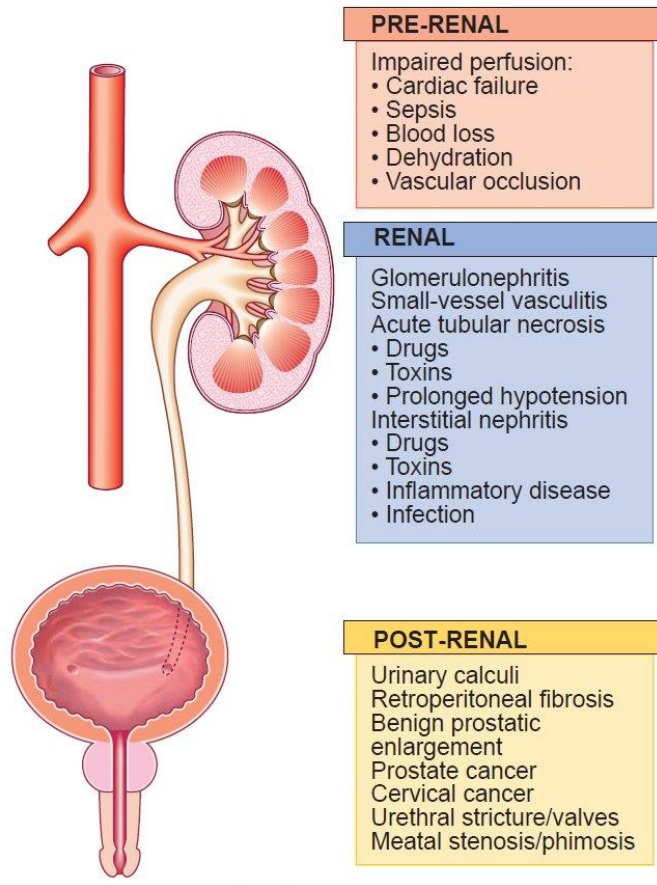
SCr	UOP
Stage 1: increase in SCr ≥ 0.3 mg/dL or $\geq 1.5\times$	Stage 1: output < 0.5 mL/kg/h for ≥ 6 h
Stage 2: increase in SCr $\geq 2\times$	Stage 2: output < 0.5 mL/kg/h for ≥ 12 h
Stage 3: increase in SCr $\geq 3\times$, or SCr > 4 mg/dL, or RRT	Stage 3: output < 0.3 mL/kg/h for ≥ 24 h or anuria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

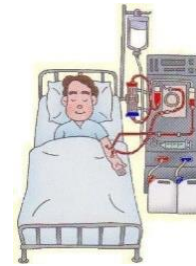
Physiologic Classification



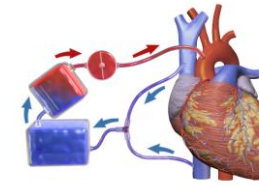
Davidsons Essentials of
Medicine, 2nd edition

Common clinical settings where AKI occurs

Sepsis



Cardiac surgery



Nephrotoxins



Exogenous

- Chemotherapy
- Antibiotics
- NSAIDs
- IV contrast

Endogenous

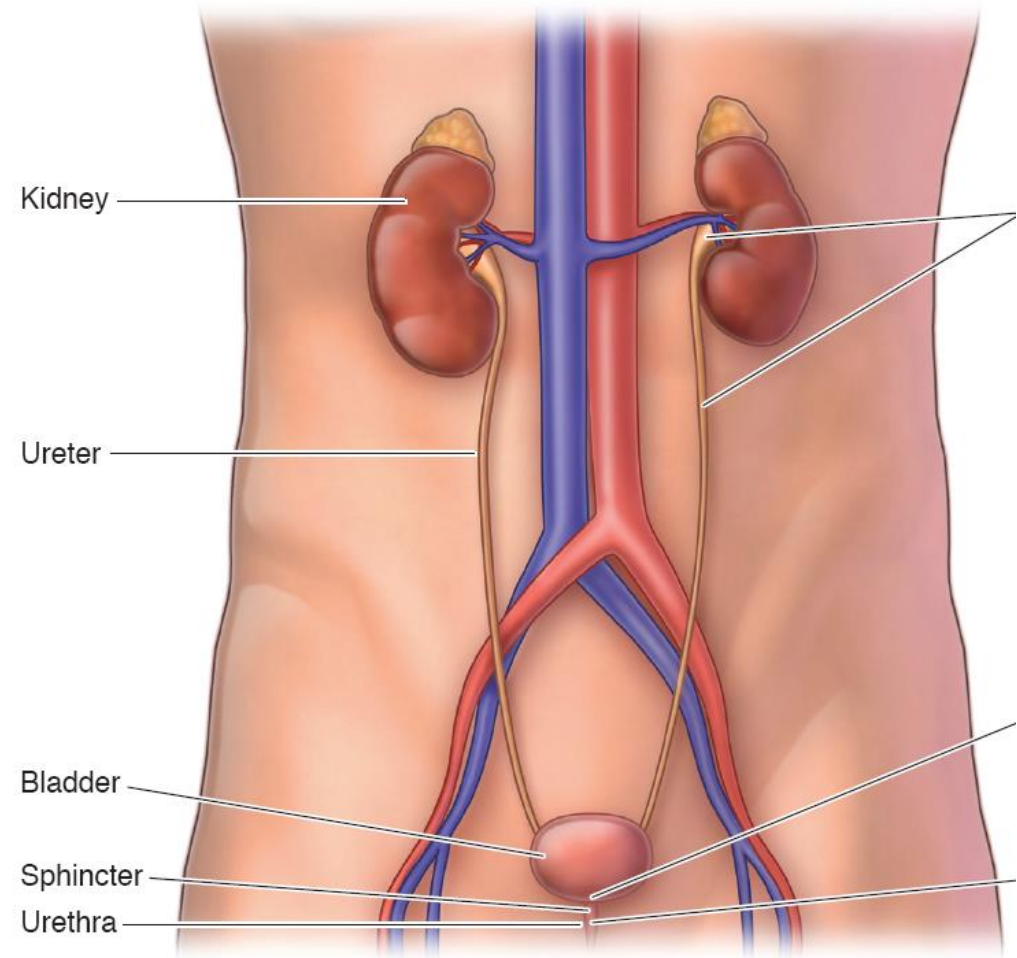
- Myoglobin (rhabdo)
- Hemoglobin (MAHA)
- Uric acid (TLS)

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

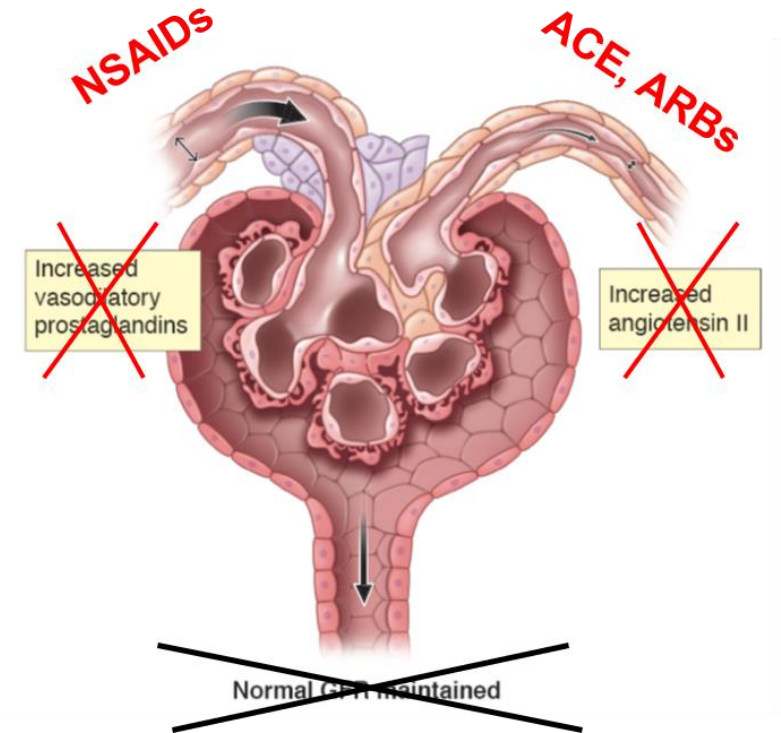
- **No structural injury to kidney**
- SCr increases due to renal hypoperfusion
- Restoration of hemodynamics -> rapid recovery

Causes

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

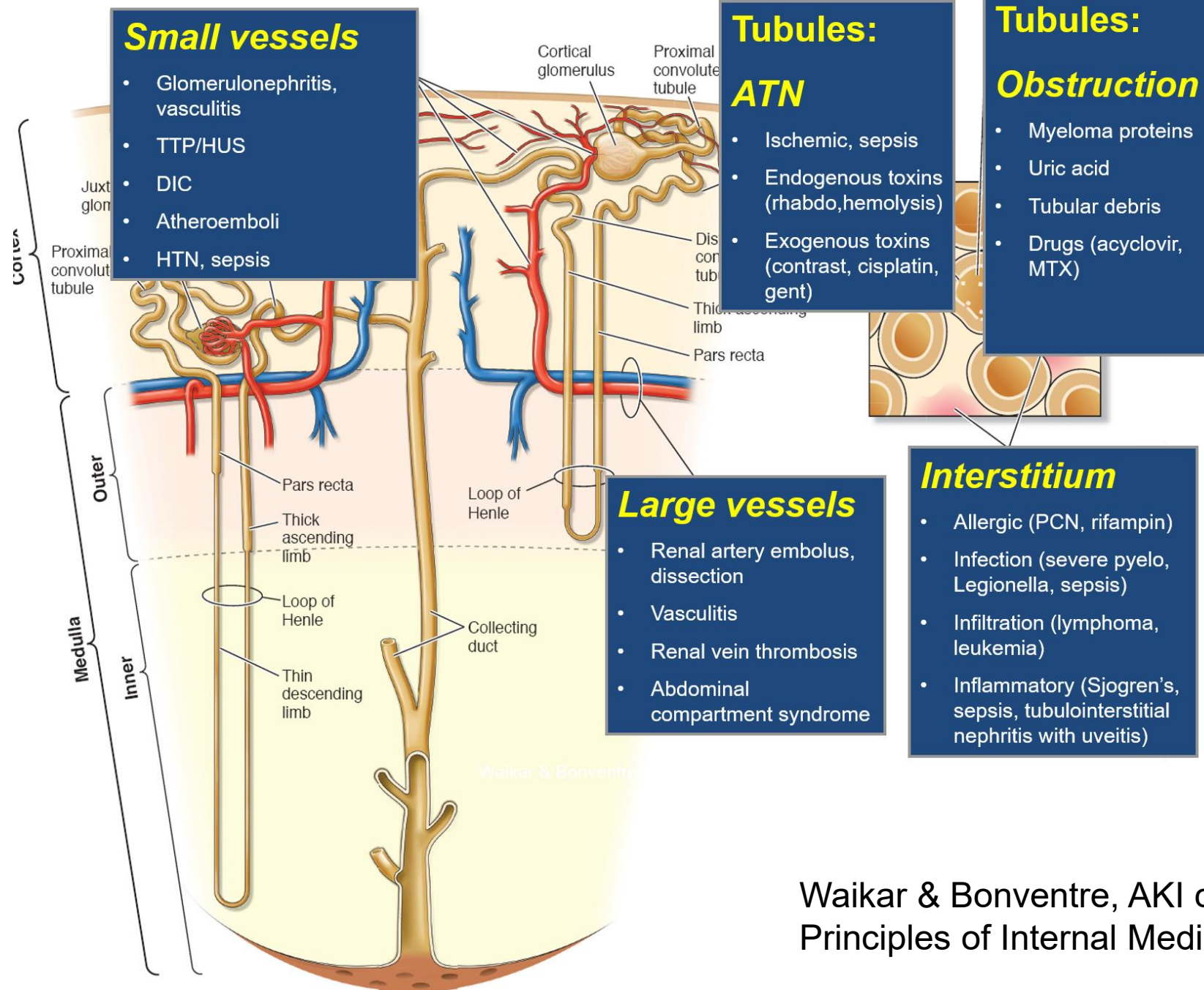
Clinical Pearl

- Pre-renal AKI and ischemic ATN are often overlapping clinical phenotypes



Intrinsic renal disease





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

Post-renal: A plumbing problem

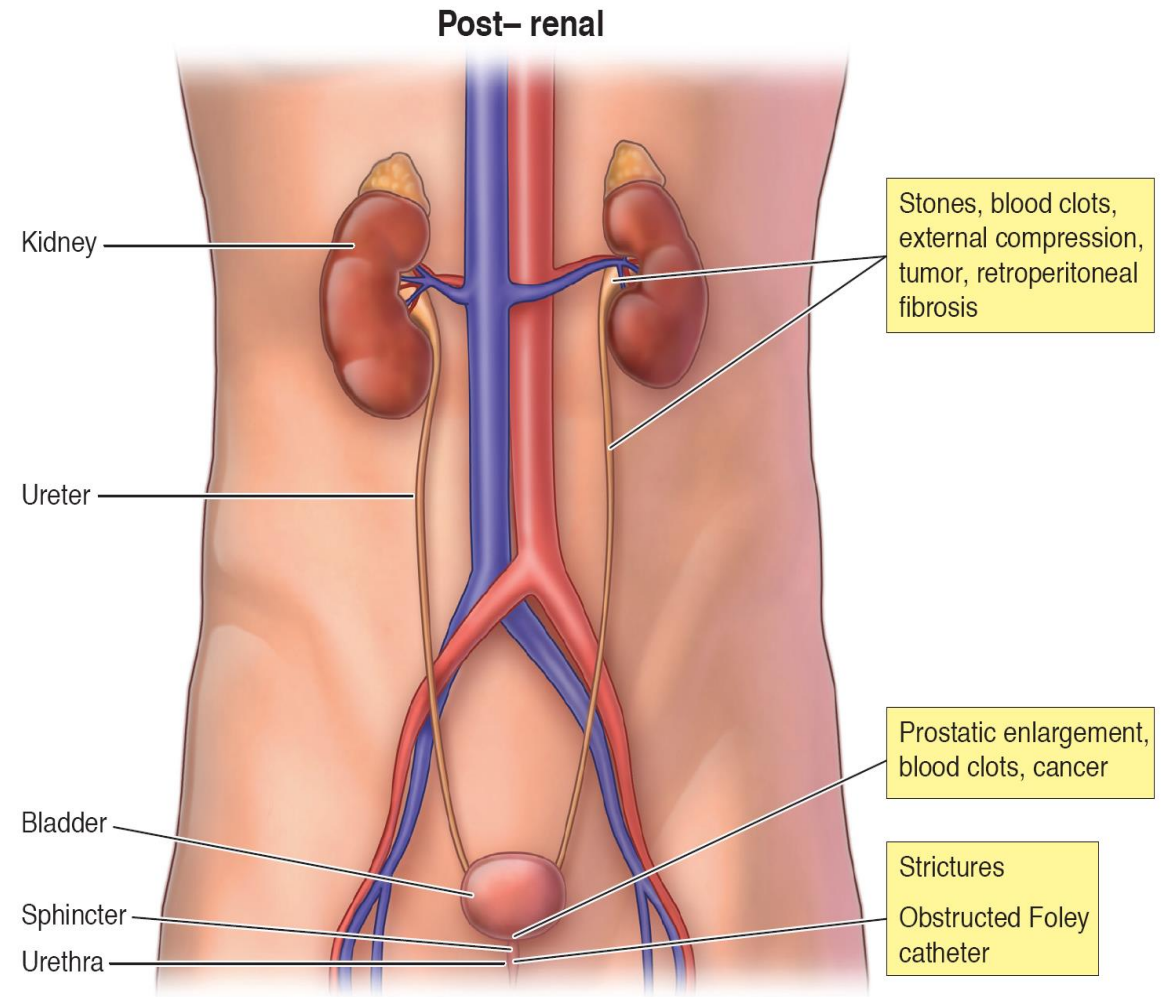
Diagnostic/imaging workup:

- 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)

Clinical 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

TESTS AND READING TIME							
LEU	LEUKOCYTES	Negative		Trace	Small +	Moderate ++	Large +++
	2 minutes						
NIT	NITRITE	Negative			Positive (any degree of uniform pink color)		
	60 seconds						
URO	UROBILINOGEN	0.2	1	2	4	8	
	60 seconds						
PRO	PROTEIN	Negative	Trace	mg/dL	30 +	100 ++	300 +++
	60 seconds						
pH	pH	5.0	6.0	6.5	7.0	7.5	8.0
	60 seconds						
BLO	BLOOD	Negative	Non-hemolyzed Trace	Moderate	Hemolyzed Trace	Small +	Moderate ++
	60 seconds						
SG	SPECIFIC GRAVITY	1.000	1.005	1.010	1.015	1.020	1.025
	45 seconds						
KET	KETONE	Negative	mg/dL	Trace 5	Small 15	Moderate 40	Large 80
	40 seconds						
BIL	BILIRUBIN	Negative			Small +	Moderate ++	Large +++
	30 seconds						
GLU	GLUCOSE	Negative	g/dL (%)	1/10 (1%)	1/4 250	1/2 500	1 1000
	30 seconds						

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

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

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

Recent RCTs: What Has Changed in AKI Management?

Several large RCTs have challenged long-held assumptions about AKI prevention and treatment

**Contrast
AKI**

**IV
Fluids**

**Dialysis
Timing**

**IV
Bicarbonate**

HRS-AKI

Can We Prevent Contrast-Associated AKI?

PRESERVE (NEJM 2018)

5177 patients undergoing coronary or non-coronary angiography

The **NEW ENGLAND**
JOURNAL *of* **MEDICINE**

ESTABLISHED IN 1812

FEBRUARY 15, 2018

VOL. 378 NO. 7

Outcomes after Angiography with Sodium Bicarbonate
and Acetylcysteine

Clinical question

Can IV sodium bicarb or NAC prevent contrast-associated AKI?

Answer

Neither intervention reduced death, dialysis, or persistent kidney dysfunction.

BOTTOM LINE

**IV hydration remains the cornerstone of prevention.
Routine NAC and bicarbonate should not be used.**

Balanced Crystalloids or Normal Saline?

PLUS (NEJM 2022)
5037 critically ill adults

Clinical question

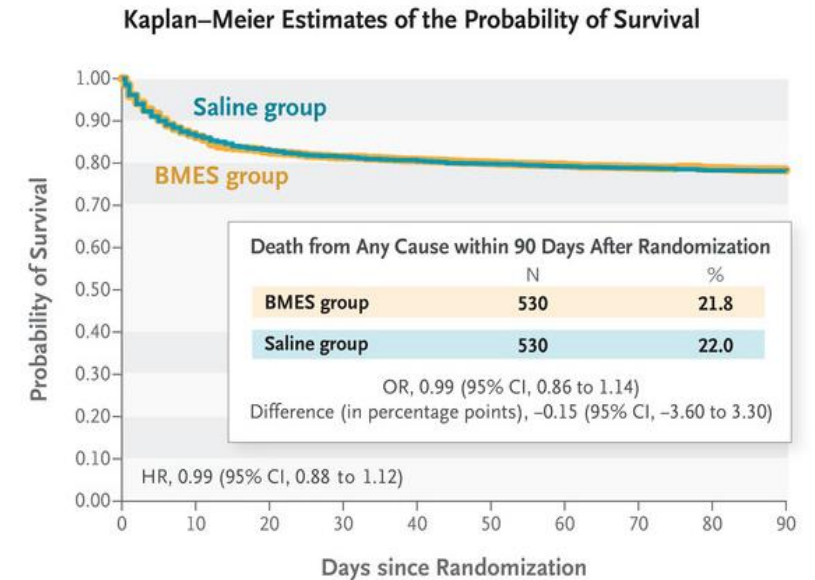
Are balanced crystalloids superior to NS?

Answer

No difference in mortality, AKI, or dialysis.

BOTTOM LINE

Balanced crystalloids are reasonable, but saline is not “wrong”.



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)

When Should Dialysis Be Started for AKI?

STARRT-AKI (NEJM 2020)

3019 critically ill patients with AKI

ORIGINAL ARTICLE

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

Clinical question

Should KRT be started early after AKI development?

Answer

Early initiation did not reduce mortality but *did* increase dialysis dependence.

BOTTOM LINE

Don't start dialysis because the creatinine looks bad. Start dialysis because the patient needs dialysis.

Should We Give IV Sodium Bicarbonate?

Research

JAMA | **Original Investigation** | CARING FOR THE CRITICALLY ILL PATIENT

Sodium Bicarbonate for Severe Metabolic Acidemia
and Acute Kidney Injury

The BICARICU-2 Randomized Clinical Trial

ORIGINAL ARTICLE

Sodium Bicarbonate for Critically Ill Adults
with Metabolic Acidosis and Shock

The SODa-BIC Investigators and the Australian and New Zealand Intensive Care
Society Clinical Trials Group*

Clinical question

Does IV sodium bicarb improve outcomes in metabolic acidosis?

Answer

Neither trial demonstrated improvement in mortality or major kidney outcomes.

BOTTOM LINE

Reserve IV bicarbonate for established indications—not simply to treat or prevent AKI.

How Should We Treat HRS-AKI?

CONFIRM (NEJM 2021)

300 patients with HRS

ORIGINAL ARTICLE

Terlipressin plus Albumin for the Treatment
of Type 1 Hepatorenal Syndrome

Clinical question

Does terlipressin improve outcomes in HRS-AKI?

Answer

Higher rate of HRS reversal w/ terlipressin, but use with caution in patients with respiratory failure.

BOTTOM LINE

Terlipressin is evidence-based therapy for HRS-AKI in appropriately selected patients.

Five Practice-Changing Lessons from Recent AKI Trials

Clinical question	Bottom line
Prevent contrast AKI?	IV hydration. No NAC or bicarbonate.
Balanced fluids?	No compelling evidence that balanced crystalloids are superior to NS.
Start dialysis early?	Wait for standard indications.
Give IV bicarb for metabolic acidosis?	No improvement in major outcomes.
Treat HRS-AKI?	Terlipressin improves HRS reversal.

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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- B) Thrombotic microangiopathy
- 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

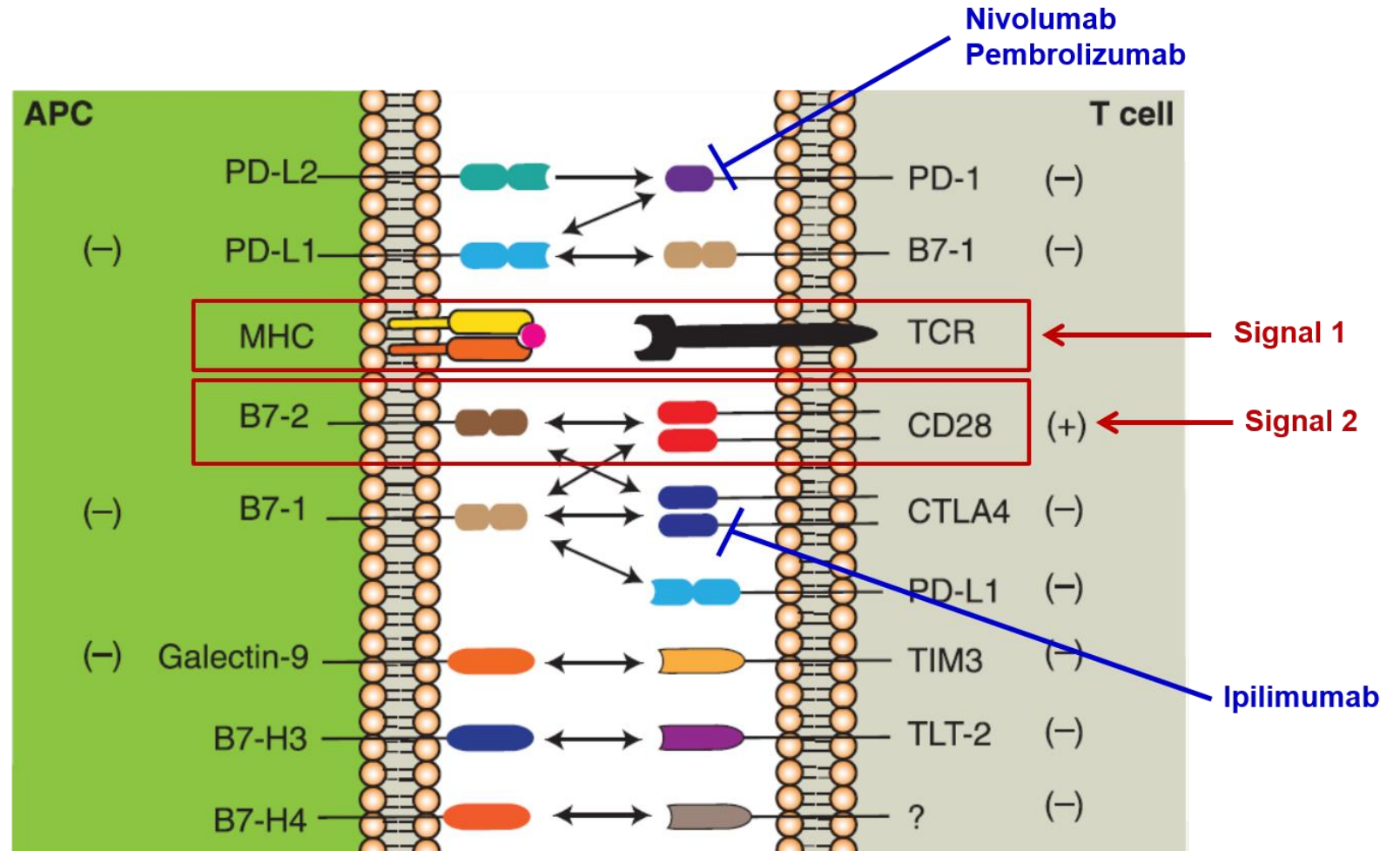
- Ipilimumab

PD-1 antagonists

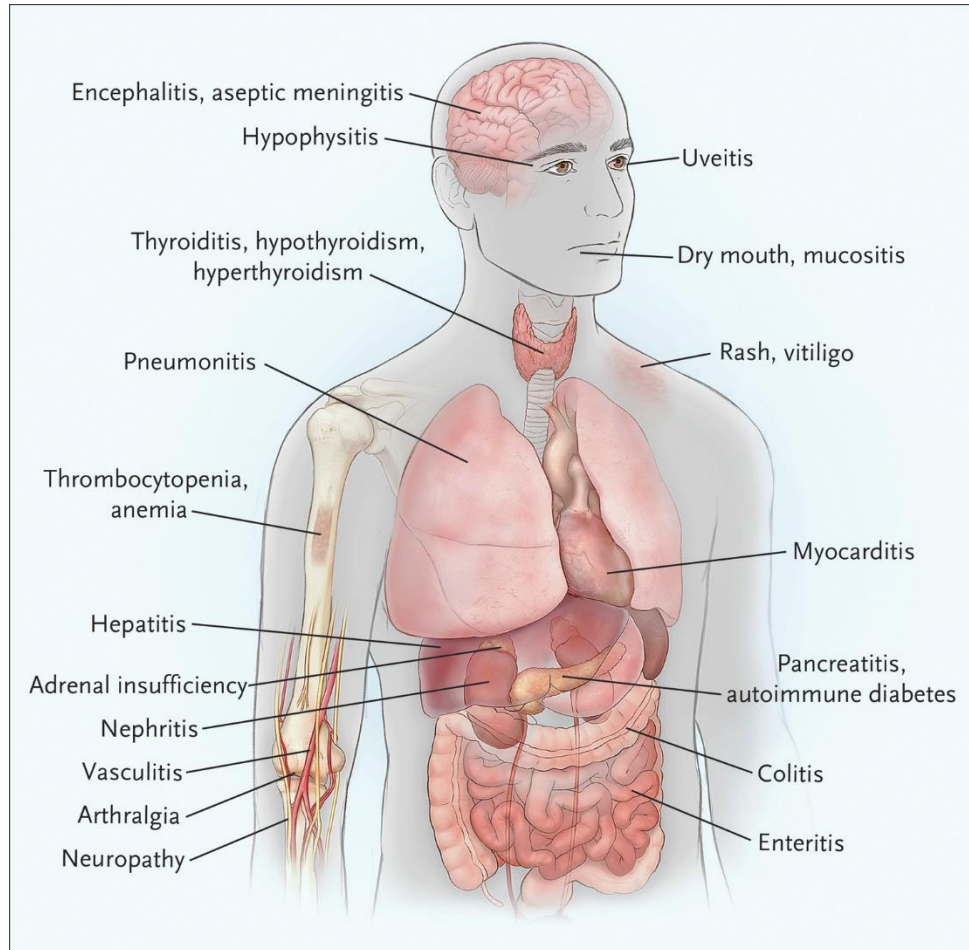
- Nivolumab
- Pembrolizumab

PD-L1 antagonists

- Atezolizumab
- Avelumab
- Durvalumab

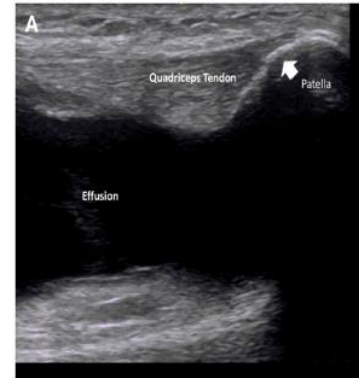


Autoimmune Toxicity (“Immune-Related Adverse Events”)

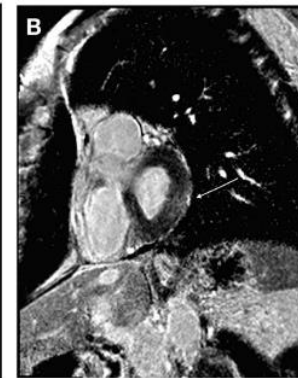


Postow et al., *N Engl J Med*, 2018

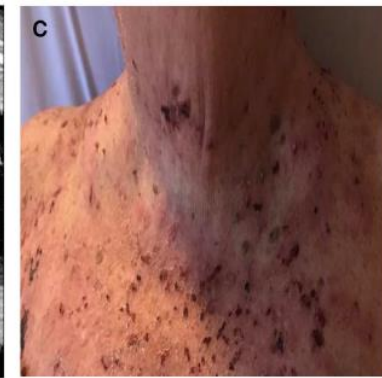
Inflammatory arthritis



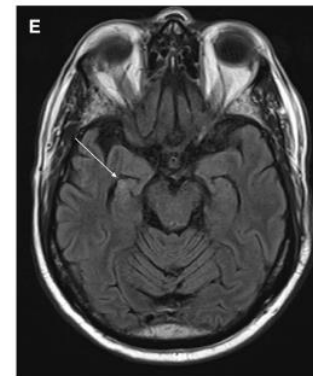
Myocarditis



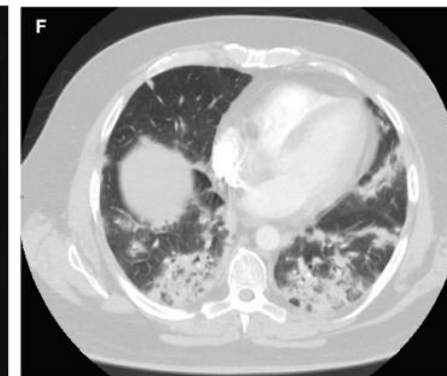
Bullous pemphigoid



Lichenoid dermatitis



Encephalitis



Pneumonitis



Colitis

Connolly et al., *Front Oncol*, 2019

Immune checkpoint inhibitor-associated AKI

Pathophysiology

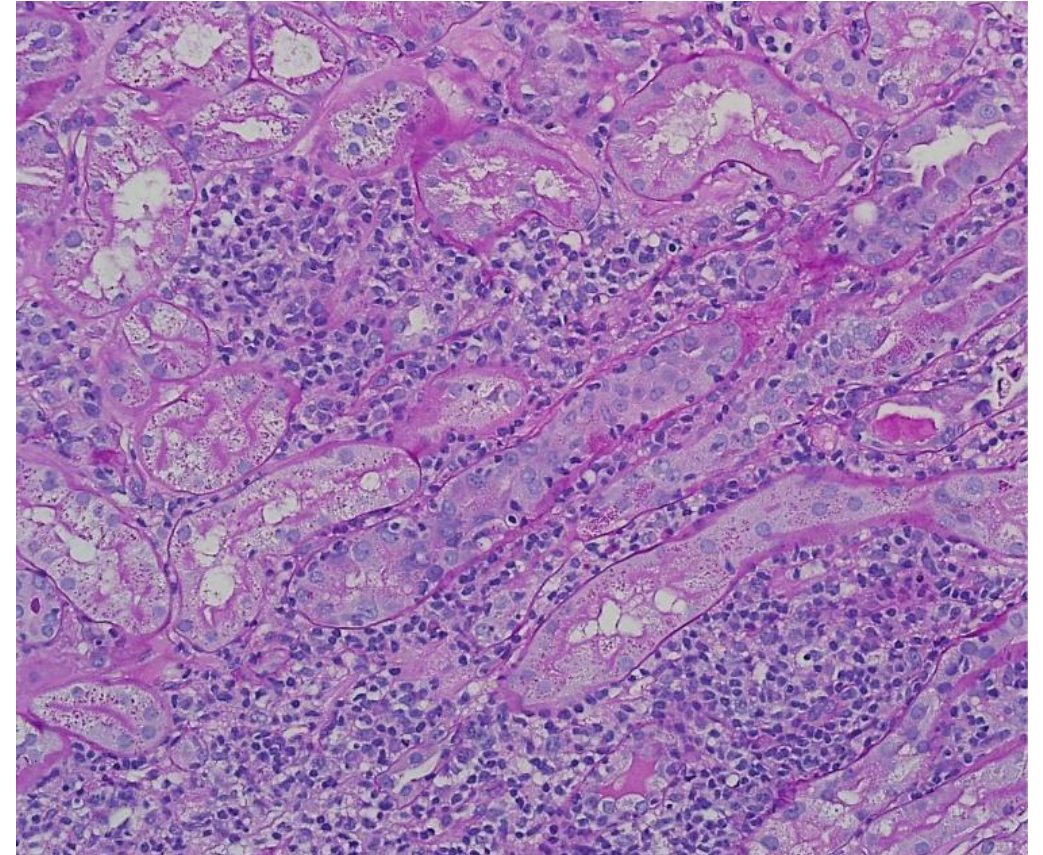
AIN = most common pathological lesion (>90%)

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



References

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- STARRT-AKI Investigators. Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. *N Engl J Med*, 2020
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Thank you!

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