Acute Kidney Injury

January 2, 2019 by Josh Farkas

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definition & significance of AKI

KDIGO definition of acute kidney injury

<table>
<thead>
<tr>
<th>Stage</th>
<th>Creatinine Criteria</th>
<th>Urine Output Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cr 1.5-1.9 times baseline, OR Cr increase &gt;0.3 mg/dL</td>
<td>&lt; 0.5 ml/kg/hr x 6-12 hours</td>
</tr>
<tr>
<td>2</td>
<td>Cr 2-2.9x baseline</td>
<td>&lt;0.5 ml/kg/hr for &gt;12 hours</td>
</tr>
<tr>
<td>3</td>
<td>Cr &gt; 3x baseline, OR Cr &gt; 4 mg/dL, OR initiation of dialysis</td>
<td>&lt;0.3 ml/kg/hr for &gt;24 hours, OR Anuria &gt; 12 hours</td>
</tr>
</tbody>
</table>

Patients are staged based on the single most concerning feature.
definitions

- Numerous similar criteria exist for defining acute kidney injury (RIFLE, AKIN, KDIGO). The KDIGO classification shown above is currently the favored definition.
- AKI is a powerful predictor of mortality. The figure above was obtained from hospitalized patients, but similar curves occur for AKI in a variety of contexts (e.g. ICU patients, septic patients).  
  - It’s unclear whether AKI causes this mortality or if this is simply a marker for underlying problems (or, most likely, both). Regardless, patients with AKI deserve serious consideration because they represent a high-risk population.
- These definitions aren’t perfect:
  - Cutoffs are somewhat arbitrary. For example, I can’t find any good evidence to support why 0.5 cc/kg/hr is the cutoff to define oliguria (some newer literature suggests that 0.3 cc/kg/hr may have a higher specificity).  
  - Prognosis varies dramatically across each stage of AKI (as shown below).

more detailed understanding of types & prognosis

- Prognosis depends on changes in urine output and creatinine (figure above). Some specific types bear mention:
  - (1) Isolated oliguria (low urine output with stable creatinine).
    - These patients rarely required dialysis, unless oliguria is profound (Stage 3).
    - This may often represent “pre-renal” renal failure – the kidney is compensating for hypoperfusion by reducing urine output, but is continuing to function adequately.
    - Oliguria should be taken seriously and evaluated adequately. However, <12 hours of oliguria isn’t necessarily a disaster – especially if the creatinine remains stable.
  - (2) Non-oliguric renal failure (elevated creatinine with normal urine output)
    - The vast majority of these patients (99.7% overall) won’t require dialysis.

causes of AKI

common causes of AKI in the ICU

- Pre-renal: Disorders of perfusion
  - Shock of any etiology
  - Hepatorenal syndrome
  - Abdominal compartment syndrome
  - Hypertensive emergency
  - Thrombotic thrombocytopenic purpura & hemolytic uremic syndrome
- Intrinsic renal failure
  - Nephrotoxic medications (listed below)
  - Cellular lysis (rhabdomyolysis, hemolysis, tumor lysis syndrome)
  - Acute glomerulonephritis
  - Acute tubulointerstitial nephritis (ATIN)
  - Acute tubular necrosis (ATN)
- Post-renal: Urologic obstruction
  - Prostate obstruction

https://emcrit.org/ibcc/acute-kidney-injury/
- Occluded or malpositioned Foley catheter
- Nephrolithiasis

**common nephrotoxins**

- Antibiotics
  - Vancomycin
  - Aminoglycosides
  - Amphoterin
  - Sulfonamides
  - Pentamidine
  - Antivirals: Acyclovir, gancyclovir, indinavir, cidofovir
  - Beta-lactams (can rarely cause interstitial nephritis)
- ACE-inhibitors, Angiotensin receptor blockers (ARBs)
- NSAIDs
- Anything reducing cardiac output (e.g. beta-blockers, diltiazem)
- Calcineurin inhibitors (cyclosporine, tacrolimus)
- Chemotherapeutics (i.e. cisplatin, methotrexate)
- Mannitol
- Intravenous immunoglobulin (IVIG)
- Sodium chloride (0.9% or 3% in large quantity)

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**tests to evaluate the cause of AKI**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Urinalysis</th>
<th>Microscopy</th>
<th>Diagnostic clues beyond UA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>Hematuria, proteinuria</td>
<td>RBC casts, dysmorphic RBCs</td>
<td>Associated with numerous diseases (e.g. ANCA vasculitis, SLE, infection)</td>
</tr>
<tr>
<td>Acute interstitial nephritis (AIN)</td>
<td>WBCs without bacteria</td>
<td>WBC casts</td>
<td>Fever, Blood eosinophilia, Causative drug (often NSAIDs or ABX)</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>WBCs, nitrites</td>
<td>WBC casts</td>
<td>Fever, Lower urinary tract symptoms, Back pain</td>
</tr>
<tr>
<td>Acute Tubular Necrosis (ATN)</td>
<td>Muddy-brown casts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Positive hemoglobin, WBCs</td>
<td>Rhodanilinemia, CK elevation</td>
<td></td>
</tr>
<tr>
<td>Hemolysis</td>
<td></td>
<td>Hemolysis: LDH, hemoglobin, haptoglobin</td>
<td></td>
</tr>
</tbody>
</table>

**AKI panel: tests to order**

- Electrolytes (including Ca/Phos/Mg)
- Creatinine Kinase
- Urinalysis
  - Interpretation shown above.
  - If urinalysis suggests glomerulonephritis or acute interstitial nephritis, consult nephrology to review the urine microscopy and consider renal biopsy.
- Additional labs if indicated
  - Relevant drug levels (e.g. vancomycin, aminoglycoside, cyclosporine, tacrolimus)
  - Tumor lysis labs if malignancy (lytes, calcium, phosphate, uric acid)
- Renal & bladder ultrasound
  - Main role is exclusion of hydronephrosis, but may provide additional information (e.g. scarred or polycystic kidneys).
  - Immediate bedside ultrasonography may expedite diagnosis (don't forget to look at the bladder).
Don't assume that every Foley catheter is functioning properly! Prompt recognition of a dysfunctional Foley catheter is essential.

**Tests not to order**

- Urine electrolytes & FENa
  - Previously, it was believed that urine sodium excretion and fractional excretion of sodium (FENa) could help differentiate between pre-renal and intrinsic renal failure. However, more recent research has shown that FENa performs poorly.\(^{4-6}\)

- Urine eosinophils
  - This has poor performance for diagnosing acute tubular interstitial nephritis.\(^{7}\)
Oliguria is a subset of acute kidney injury defined by low urine output (<0.3-0.5 ml/kg/hr for several hours, or roughly <500 ml/day). Although oliguria has traditionally often been interpreted as a surrogate for hypovolemia, this is not accurate. Oliguria can be caused by any type of renal failure (if sufficiently severe).

This is intended merely as a rough conceptual schema to oliguria, not a rigid protocol. For example, if evaluation reveals the presence of a specific diagnosis (e.g. septic or cardiogenic shock), then further treatment will be aimed at that problem. The main issue is to put some thought into this, rather than reflexively administering fluids.
#1: exclude obstruction

- Obstruction is rare, but this is a must-not-miss diagnosis.
- The gold standard is bedside ultrasonography of the bladder and kidneys. In thin patients, this is often fast and easy.
- Placement and trouble-shooting of a Foley catheter (via flushing) is a reasonable alternative. Most obstructions that cause oliguria are located in the urethra and may be managed with Foley placement (unilateral ureteral obstruction shouldn't cause oliguria, due to urine production from the contralateral kidney).

#2: hemodynamic evaluation

- Perform a brief chart review focusing on vital sign trends, new medications added (e.g. antihypertensives), cardiac history.
- The focus of this evaluation is generally on volume status, but other factors should be considered as well (e.g. cardiac output).
- If the patient is hypertensive, this suggests the presence of intrinsic renal failure (rather than shock or hypovolemia).

#3a: volume challenge?

- Indicated for total-body hypovolemia.
- The best indications for providing fluid are one of the following:
  - 1) Input/output trends showing that the patient is substantially net negative over the past day (e.g. salt-wasting nephropathy or aggressive diuresis).
  - 2) Clinical history of nausea/vomiting, diarrhea, and poor oral intake combined with echocardiogram showing hypovolemia.
- If the patient is hypertensive this argues against hypovolemia, making fluid administration less likely to help.
- **Note of caution:** volume challenge isn't very helpful for new-onset oliguria in the ICU:
  - Genuine hypovolemia is most often encountered among patients being initially admitted to the hospital (e.g. due to gastroenteritis and poor oral intake).
  - It's pretty uncommon for ICU patients to suddenly develop hypovolemia without an obvious cause (e.g. hemorrhage or negative fluid balance on recorded I/O's). On the contrary, most ICU patients will tend to retain fluid and develop hypervolemia during their ICU stay.

#3b: vasopressor challenge?

- Although a MAP>65 mmHg is adequate for most patients, some patients with chronic hypertension may require a higher blood pressure to perfuse their kidneys adequately.
- If there is concern that the MAP is too low, then the blood pressure can be raised for a couple hours with an infusion of norepinephrine or phenylephrine (e.g. to MAP >75 mmHg). If this stimulates urine output, then maintain the higher MAP should be maintained.

#3c: inotrope challenge?

https://emcrit.org/ibcc/acute-kidney-injury/
If there is evidence of poor cardiac output and concern for cardiogenic shock, it may be reasonable to trial an inotrope.

Improved urine output following inotrope initiation confirms a diagnosis of cardiogenic shock. In this case, continue to treat the cardiogenic shock as discussed previously in this chapter.

#3d: furosemide stress test

This is a validated test of renal function, which predicts the likelihood of persistent renal failure and dialysis. If the patient fails the furosemide stress test, this suggests significant intrinsic renal failure. In this situation, further hemodynamic manipulation (e.g. additional IV fluids) is unlikely to help.

More on the furosemide stress test here.

Renal failure in the ICU is generally multifactorial. Treatment involves identifying and addressing all contributory factors.

#1. investigate & treat any identifiable cause(s)

- Review the chart for possible renal insults and consider the differential diagnosis (listed above).
- Obtain relevant labs and imaging studies. Any specific cause(s) should be treated.

#2. discontinue any nephrotoxic medications

- Carefully review the medication list. Discontinue any nephrotoxic medications if at all possible.
- Below is a list of more common nephrotoxic medications, but it’s not exhaustive. When in doubt look up unfamiliar drugs to determine if they may be nephrotoxic:
  - Antibiotics
    - Vancomycin
    - Aminoglycosides
    - Amphotericin
    - Sulfonamides
    - Pentamidine
    - Antivirals: Acyclovir, gancyclovir, indinavir, cidofovir
  - Beta-lactams can rarely cause interstitial nephritis
  - ACE-inhibitors, Angiotensin receptor blockers (ARBs)
- NSAIDs
- Anything reducing cardiac output (e.g. beta-blockers, diltiazem)
- Calcineurin inhibitors (cyclosporine, tacrolimus)
- Chemotherapeutics (i.e. cisplatin, methotrexate)
- Mannitol
- Intravenous immunoglobulin (IVIG)

Consider avoiding medications that may decrease cardiac output and renal perfusion (e.g. beta-blockers, other anti-hypertensives). Although these may not be directly nephrotoxic, they can still reduce renal perfusion and indirectly harm the kidneys.

### #3. Dose-Adjust Renally Cleared Drugs

- Note that calculations of the glomerular filtration rate (GFR) based on creatinine level will be misleading in the context of acute kidney injury.
  - Formulas for the GFR only work in steady state (equilibrium) conditions. This usually isn't the case in acute kidney injury.
  - For example: with complete cessation of renal function, the creatinine will often increase by roughly ~1 mg/dL daily. So if a patient’s creatinine increases from 0.7 mg/dL to 1.7 mg/dL their GFR may be extremely low (much lower than the calculated GFR).
- Pharmacist consultation can be helpful with this.

### #4. Avoid Giving Potassium

- Discontinue potassium supplements and potassium-sparing diuretics.
- In the absence of digoxin toxicity or hypomagnesemia, moderate hypokalemia is generally well tolerated.
- In acute kidney injury, it may be wise to avoid potassium supplementation unless the potassium is substantially reduced (e.g. <3 mM).
  - If you’re worried about the risk of Torsade de Pointes, make sure that the magnesium level isn’t low. Giving magnesium is safer than giving potassium in this context.

### #4. Maintain an Adequate MAP

- MAP >65 mmHg is usually the target MAP for patients in AKI. MAP >80 mmHg may improve renal outcomes in some patients, especially those with chronic hypertension.
  - When in doubt, consider a vasopressor challenge. Give the patient pressor to increase the MAP, and determine whether this improves urine output.
  - In terms of renal outcomes, vasopressin might have a small advantage over other vasopressors, particularly among patients with tachycardia and systemic vasodilation.

### #5. Maintain Euvolemia

- Generally avoid fluids
  - Non-oliguric AKI generally isn't due to hypoperfusion and shouldn’t be an indication for extra fluids.
  - Fluid should be given only if, after thoughtful assessment, there is evidence of hypovolemia (more on this above).
- If fluids are used, choose the best one
  - For patients with hypovolemia and uremic acidosis, the fluid of choice is isotonic bicarbonate (D5W with 150 mEq/L sodium bicarbonate). More on this below (see #6).
  - For patients with hypovolemia and normal serum bicarbonate, the fluid of choice is a balanced crystalloid (e.g. lactated ringers or plasmalyte). Avoid normal saline. Contrary to popular dogma, LR is entirely safe in hyperkalemia and is superior to NS.
- Avoid volume overload
  - Overload may cause renal intra-capillary edema (swelling within the kidney that impairs perfusion, a bit like compartment syndrome). Furthermore, increased central venous pressure impairs renal perfusion by hampering venous blood flow out of the kidney.
  - Basic steps to avoid volume overload include avoiding maintenance fluid or repeated fluid boluses.
  - Follow fluid balance (inputs vs. outputs) and avoid ongoing volume accumulation or total net gain of more than a few liters. For example, if the patient is running net 1-2 liters positive per day this will rapidly become a major problem.
  - Diuresis (furosemide with or without a thiazide) should be used to prevent or treat volume overload. Patients with renal failure may require prodigious diuretic doses. If this isn’t effective, dialysis may be needed to control the volume status.

### #6. Treatment of Acidosis
Nephrologists have used bicarbonate to stave off dialysis for decades. More recently, the BICAR-ICU trial demonstrated that bicarbonate use in the ICU for treatment of anion-gap metabolic acidosis does indeed avoid dialysis.\(^\text{16}\) It’s not entirely clear whether bicarbonate actually improves renal function, or whether it merely improves the acidosis. Regardless, avoidance of dialysis is a meaningful patient-centered outcome.

Sodium bicarbonate is generally the first-line therapy for uremic acidosis. The exact target level isn’t clear, but shooting for a pH >7.2 may be reasonable (roughly equivalent to a bicarbonate level over ~17 mEq/L).\(^\text{16}\)

- **Formulation & route of bicarbonate** depend on the clinical scenario and severity of acidosis:
  - **Isotonic bicarbonate** is useful for patients with volume depletion (DSW with 150 mEq/L sodium bicarbonate). The problem with isotonic bicarbonate is that for patients who are euvolemic or hypervolemic it provides a substantial volume load.
  - **Hypertonic bicarbonate ampules** (50 ml ampules of 1 mEq/ml bicarbonate) are great for patients with hyponatremia. For example, two ampules (100 mEq/L) will typically increase the bicarbonate and sodium by ~3 mEq/L. Ampules should be pushed slowly over ~10 minutes each, to avoid rapid swings in pH. The problem with this strategy is that for patients with a baseline sodium over ~140 mEq/L, it may cause hyponatremia.
  - **Oral bicarbonate tablets** can be used for patients with mild acidosis, to prevent worsening over time. Each 650 mg tablet contains 7.6 mEq of sodium bicarbonate (which isn’t much). Depending on the severity, 650-1300 mg may be given twice or three times daily.
  - **Dialysis** is the second-line therapy for acidosis, in situations where bicarbonate is ineffective or contraindicated.

### #7. treatment of hyperkalemia

- This is summarized in the figure below. For more, see the chapter on *hyperkalemia* ([https://emcrit.org/ibcc/hyperkalemia/](https://emcrit.org/ibcc/hyperkalemia)).

### #8. evaluation of indications for dialysis

- Potential indications:
  - Acidosis refractory to IV bicarbonate.
  - Electrolyte abnormalities (typically diuresis-refractory hyperkalemia).
  - Fluid overload refractory to diuretics.
  - Uremic symptoms (e.g. delirium, asterixis, pericardial effusion).

- Early versus late initiation of dialysis remains controversial. The best indication for earlier dialysis may be a patient who is progressively accumulating fluid and rapidly developing severe volume overload. As discussed above, even in the absence of frank pulmonary edema, systemic congestion may directly harm the kidneys, perpetuating renal dysfunction.

### #7. initiate phosphate binders if phosphate > 6 mg/dL

  - 667 mg tablets, start with two tablets TID with meals
  - Useful in patients with hypocalcemia. Avoid in hypercalcemia or vitamin D intoxication.

  - Start at 800 mg PO TID with meals, double dose if needed.
  - Nonabsorbable resin avoids problems with Mg, Ca (may be preferable for patients on dialysis).
  - May impair absorption of some drugs from the gut.
# Acute Kidney Injury - EMCrit Project

## checklist

**Approach to Oliguria**

Oliguria (urine output <0.3-0.5 cc/kg IBW)

- Is there urinary obstruction?
  - Ideal: POCUS bladder & kidneys
  - Alternative: flush Foley

- No

- Yes
  - Treat, e.g.:
    - Flush or replace Foley
    - CT scan, urology consult

**Hemodynamic evaluation:**

- Review hemodynamic trends (MAP, shock index = RR/HRBP)
  & medication administration history
- ECG if available
- History of volume loss (e.g., diarrhea, vomiting, poor oral intake)
- History of fluid retention & need for chronic diuretics?
- Evidence of low cardiac output? (e.g., cold, diaphoretic, narrow pulse pressure)
- Evidence of septic shock? (e.g., fever, active infection, unexplained changes in WBC, wide pulse pressure)
- Evidence of systemic congestion? (e.g., IVC dilatation, pulsatile portal vein, peripheral edema)

**Suspect hypovolemia**

- Volume challenge

**Suspect MAP inadequate**

- Vasopressor challenge

**Suspect cardiac output inadequate**

- Inotrope challenge

**Suspect intrinsic renal failure or congestion**

- Furosemide stress test

**Improved urine output?**

- Yes
  - Continue to follow carefully
  - At risk for AKI: avoid nephrotoxins

- No
  - Evaluate for causes of AKI
  - Avoid any additional fluid boluses.

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## General Approach to AKI

### Diagnostic Tests

- Complete electrolytes (including Ca/Mg/Phos)
- Creatinine Kinase
- Urinalysis
- Renal ultrasound
- Additional labs if indicated:
  - Drug levels (e.g., vancomycin, aminoglycoside, cyclosporine etc.)
  - Uric acid if concern for possible tumor lysis syndrome

### Management

- Treat any identifiable cause(s)
- Discontinue any nephrotoxic medications
- Dose-adjust renally cleared drugs
- Discontinue any standing or PRN potassium orders (don't give potassium unless hypokalemia is severe)
- Target euvolemia (e.g. treat congestion with diuretics)
  - Follow inputs/outputs carefully and avoid progressive volume overload.
- Treat acidosis with bicarbonate
- Indications for dialysis:
  - Hyperkalemia, acidosis, or overload refractory to medical therapy
  - Uremic symptoms (e.g., encephalopathy, pericarditis)
- Consider phosphate binder if phosphate >5-6 mg/dL

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https://emcrit.org/ibcc/acute-kidney-injury/
Failing to fully evaluate AKI in the ICU. Most cases of AKI will resolve without specific intervention (e.g. with treatment of underlying sepsis). However, occasionally a specific issue is identified which requires specific therapy (e.g. Foley catheter obstruction, glomerulonephritis). Finding these patients is a bit like hunting for a needle in a haystack.

Measurement of urine electrolytes and calculation of fractional excretion of sodium (FENa) isn’t helpful. Blind assumption that any patient with oliguria requires a fluid bolus.

**Going further:**

- **AKI:**
  - [Acute Kidney Injury](https://lifeinthefastlane.com/ccc/acute-kidney-injury/) (Chris Nickson, LITFL)
  - [Acute Kidney Injury](http://foamcast.org/2014/12/26/episode-21-acute-kidney-injury/) (Westafer & Faust, FOAMCast)
- **Fluid selection:**
  - [Nine reasons to avoid normal saline](https://emcrit.org/pulmcrit/smart/)
  - [BICAR-ICU & discussion of IV bicarbonate](https://emcrit.org/pulmcrit/bicar-icu/)
  - [Hypertonic amps of bicarbonate](https://emcrit.org/pulmcrit/emergent-treatment-of-hyponatremia-or-elevated-icp-with-bicarb-ampules/)
- **Things I don’t really think are nephrotoxic:**
  - [Contrast dye](https://emcrit.org/pulmcrit/do-ct-scans-cause-contrast-nephropathy/)
  - [Piperacillin-Tazobactam](https://emcrit.org/pulmcrit/piperacillin-tazobactam-nephrotoxic/)
- **Furosemide stress test** (https://emcrit.org/pulmcrit/furosemide-stress-test/)
- **The importance of MAP:** [Vasopressors and Athos 3 with Mink Chawla](https://emcrit.org/emcrit/deeper-vasopressors-athos-3/) (EMCrit 201).
- **Low-volume resus trial:** [CLASSIC trial](http://www.thebottomline.org.uk/summaries/icm/classic/) (Segun Olusanya via TheBottomLine)
References


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.

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