Acute Kidney Injury: A Practical Framework

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Disclosures

- I have no disclosures related to this topic

Learning Objectives: Acute Kidney Injury (AKI)

- Nuts and bolts
  - Definition & Mechanics
  - Differential
  - Outcomes & Management
- New developments
  - Contrast Nephropathy
  - COVID
  - Onconephrology
  - Critical Care

Two cases

Case #1

50 year old healthy male presents with nausea, vomiting & diarrhea

-Poor po intake for 5 days

-Some decrease in urine output

-Using 600mg ibuprofen twice daily for muscle aches

-BUN: 40, Cr: 1.5 (baseline Cr: 1.0 last week)

-Urinalysis: no hematuria or proteinuria, specific gravity: 1.030

Case #2

88 year old male with hypertension, diabetes, tobacco use, CKD3 presents with hypotension

-On levophed in the emergency room

-Blood cultures positive, he has a new rash

-Minimal UOP over the past 24 hours

-BUN: 110, Cr: 4.5, K: 5.7

-Baseline Cr: 1.4 three days ago at PCP appointment

-Urinalysis: 2+ hematuria (50-100 RBCs on sediment), 2+ proteinuria (ACR: 2500)

Do these patients have acute kidney injury (AKI)?

Which of the following are part of the current KDIGO definition of AKI?

A. A 0.3 mg/dL increase in Cr over 48 hrs
B. A 50% increase in KIM-1 or NGAL over 24 hrs
C. A 50% increase in Cr over the past 7 days
D. A & C
E. A, B & C

AKI simplified

Table 2. AKI definition and staging according to KDIGO criteria - modified from reference (8)

AKI is *defined* as any of the following:		
1	Increase in sCr ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours; or	
2	Increase in sCr ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or	
3	Urine volume <0.5 mL/kg/h for 6 hours.	
AKI is *staged for severity* according to the following criteria		
Stage 1	1.5–1.9 times baseline OR ≥0.3 mg/dL (≥26.5 μmol/L) absolute increase in sCr	Urine volume <0.5 mL/kg/h for 6–12 hours
Stage 2	sCr ≥2.0–2.9 times baseline	Urine volume <0.5 mL/kg/h for ≥12 hours
Stage 3	sCr ≥3.0 times from baseline OR Increase in sCr to ≥4.0 mg/dL(≥353.6 μmol/L) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	Urine volume <0.3 mL/kg/h for ≥24 hours OR Anuria for ≥12 hours

sCr=serum creatinine, eGFR= estimated glomerular filtration rate

Makris et al, *Clin Biochem Rev*, 2016

The incidence of AKI is increasing

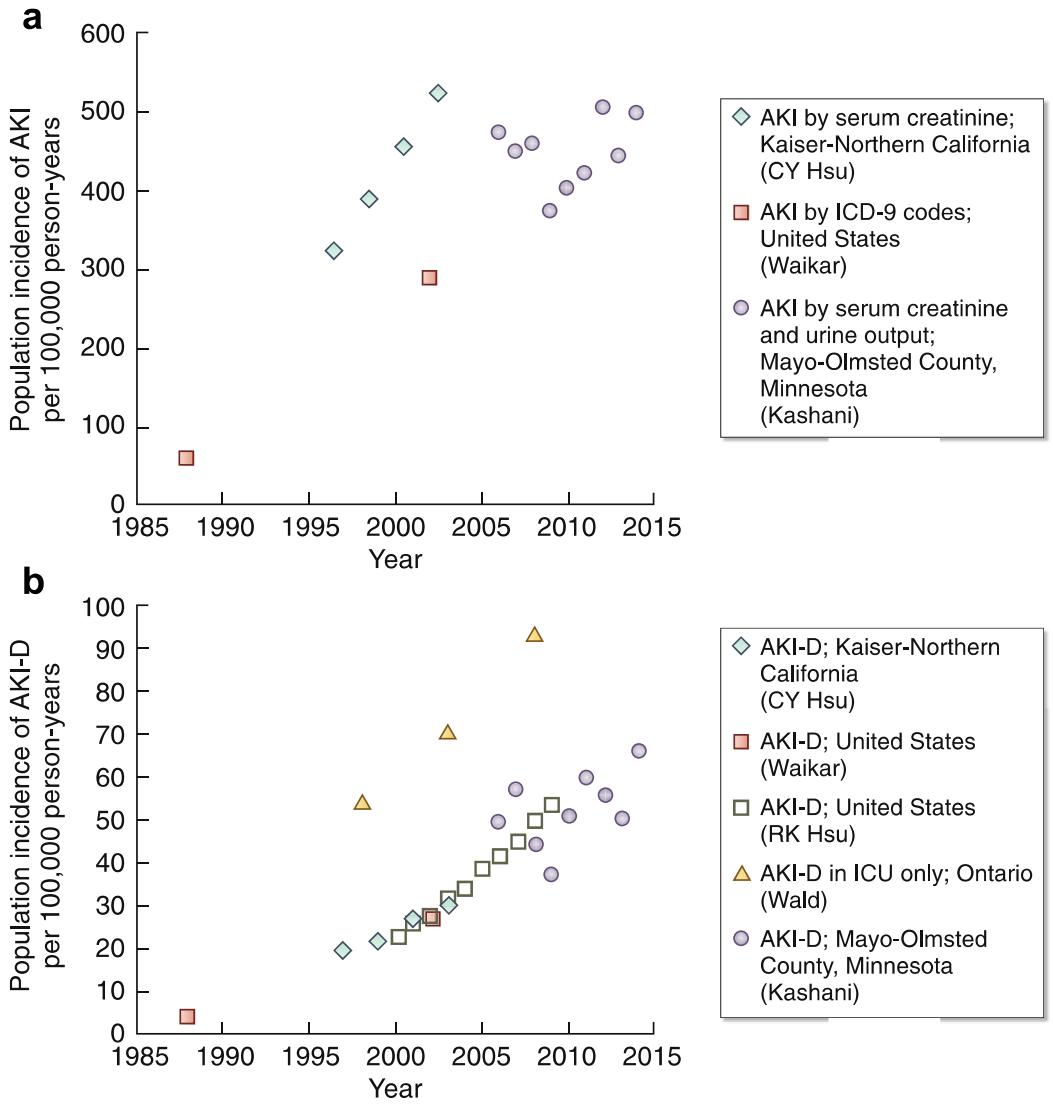


Figure 1 | Temporal trends in the population incidence rate of (a) AKI and (b) dialysis-requiring AKI in North American populations.[1–5] AKI, acute kidney injury; AKI-D, dialysis-requiring acute kidney injury.

Hsu et al, *KI*, 2017

The mechanics of AKI

Case #2

88 year old male with hypertension, diabetes, tobacco use, CKD3 presents with **hypotension**

-On levophed in the emergency room

-Blood cultures positive, he has a new **rash**

-**Minimal UOP over the past 24 hours**

-BUN: 110, **Cr: 4.5**, K: 5.7

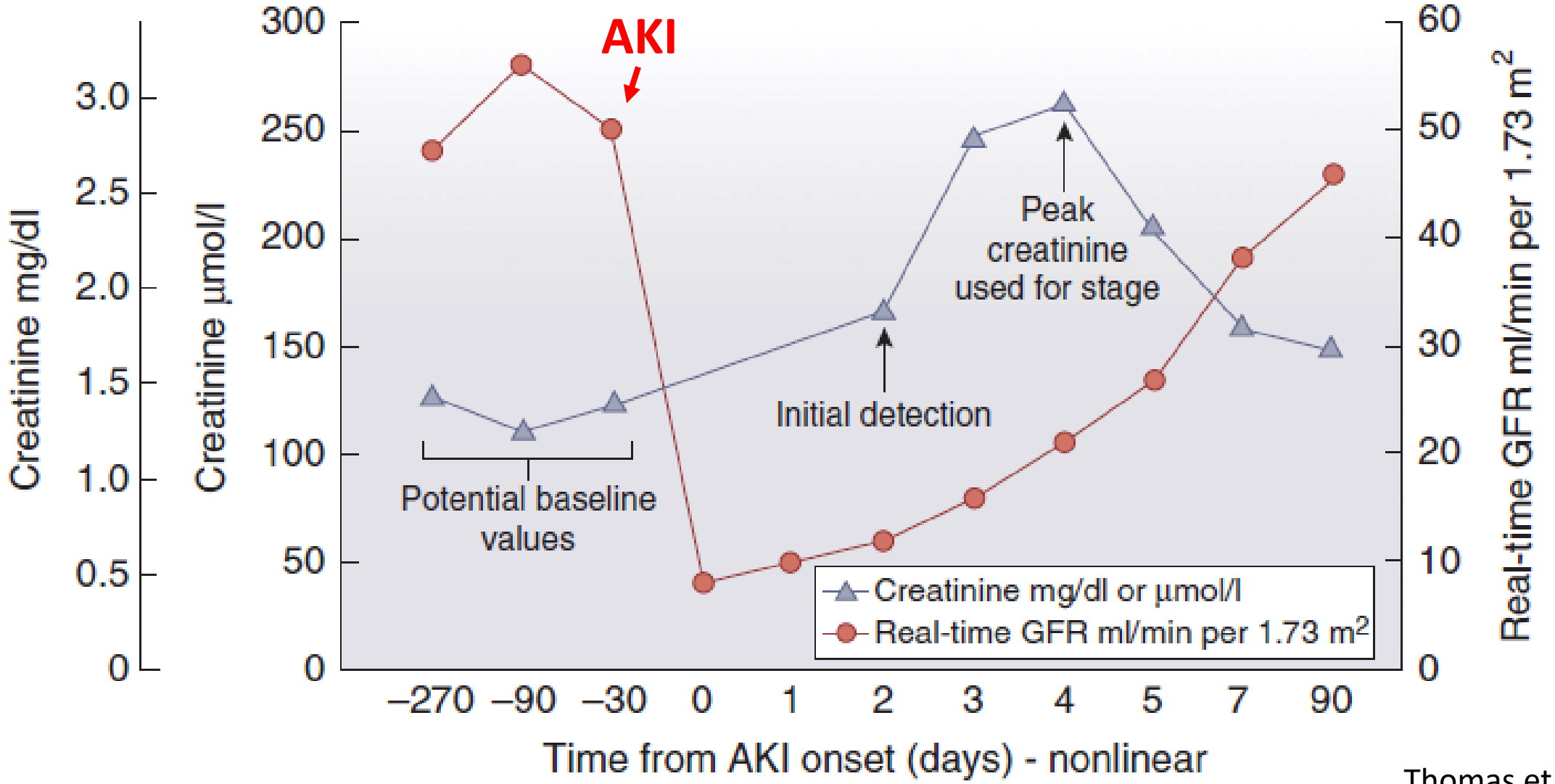
-**Baseline Cr: 1.4 three days ago at PCP appointment**

-**Urinalysis: 2+ hematuria (50-100 RBCs on sediment), 2+ proteinuria (ACR: 2500)**

What is an estimate of his current GFR and a possible cause of his AKI?

A. eGFR ~50, UTI
B. eGFR ~0, RPGN
C. eGFR ~0, ATN
D. eGFR ~30, AIN
E. B & C

The Relationship Between Creatinine and GFR in AKI and Renal Recovery



Thomas et al, *KI* 2015

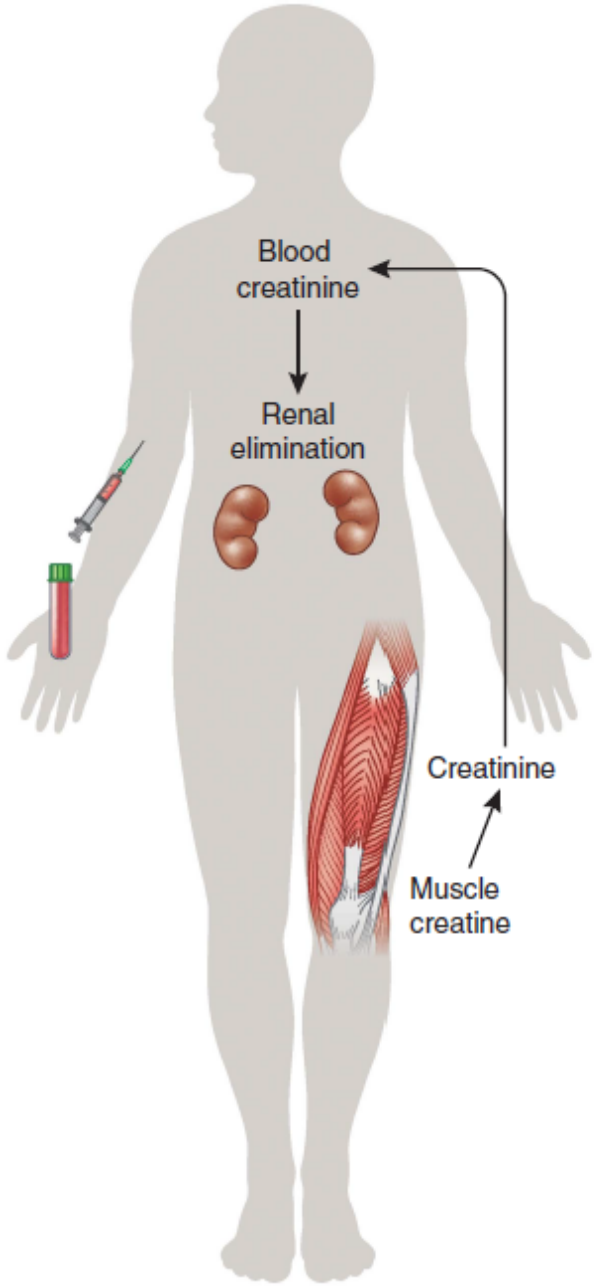
Factors that affect serum Cr measurement

Factors having an acute effect on creatinine

Acute rise in creatinine:
- Dietary creatine intake
  - a meat meal[50]
- Increased creatinine generation
  - rhabdomyolysis[51]
- Decreased glomerular filtration
  - AKI
- Reduced tubular secretion
  - trimethoprim and cimetidine

False elevation of creatinine:
- Jaffe assay interference
  - hyperglycemia and DKA[52]
  - delayed centrifugation
  - other: hemolysis; high total protein
- Enzymatic assay interference
  - high total protein, lidocaine

Acute fall / blunted rise in creatinine:
- Reduced creatinine generation
  - sepsis[53]
- Increased volume of distribution
  - edematous states*
  - acute fluid overload[54–57]



Factors having a chronic effect on creatinine – affecting baseline eGFR and ability to generate creatinine rise during AKI

Chronic 'elevation' of creatinine:
- Increased creatinine generation
  - muscular body habitus
- Decreased glomerular filtration
  - chronic kidney disease

False reduction of creatinine:
- Jaffe assay interference
  - hyperbilirubinemia
- Enzymatic interference
  - hyperbilirubinaemia, hemolysis

Chronic 'reduction' in creatinine:
- Low dietary protein (cooked meat) intake
- Reduced creatinine generation with lower muscle mass
  - old age and female sex
  - muscle-wasting conditions
  - amputation
  - malnutrition and critical illness[58]

Consider checking Cystatin C

Thomas et al, *KI* 2015

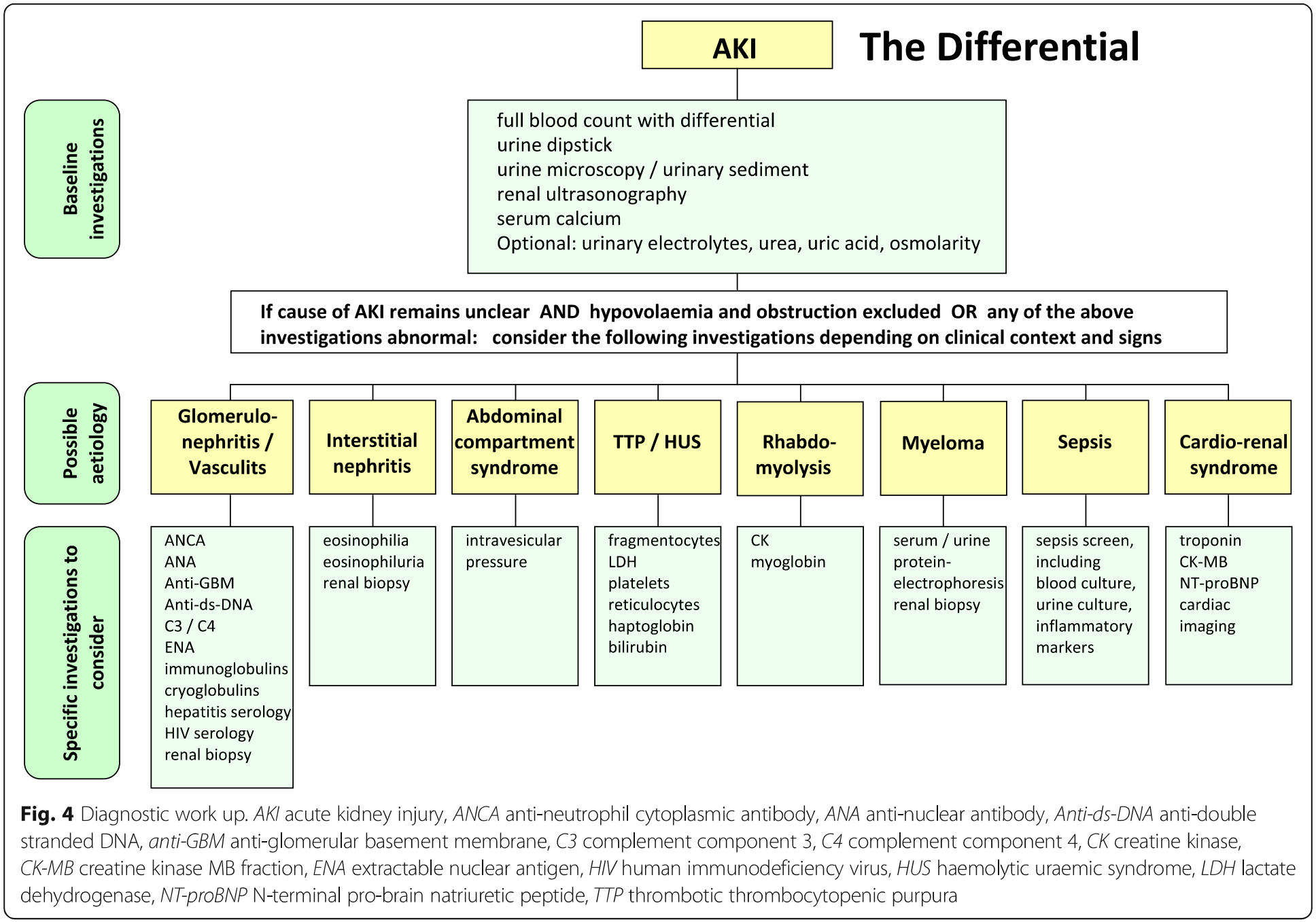
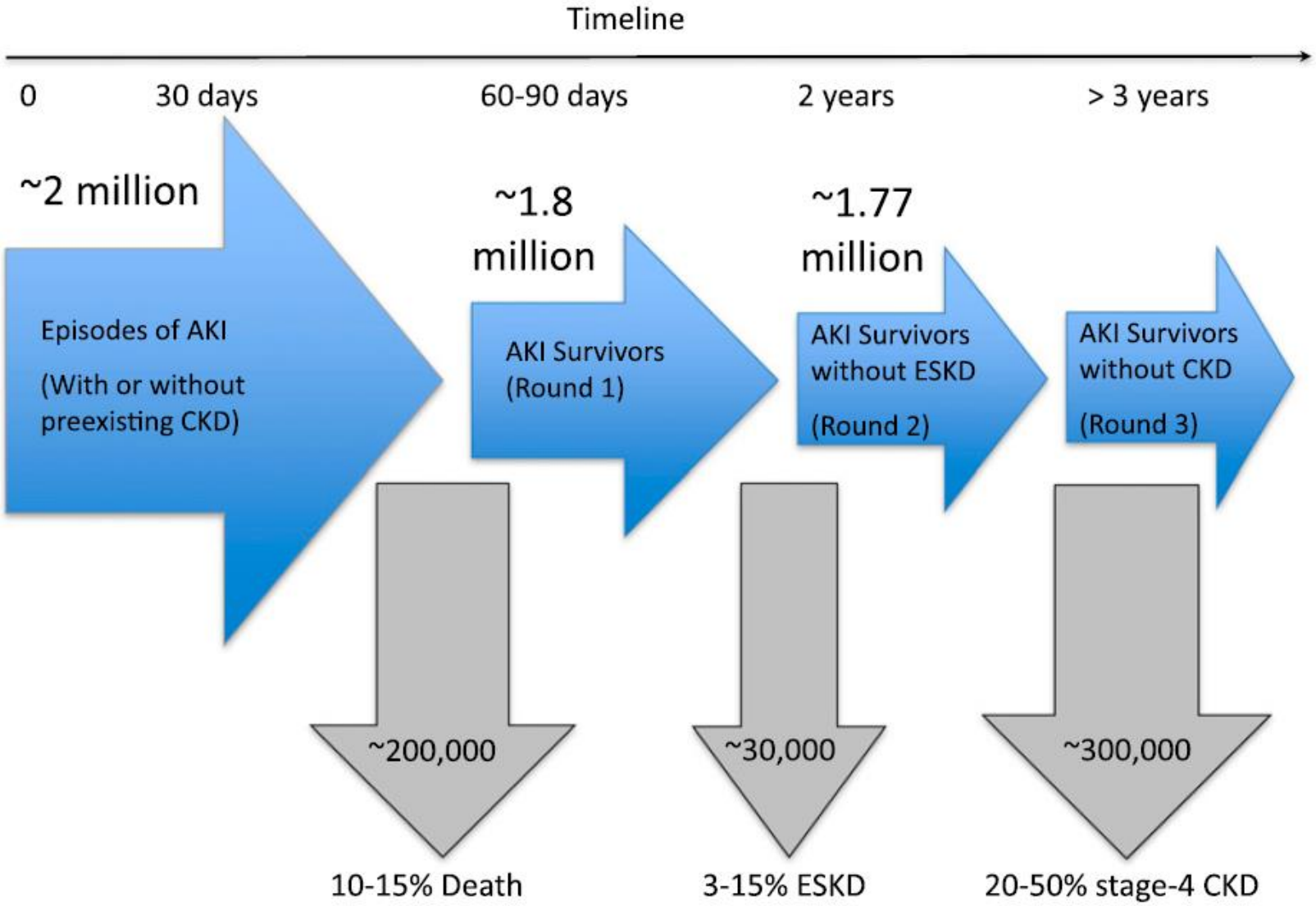


Fig. 4 Diagnostic work up. *AKI* acute kidney injury, *ANCA* anti-neutrophil cytoplasmic antibody, *ANA* anti-nuclear antibody, *Anti-ds-DNA* anti-double stranded DNA, *anti-GBM* anti-glomerular basement membrane, *C3* complement component 3, *C4* complement component 4, *CK* creatine kinase, *CK-MB* creatine kinase MB fraction, *ENA* extractable nuclear antigen, *HIV* human immunodeficiency virus, *HUS* haemolytic uraemic syndrome, *LDH* lactate dehydrogenase, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *TTP* thrombotic thrombocytopenic purpura

Ostermann et al, *Critical Care*, 2016

Modeling renal outcomes after an episode of AKI



- Only 13.2% of patients saw a nephrologist within 3 months of an episode of AKI

Goldstein et al, *CJASN*, 2013

Renal recovery from AKI depends on the initial substrate

Case #1

50 year old healthy male presents with nausea, vomiting & diarrhea

Case #2

88 year old male with hypertension, diabetes, tobacco use, CKD3 presents with hypotension

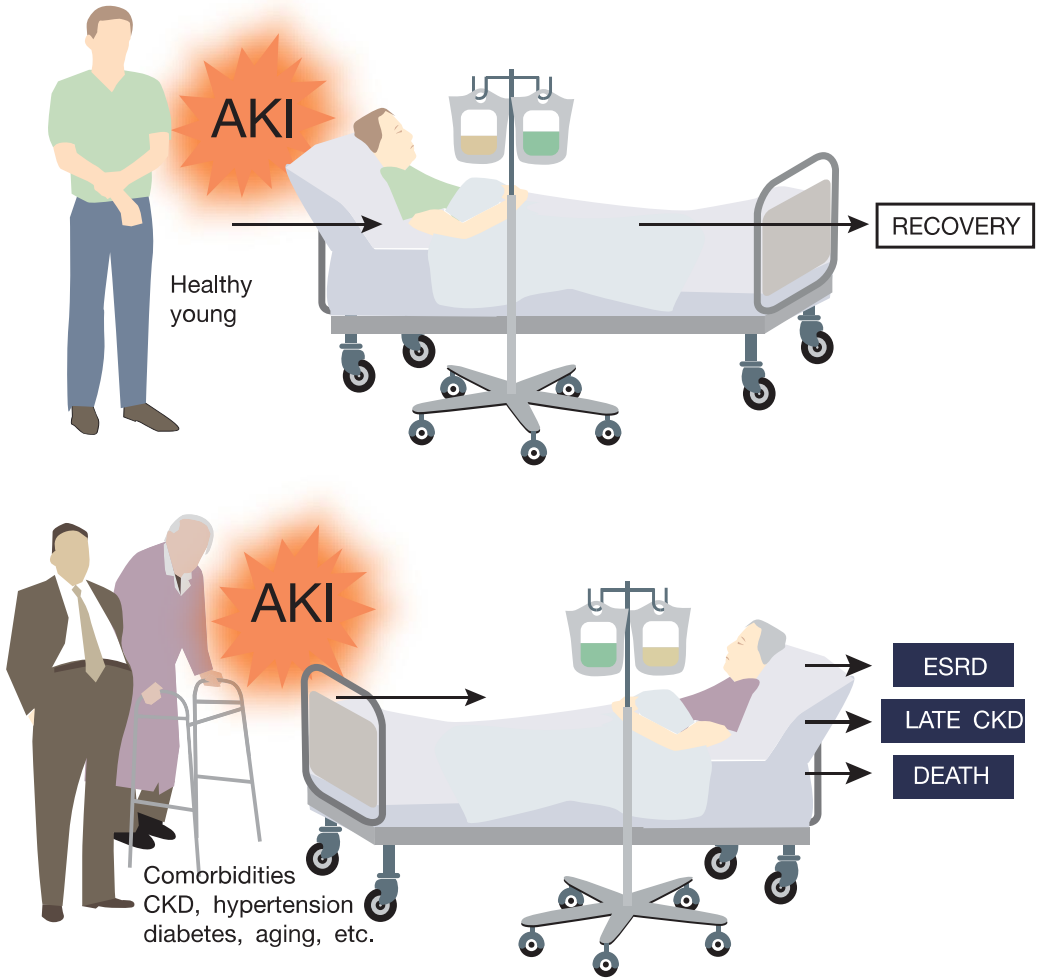


Figure 1 | Poor prognosis of acute kidney injury (AKI) in patients with chronic kidney disease (CKD) and related comorbidities. ESRD, end-stage renal disease.

He et al, *KI*, 2017

The spectrum of AKI

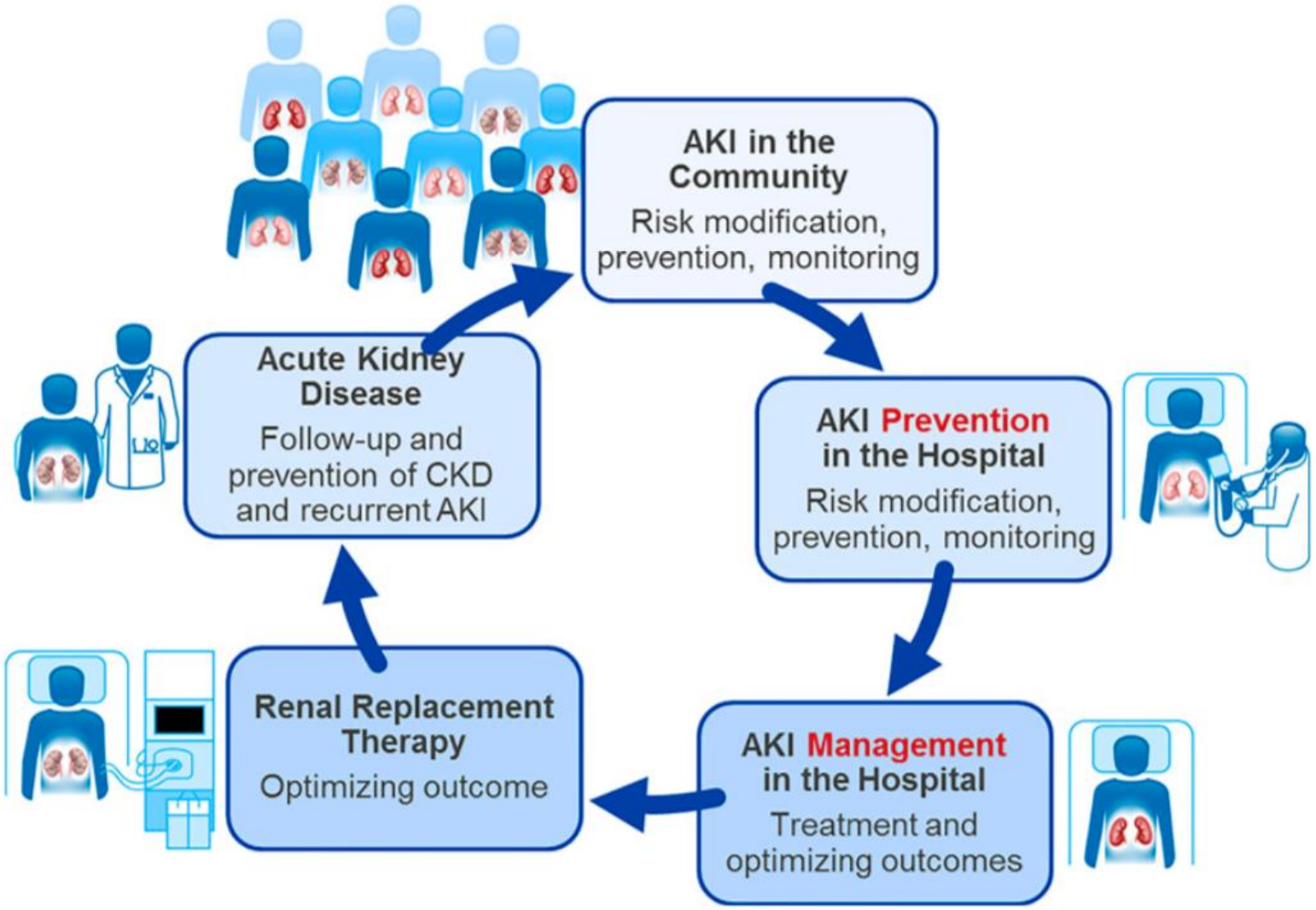
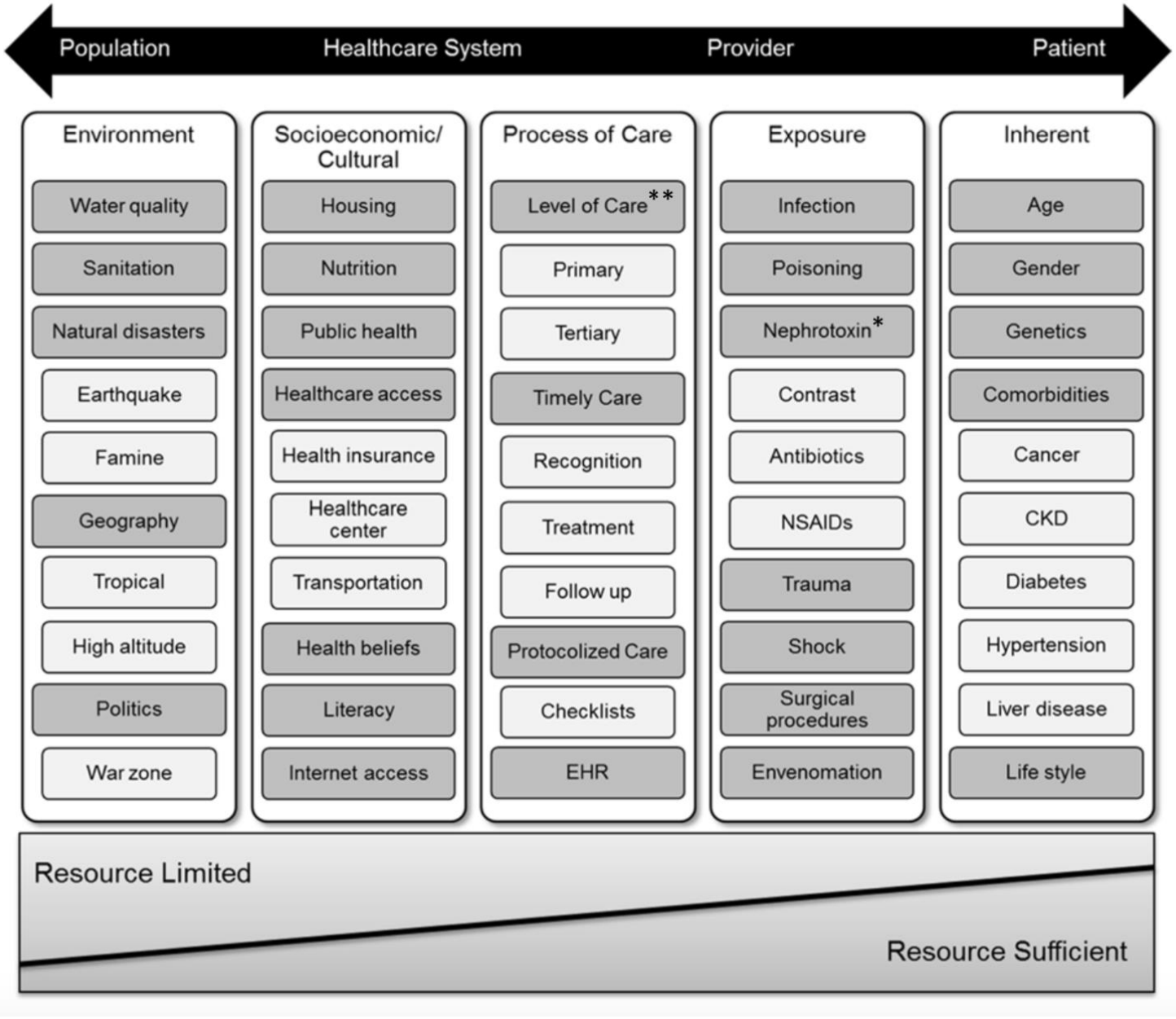


Figure 2. | **AKI quality care in a continuity.** Reprinted from Acute disease quality initiative (ADQI) (12), with permission.

Kashani et al, *CJASN*, 2019

Assessing risk for AKI in the community



Kashani et al, *CJASN*, 2019

AKI monitoring and prevention in the community

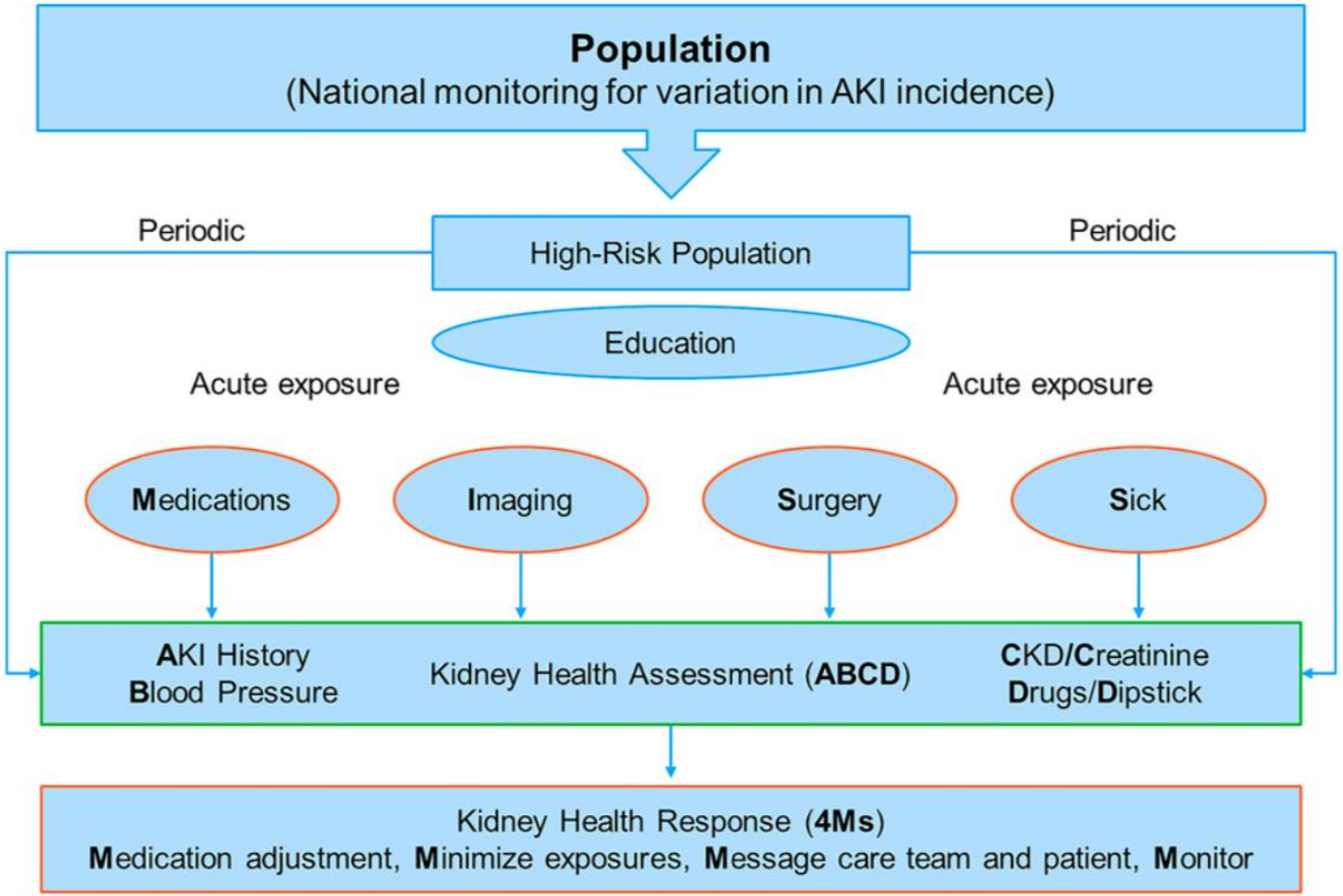


Figure 3. | **KHA and response.** KHA includes AKI history, BP, CKD, serum Creatinine level, Drug list, and urine Dipstick (ABCD). Exposures include Nephrotoxic Medications, Imaging, Surgery, Sickness (NISS). KHR (4Ms) that encompasses Medication review to withhold unnecessary medications (*e.g.*, nonsteroidal anti-inflammatory drugs [16,17]), the Minimization of nephrotoxic exposures (*e.g.*, intravenous contrast [18]), Messaging the healthcare team and patient to alert the high risk of AKI, and Monitoring for AKI and its consequences. Reprinted from Acute disease quality initiative (ADQI) (12), with permission.

Kashani et al, CJASN, 2019

Risk Factors for AKI in Hospitalized Patients

Table 3. AKI risk assessment among hospitalized patients

Risk Category	Examples
Comorbid conditions	CKD
	Diabetes mellitus
	Heart failure
	Liver disease
	History of AKI
	Anemia
	Neurologic for cognitive impairment or disability
Illnesses	Sepsis
	Rhabdomyolysis
	Hemorrhage
	Hemolysis
	ARDS
	Severe diarrhea
	Hematologic malignancy
	Trauma
Symptoms and signs	Hypotension and hypovolemia
	Hypertension and fluid overload
	Oliguria (urine output <0.5 ml/kg per h)
	Symptoms/history of urological obstruction or conditions that may lead to obstruction
	Symptoms or signs of glomerulo-interstitial nephritis (*e.g.*, edema, hematuria)
Others	Use of KENDs within a week before admission

KEND medications include (*1*) cleared by the kidney but not nephrotoxic (*e.g.*, digoxin), (*2*) cleared by the kidney and nephrotoxic (*e.g.*, vancomycin), and (*3*) not cleared by the kidney but are nephrotoxic (*e.g.*, calcineurin inhibitors). KEND, kidney eliminated and nephrotoxic drugs; ARDS, adult respiratory distress syndrome.

Kashani et al, *CJASN*, 2019

Box 2. Key Medications Requiring Dose Adjustment (or Cessation) in AKI

- Analgesics (morphine, meperidine, gabapentin, pregabalin)
- Antiepileptics (lamotrigine)
- Antivirals (acyclovir, gancyclovir, valgancyclovir)
- Antifungals (fluconazole)
- Antimicrobials (almost all antimicrobials need dose adjustment in AKI, with important exceptions of azithromycin, ceftriaxone, doxycycline, linezolid, moxifloxacin, nafcillin, rifampin)
- Diabetic agents (sulfonylureas, metformin)
- Allopurinol
- Baclofen
- Colchicine
- Digoxin
- Lithium
- Low-molecular-weight heparin
- NOACs

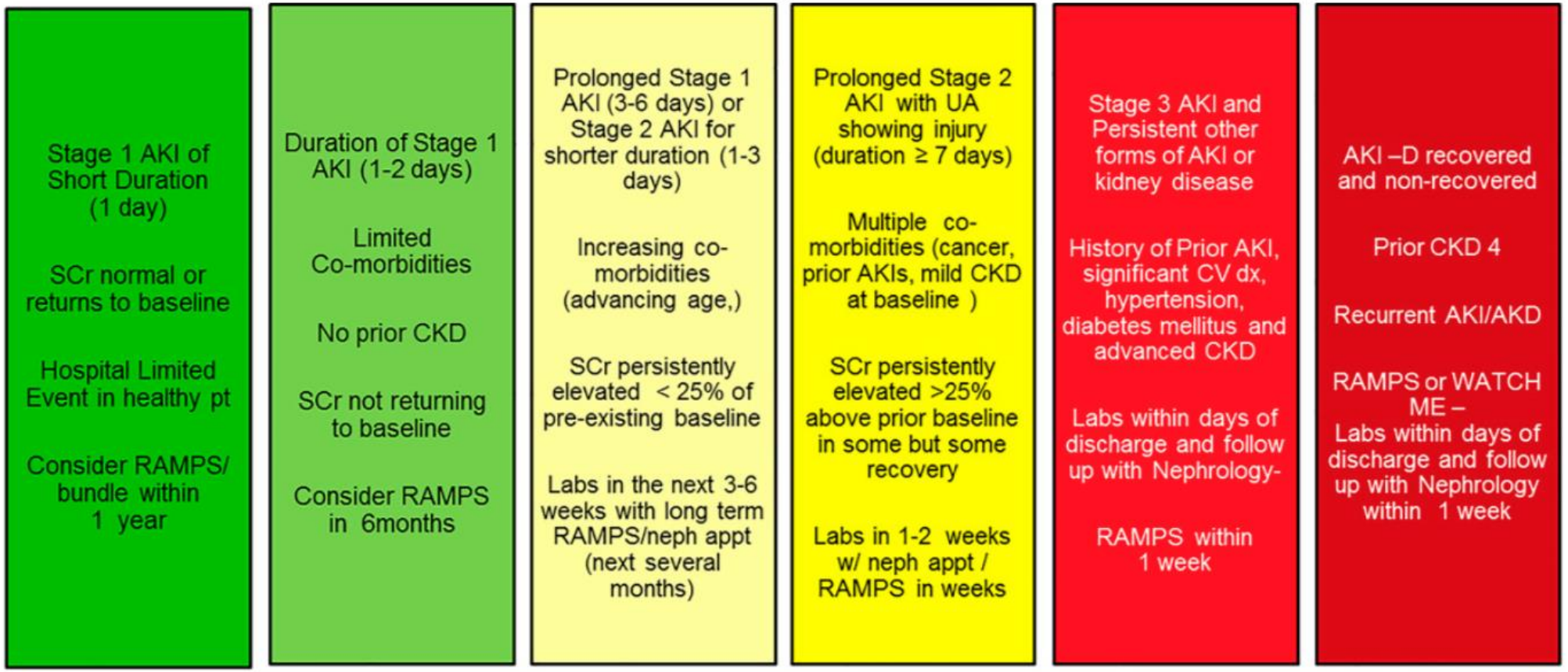
Note: Medications that are associated with acute tubular necrosis (Box 1) should be withheld, if possible.
Abbreviations: AKI, acute kidney injury; NOAC, novel anticoagulants.

You would **avoid** all of the following medications **except…**

A. IV morphine
B. Fleets enema
C. Toradol
D. Miralax
E. Neutra-phos

Moore et al, *AJKD*, 2018

Guidance for Follow Up of AKI



Kashani et al, *CJASN*, 2019

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- Nuts and bolts
  - Definition & Mechanics
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  - Outcomes & Management
- New developments
  - **Contrast Nephropathy**
  - COVID
  - Onconephrology
  - Critical Care

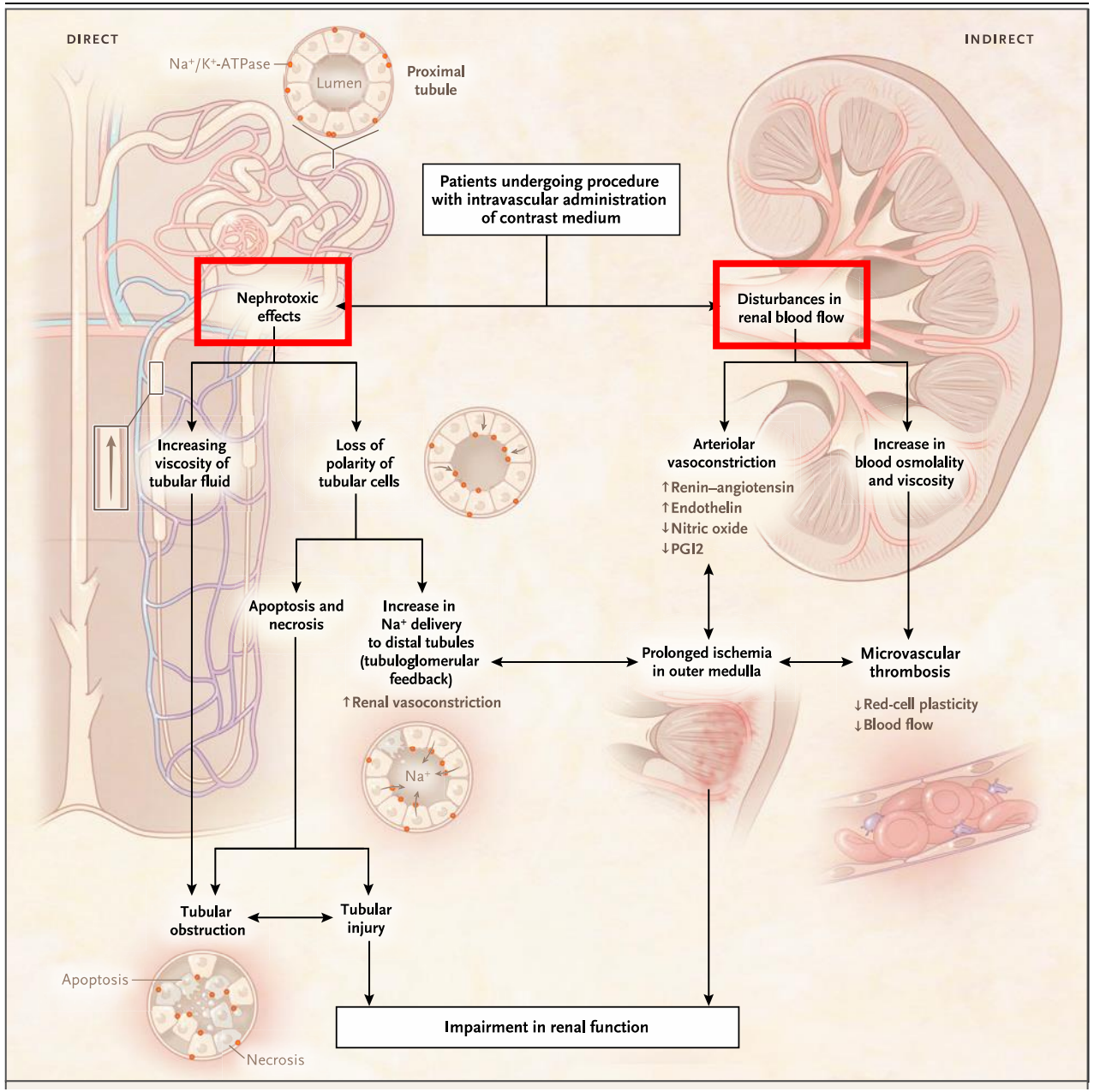
Contrast associated AKI

- A 72 yo M with DM, HTN and CKD 3/4 (baseline eGFR ~30) presents with an NSTEMI, planning cardiac cath.

- Recent data support which of the following to minimize the risk of contrast induced kidney injury?

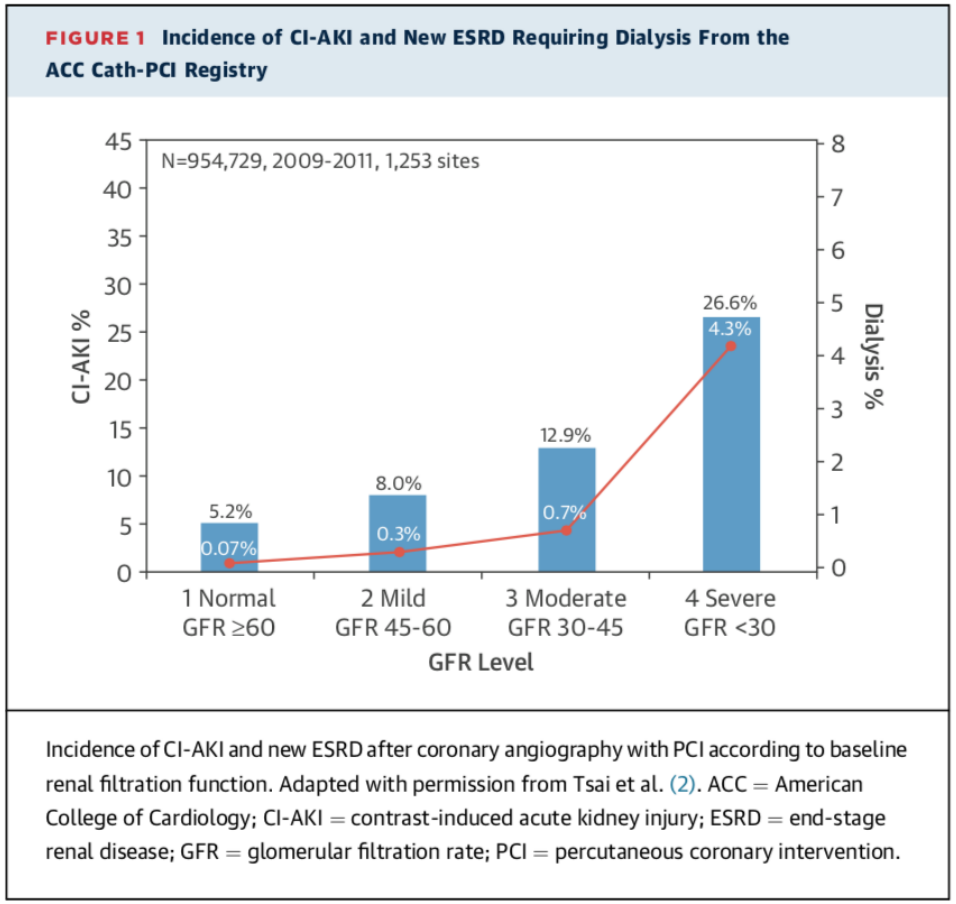
    A. Hold ACEi or ARB
    B. N-acetylcysteine 1200mg BID x 4 doses
    C. Hydration with normal saline or D5W + $NaHCO_3$
    D. Dialysis post contrast exposure

Mechanisms of contrast associated AKI



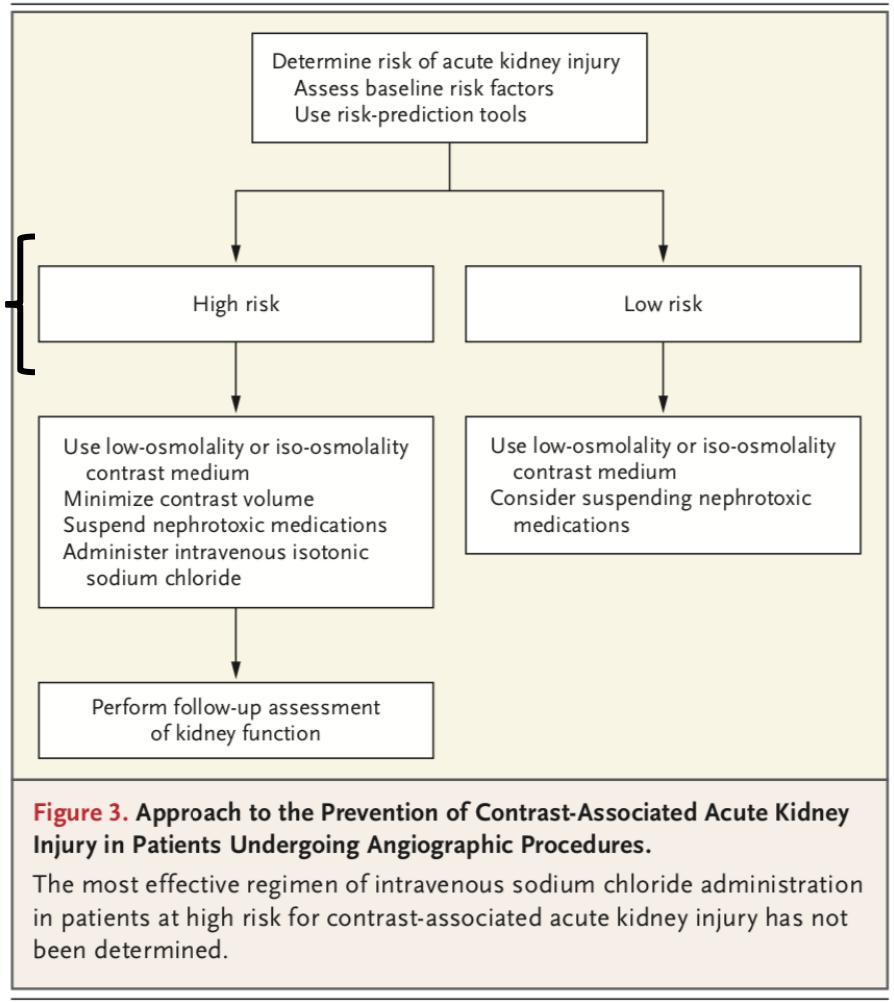
Mehran et al, *NEJM*, 2019

Managing contrast nephropathy



McColough et al, *JACC*, 2016

- eGFR < 30
- eGFR < 45 + DM or CHF
- AKI
- Paraprotein



Mehran et al, *NEJM*, 2019

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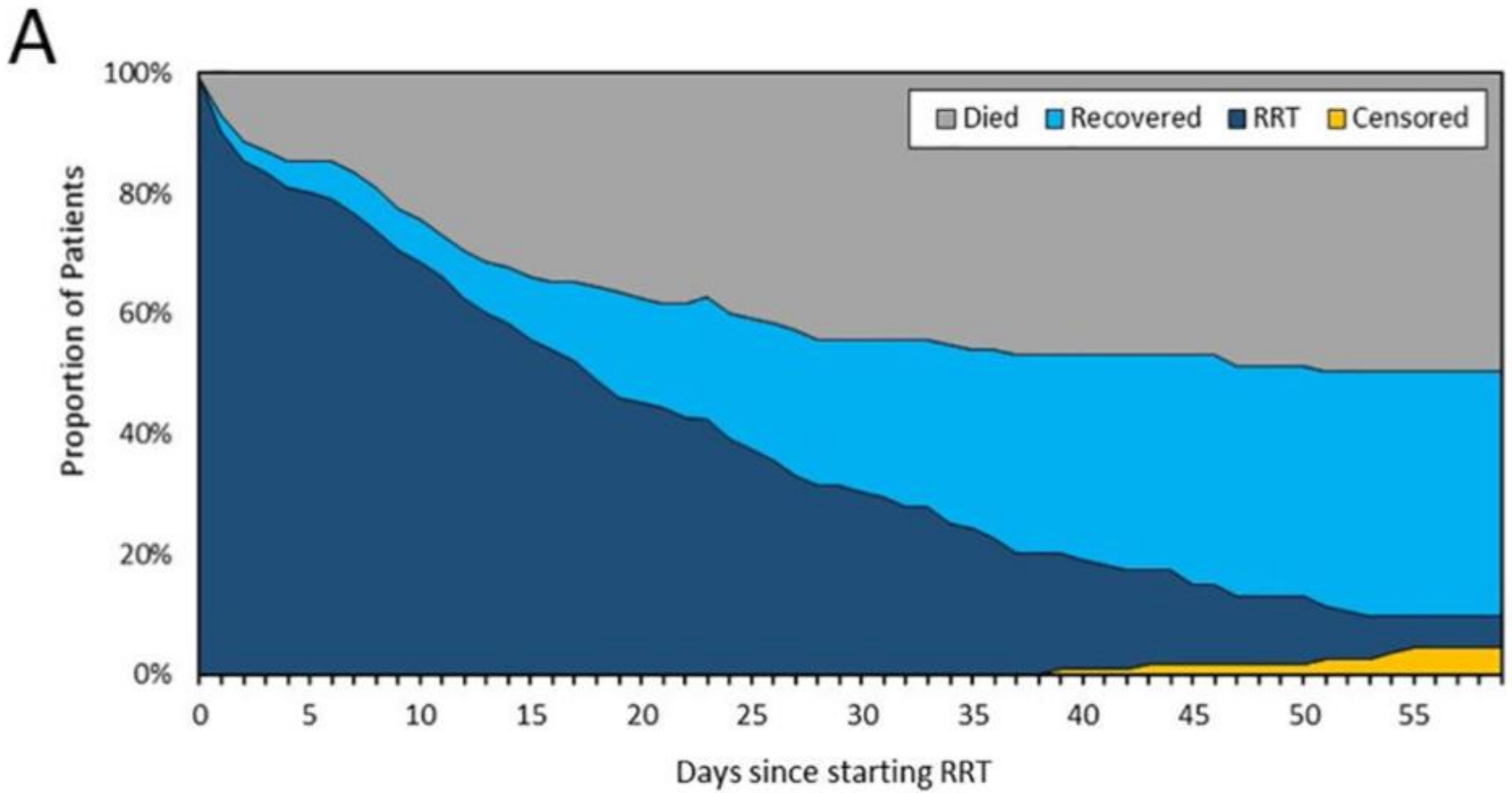
COVID associated AKI

- A 72 yo M with DM, HTN and CKD 3 (baseline eGFR ~40) was admitted to the ICU in the setting of COVID infection and AKI, started on RRT. He is extubated and improving overall, but remains on dialysis.

- Recent studies suggest that he is likely to experience renal recovery over the next 2 months:

    A. True
    B. False

For COVID patients that survive on RRT, the majority experience renal recovery



Stevens et al, *PLOS ONE* 2020

COVID and AKI

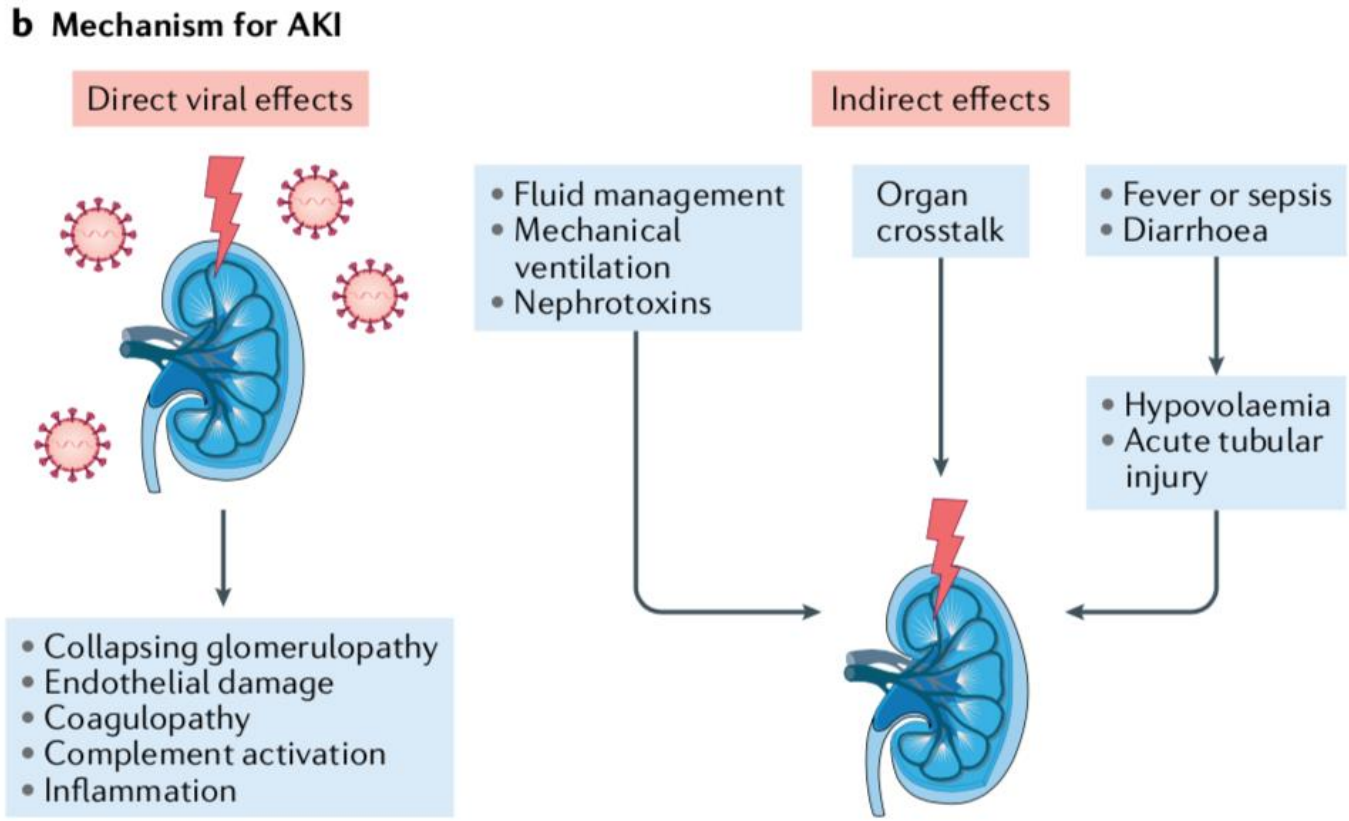


Fig. 1 | **Pathogenesis of COVID-19 AKI. a,b** | The pathogenesis of AKI in patients with COVID-19 (COVID-19 AKI) is likely multifactorial, involving both the direct effects of the SARS-CoV-2 virus on the kidney and the indirect mechanisms resulting from systemic consequences of viral infection or effects of the virus on distant organs including the lung, in addition to mechanisms relating to the management of COVID-19. AKI, acute kidney injury. Adapted from Acute Disease Quality Initiative 25, www.ADQI.org, CC BY 2.0 (https://creativecommons.org/licenses/by/2.0/).

Nadim et al, *Nat Rev Neph* 2020

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AKI and malignancy

- A 60 year old male with HTN, HLD, BPH and malignant melanoma presents with fatigue
  - Poor po intake recently, occasional NSAID use
  - Medications: norvasc 5mg QD, lisinopril 5mg, ipilimumab
  - Exam: BP: 160/80, euvolemic, + rash
  - Labs: K: 5.3, BUN: 70, Cr: 4.5 (baseline 1.3), UA: neg blood, 50-100 WBCs, TP/Cr: 0.75, C3, C4 normal

His acute kidney injury could be due to:

A. Hypovolemia
B. Use of ACEi
C. NSAID use
D. Chemotherapy
E. All of the above

Table 2. Types of Acute Kidney Injury in Patients with Hematologic Cancers.*

Cancer-related injury
Tumor infiltration of the kidneys
Obstructive nephropathy related to retroperitoneal lymphadenopathy
Lysozymuria (CMML or AML) with direct tubular injury
Hemophagocytic lymphohistiocytosis with acute interstitial disease
Vascular occlusion associated with DIC and hyperleukocytosis (rare)
Hypercalcemia with hemodynamic acute kidney injury and acute nephrocalcinosis
Glomerular diseases (minimal change disease, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous nephropathy, amyloidosis, immunotactoid glomerulonephritis, fibrillary glomerulonephritis, crescentic glomerulonephritis)†
Therapy-related injury
Nephrotoxicity (including thrombotic microangiopathy, acute tubular injury, tubulointerstitial nephritis, and glomerular disease)
Tumor lysis syndrome with acute uric acid nephropathy (may occur spontaneously)
Intratubular obstruction from medications (e.g., methotrexate)
Other types of injuries
Volume depletion
Sepsis and septic shock
Nephrotoxicity of radiocontrast agents
Nephrotoxicity of common medications, such as NSAIDs, ACE inhibitors, ARBs, and antibiotics

Rosner et al, *NEJM* 2017

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Timing of Renal Replacement Therapy in Sepsis

Case #2

88 year old male with hypertension, diabetes, tobacco use, CKD3 presents with hypotension

-On levophed, 2L NC, CXR clear

-Blood cultures positive, he has a new rash

-Minimal UOP over the past 24 hours

-BUN: 110, Cr: 4.5, K: 5.7

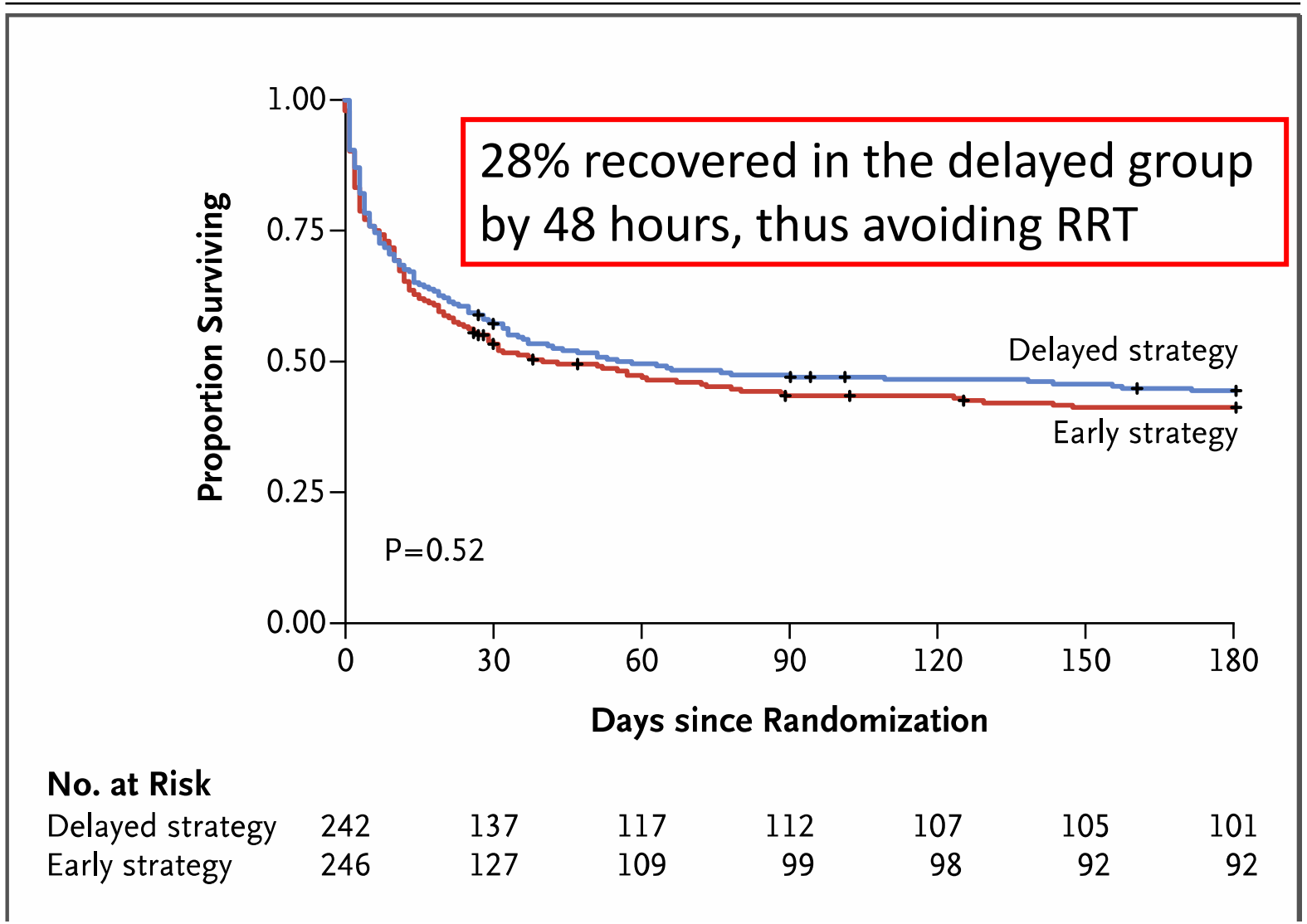
-Baseline Cr: 1.4 three days ago at PCP appointment

-Urinalysis: 2+ hematuria (50-100 RBCs on sediment), 2+ proteinuria (ACR: 2500)

- Recent studies suggest a mortality benefit to starting renal replacement therapy within 12 hours of severe AKI (early) compared to 48 hours (late)?

A. True
B. False

IDEAL-ICU: no benefit with early RRT



Barbar et al, *NEJM*, 2018

Take home points

- There is a unified definition of AKI
- The differential for AKI is broad
- Recovery from AKI depends on the initial substrate
- Patients with significant AKI should have nephrology follow up
- Hydration is the main strategy to reduce the risk of contrast nephropathy
- There are many possible causes of AKI in oncology patients
- The majority of patients with AKI requiring RRT due to COVID will experience renal recovery
- There is no benefit to early RRT in the setting of septic shock