Acute Kidney Injury
workshop
CSIM 2018
Banff

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• No Disclosures
Objectives

• Through cases work through
  – Definitions of AKI
  – Epidemiology of AKI
  – Approach to AKI
  – Identifying risk factors for AKI
  – Preventative strategies for those at risk
  – General management strategies and specific management strategies
  – Prognosis of AKI and need for monitoring
Case 1

- 58 yo female
- History of HTN on amlodipine 10 mg and ramipril 5 mg
- Admitted with 4 day history of feeling unwell with nonspecific aches and chills and abdominal pain and vomiting
- O/E: BP 100/62, HR 110, T 37.9, abdo tender with percussion tenderness over left side, normal cardiac and resp exam, examines to be hypovolemic, no rash and no active joints
Case 1

- Bloodwork
- WBC 13, neut 10, Hgb 155, plt 290
- Na 137, K 3.2, HCO3 26 Cr 95 eGFR 60
- Lactate 3.2
Case 1 Questions

• Does this patient have AKI?
  – How do we define AKI?

• Does this patient have AKI risk factors?
  – What are AKI risk factors?
# Criteria for acute kidney injury

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Diagnostic criteria</strong>^</td>
<td>Increase in serum creatinine of ≥0.3 mg/dL or ≥240% within 48 hours OR Urine output of &lt;0.5 mL/kg/hour for ≥6 hours</td>
<td>Increase in serum creatinine of ≥0.3 mg/dL or ≥50% within 48 hours OR Urine output of &lt;0.5 mL/kg/hour for ≥6 hours</td>
<td>Increase in serum creatinine of ≥0.3 mg/dL or ≥50% within 7 days OR Urine output of &lt;0.5 mL/kg/hour for ≥6 hours</td>
</tr>
<tr>
<td><strong>Staging criteria</strong></td>
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<tr>
<td><strong>Risk (RIFLE) or stage 1</strong> (AKIN/KDIGO)</td>
<td>Increase in serum creatinine of 30 to 99% OR Urine output of &lt;0.5 mL/kg/hour for 6 to 12 hours</td>
<td>Increase in serum creatinine of ≥0.3 mg/dL or ≥50% to 100% OR Urine output of &lt;0.5 mL/kg/hour for 6 to 12 hours</td>
<td>Increase in serum creatinine of ≥0.3 mg/dL or ≥50% to 99% OR Urine output of &lt;0.5 mL/kg/hour for 6 to 12 hours</td>
</tr>
<tr>
<td><strong>Injury (RIFLE) or stage 2</strong> (AKIN/KDIGO)</td>
<td>Increase in serum creatinine of 100 to 199% OR Urine output of &lt;0.5 mL/kg/hour for 12 to 24 hours</td>
<td>Increase in serum creatinine of ≥100 to 200% OR Urine output of &lt;0.5 mL/kg/hour for 12 to 24 hours</td>
<td>Increase in serum creatinine of ≥100 to 199% OR Urine output of &lt;0.5 mL/kg/hour for 12 to 24 hours</td>
</tr>
<tr>
<td><strong>Failure (RIFLE) or stage 3</strong> (AKIN/KDIGO)</td>
<td>Increase in serum creatinine of ≥200% OR Increase in serum creatinine by ≥0.5 mg/dL to ≥4.0 mg/dL OR Urine output of &lt;0.5 mL/kg/hour for ≥24 hours or anuria for ≥12 hours OR Initiation of renal replacement therapy</td>
<td>Increase in serum creatinine of ≥200% OR Increase in serum creatinine by ≥0.5 mg/dL to ≥4.0 mg/dL OR Urine output of &lt;0.5 mL/kg/hour for ≥24 hours or anuria for ≥12 hours OR Initiation of renal replacement therapy</td>
<td>Increase in serum creatinine of ≥200% OR Increase in serum creatinine of ≥0.3 mg/dL to ≥4.0 mg/dL OR Urine output of &lt;0.5 mL/kg/hour for ≥24 hours or anuria for ≥12 hours OR Initiation of renal replacement therapy</td>
</tr>
<tr>
<td><strong>Loss (RIFLE)</strong></td>
<td>Need for renal replacement therapy for ≥4 weeks</td>
<td></td>
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<tr>
<td><strong>End stage (RIFLE)</strong></td>
<td>Need for renal replacement therapy for ≥3 months</td>
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</table>


^ AKIN and KDIGO provided both diagnostic and staging criteria. RIFLE provided a graded definition of AKI that is implicit in the staging criteria.

† In patients <18 years, stage 3 AKI is also defined by KDIGO as a decrease in estimated glomerular filtration rate (eGFR) to <35 mL/min/1.73 m².

References:
Definitions

• Use the first documented serum Cr as the baseline or baseline Cr from the last few months or back calculate the Cr to a eGFR of 75
  – Lots of problems in clinical practice identifying bCr
  – ???use of newer biomarkers in the future

• Helps with recognition of AKI and evaluation of risk

• For research and outcome studies

• KDIGO definition most current
Cr and GFR curve
Case 1

- Baseline Cr is 55 from outpt BW 2 months ago.
- She meets the KDIGO definition of AKI, Stage 1
- Important to not miss AKI in patients who have lower levels of Cr
- Even if didn’t have her baseline, anticipate that with patient’s story and risk factors there is risk of renal impairment
Case 1 Questions

• Does this patient have AKI?
  – How do we define AKI?

• Does this patient have AKI risk factors?
  – What are AKI risk factors?
AKI risk factors and prevention

• Move towards identifying high risk pts for ATN and then implementing “prevention” methods
• autoregulation
  – Major surgery (cardiac, major abdominal)
  – Shock
  – Sepsis, severe pancreatitis
  – Prerenal risk factors
  – Atherosclerosis and its risk factors
  – CKD
  – malnutrition
# Major Risk Factors for AKI

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Medications and agents</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age (&gt;75)</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Cardiopulmonary bypass procedures</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Cyclooxygenase-2 inhibitors</td>
<td>Surgery involving aortic clamp</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>Cyclosporine or tacrolimus</td>
<td>Increased intra-abdominal pressure</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Large arterial catheter placement with risk for atheroembolization</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Angiotension receptor blockers</td>
<td>Liver transplantation</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>Iodinated contrast agents</td>
<td>Kidney transplantation</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hydroxyethyl starch (HES)</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>Aminoglycosides</td>
<td></td>
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<tr>
<td>Hypercalcemia</td>
<td>Amphotericin B</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td></td>
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<tr>
<td>Perioperative cardiac dysfunction</td>
<td>Vanco alone or in combo with piptazo</td>
<td></td>
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<tr>
<td>Rhabdomyolysis</td>
<td></td>
<td></td>
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<tr>
<td>Tumor lysis syndrome</td>
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Case 1

- What is the etiology of this pt’s AKI?
- How do we establish a Dx?
General Approach

• Good History (HPI, AKI risk factors, CKD risk factors, prerenal RF, full renal ROS) and Physical
  – Will lead to a most likely diagnosis
• After clinical reasoning through the diagnosis
  – Then interpret the urinalysis and microscopy
  – Sensitivity and specificity for etiology??
• Pattern of practice:
  – always check Ca, CK, and purposefully look at CBC
  – Give fluids if can and R/O obstruction (PVR, or if necessary foley/US)
  – The rest of work up is guided by above results
• Renal bx: if unclear dx and GFR remains low, nephritic/nephrotic picture and need to guide tx/prognosis
Know your illness scripts and renal ROS

Acute kidney injury

Clinical history
- HPI, PMH, medication history, allergies, rule out pseudorenal causes;
- Physical exam
  - Blood pressure, weight, fluid status, urine output;
- Laboratory tests
  - Chemistry assays, hematologic tests, urine sediment, urinalysis, serologic tests, etc;
- Diagnostic tests
  - Renal imaging, biopsy

Prerenal azotemia
- Volume depletion
  - Hemorrhage, GI losses, Renal losses (drug-induced or osmotic diuresis, diabetes insipidus), Skin losses (burns), Third-space losses (hypoalbuminemia)
- Decreased effective circulatory blood volume
  - Decreased cardiac output, pulmonary HTN, valvular diseases, systemic vasodilatation, sepsis, liver failure
- Functional
  - NSAIDs, ACEIs-I, ARBs, etc

Intrinsic AKI
- Vascular damage
  - Renal artery/vein thrombosis, atherothromboembolism, vasculitis, accelerated HTN, HUS or TTP

Glomerular damage
- Nephrotic/nephritic glomerulopathies, autoimmune diseases

Acute tubular necrosis
- Ischemic
  - Hypotension, sapsis
- Endogenous toxins
  - Myoglobin, hemoglobin, uric acid, myeloma light chains
- Exogenous toxins
  - Nephrotoxic drugs, contrast dyes

Acute interstitial nephritis
- Drugs
  - NSAIDs, certain antibiotics, etc;
- Infection

Postrenal AKI
- Bladder outlet obstruction
  - BPH, malignancy, anticholinergic drugs, displaced bladder catheter;
- Ureteral obstruction
  - Malignancy, retroperitoneal fibrosis, nephrolithiasis;
- Renal pelvis/tubular obstruction
  - Nephrolithiasis, drugs

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Hospital etiologies of AKI

- ATN 45%
- Prerenal 21%
- AKI on CKD 13% (mostly aATN or prerenal)
- Urinary tract obstruction 10%
- GN or vasculitis 4%
- AIN 2%
- Atheroemboli 1%

AKI as defined by RIFLE criteria: in 9% of hospitalized pts and in more than 50% of ICU pts
AKI

- 2 major causes of AKI in hospital: prerenal and ATN
  - 65-75% of in-hospital AKI
- Prerenal
  - Systemic hypoperfusion → adaptive mechanisms to maintain perfusion to brain and heart (renin/AngII, SNS) → renal vasoconstriction → diminishes RBF and GFR
  - If the adaptive mechanisms don’t lead to preserved CO then get even more decreased RBF and GFR
  - Glomeruli/tubules/interstitium are ok
- Ischemic ATN:
  - Prolonged prerenal insult
  - Severe prerenal insult
  - Mild to moderate prerenal insult in at risk pts (diagram)
  - Tubular damage
Arteriolar resistance and GFR

Relationship between arteriolar resistance, glomerular filtration rate (GFR), and renal plasma flow (RPF). (a) If flow is constant, constriction of a vessel results in a rise in pressure proximally (P1) and a fall distally (P2). (b) Constriction of the afferent arteriole reduces Pgc and GFR. (c) Constriction of the efferent arteriole, on the other hand, tends to increase Pgc and, in some cases, GFR (depending in part on the effect on RPF). Since constriction of either arteriole also raises renal vascular resistance, RPF will fall in both (b) and (c). Arteriolar vasodilation has the opposite effects.
Prerenal vs ATN

• U/A and microscopy (muddy brown, granular casts, epithelial cell casts, free renal tubular epithelial cells)
• FENa <1% vs >1-2%
• Una <10
• Response to fluids (only give if can, if volume overloaded don’t give: volume overload has been associated with worse outcomes in critically ill pts with AKI)
Principles of management

• What are the management principles for all pts with AKI
  – And for our pt with likely prerenal/ischemic ATN
General Approach

• Monitor Cr and urine output in order to assess severity of AKI
  – Oliguria <0.3ml/kg/h or < 500ml /d
  – Anuria < 50 ml/d, severe AKI

• Oliguric AKI worse prognosis than nonoliguric AKI

• Monitor for complications of AKI
  – Need for RRT
Principles of management

- Make dx of AKI
- Look for etiology
- Optimize the diagram
- Avoid nephrotoxins/ minimize new injury
- Remove the insult
- Tx underlying cause
- avoid over rescuscitating
- Assess for RRT needs
<table>
<thead>
<tr>
<th>AKI Stage</th>
<th>KDIGO treatment of AKI 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>Discontinue all nephrotoxic agents when possible</td>
</tr>
<tr>
<td>1</td>
<td>Ensure volume status and perfusion pressure</td>
</tr>
<tr>
<td>2</td>
<td>Consider functional hemodynamic monitoring</td>
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<tr>
<td>3</td>
<td>Monitor Serum creatinine and urine output</td>
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<tr>
<td></td>
<td>Avoid hyperglycemia</td>
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<tr>
<td></td>
<td>Consider alternatives to radiocontrast procedures</td>
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<tr>
<td></td>
<td>Non-invasive diagnostic workup</td>
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<tr>
<td></td>
<td>Consider invasive diagnostic workup</td>
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<tr>
<td></td>
<td>Check for changes in drug dosing</td>
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<tr>
<td></td>
<td>Consider Renal Replacement Therapy</td>
</tr>
<tr>
<td></td>
<td>Consider ICU admission</td>
</tr>
<tr>
<td></td>
<td>Avoid subclavian catheters if possible</td>
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</table>
Fluids

• Which fluids?
Fluid Resuscitation

• Goldilocks approach, not too much, not too little, just right. Right fluid, for the right scenario, right amount

• We have to prescribe IVF like it’s a drug

• Too much fluid has been associated with volume overload and increased mortality in critically ill patients
  – cJASN 2011;6
  – Use of invasive monitoring/pressors as needed

• Choice of fluid
  – Large US data base of pts going for abdominal surgery, pts receiving 0.9% saline had a higher in hospital mortality and need for RRT vs plasmalyte (5.6% vs 2.9%) AnnSurg2012;255
    • From animal models: chloride induced renal vasoconstriction and decreased RBF
    • Other observational studies
    • RCT is needed
  – Split trial JAMA 2015: no difference in AKI between plasmalyte and NS
  – SALT-EM trial NEJM 2018;378: in non ICU pts, no diff’nce in primary outcome of hospital-free days btwn NS and balanced solutions, secondary outcome of AKI, NS group had higher rates of AKI, especially if CR >132
  – Need larger RCT: PLUS trial in progress (2017-est2020), in critically ill pts
Case 1 continued

- Emergency Dr is worried about pt’s abdomen and wants to order a contrast CT of abdomen
- What do you recommend?
- Is this patient at risk for contrast induced nephropathy?
- Who is at risk?
Case 1

- Decision to go for CT abdomen with contrast after risk benefit analysis
  - What is her risk of CIN?
  - What preventative strategies should we use?
Contrast induced Nephropathy

• Risk with arterial procedures ***
• Not much evidence of risk with venous procedures
  – Likely increased risk if GFR <30, no great studies
• Risk
  – If no risk factors: risk is negligible
  – Pt related: CKD, DM, chronic prerenal risk factors: CHF/cirrhosis/nephrotic syndrome/hypovolemia/hemodynamic instability and possibly MM (diagram)
  – Procedure related: dose and type of contrast, intrarterial vs intravenous, diagnostic vs therapeutic intervention
CIN

• Risk of CIN
  – GFR < 30 or AKI: risk benefit ration
  – GFR > 30 is considered safe

• Intravenous contrast and CIN: controversial

• Radiology 2006: venous contrast “fail to demonstrate renal damage”

• Radiology 2013: “IV low osmolality contrast is a nephrotoxic risk factor but not in pts with satble <120

• Radiology 2013: similar incidence of AKI, dialysis, death between contrast and control group
• Rise in Cr of >25% or > 44 umol/l, or use KDIGO definition
• 24-48 hours after contrast (sooner if CKD), usually nonoliguric,
• As opposed to ischemic ATN (1-3 weeks), CIN usually has rapid recovery of renal function (3-5 days) Likely less necrosis of tubules
  – Prerenal factors or intratubular obstruction (FENa <1%)
• Urine: may have classic ATN findings, may have mild proteinuria
• Proposed mechanism is ATN from renal vasoconstriction
• Exclusion of other causes of AKI

***Know your illness scripts
CIN prevention

- For arterial contrast
- Identify at risk patients
- Avoid volume depletion
- Avoid nsaids
- ??hold ACEI/ARB: need more studies
- Use lowest effective contrast dose, low osmolar (iso osmolar or hypoosmolar) contrast
- If can, give IVF: pre and post and during procedure
  - Multiple RCT: benefit of IVF in preventing CIN
  - 0.9% better than hypotonic solution
  - IV probably better than po
  - Conflicting results with NaHCO3 some studies show benefit over saline, others show no benefit. Need a large RCT
- No role for HD or HF AMJ 2006;119, NEJM 2003; 349
  - Small studies
  - Invasive
  - Need ICU
  - Benefit may have been from volume given
prognosis

- Risk calculator QxMD
- Most cases are reversible, the minority have some persistent renal dysfunction
- Recovery within 5-10 days
- If severe CKD at baseline, Cr may not return to baseline
- <1% end up on dialysis: temporary > chronic
- Even if Cr returns to baseline, the development of CIN is associated with short and long term adverse events
  - 30 day, 1 yr, 5 yr mortality are higher in pts who developed CIN
  - One study: 4.9% 30 day mortality rate in pts who had CIN post coronary angio vs 0.7% for those with no CIN
  - Assoc with increased CV risk, CHF
CIN

• Need to consider all causes of AKI
• Ischemic ATN
• Prerenal changes caused by diuretics or acei/ arbs in pts who are sick
• Renal atheroemboli
  – Embolic lesions (digital ischemia)
  – Livedo reticularis
  – Eosinophelia or urine with wbc/eos
  – Develop AKI days to weeks after procedure
  – Slow to no recovery
CIN post PCI Calculator QxMD

- Gender
- Age > or < 75
- Hematocrit
- Volume of contrast
- Diabetes
- Hypotension (<80 for greater than an hour, need for inotropes)
- IABP
- CHF
- eGFR
Gender?

- Male
- Female

Age?

- \(\leq 75\) Years
- \(>75\) Years

Hematocrit?

- Unanswered

Volume of Contrast?

- Unanswered

Diabetes Mellitus?

- No
- Yes

Hypotension?

- Hypotension - Systolic blood pressure <80 mm Hg for at least 1 h requiring inotropic support with medications or intra-aortic balloon pump (IABP) within 24 hours periprocedurally

Points:

- 4 points
- 3 points if <39%
  - For men, <36%
  - For women
- 1 point for each 100ml
- 3 points
- 5 points
## Intra-aortic Balloon Pump Use?

<table>
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<tr>
<th>No</th>
<th>Yes</th>
<th>5 points</th>
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## Congestive Heart Failure?

| Congestive Heart Failure defined as: NYHA Class III or IV AND/OR Prior Pulmonary Edema |
| No | Yes | 5 points |

## Estimated GFR?

| >60 mL/min/1.73m² | 2 points |
| 40-60 mL/min/1.73m² | 4 points |
| 20-40 mL/min/1.73m² | 6 points |
| <20 mL/min/1.73m² | 6 points |
Definitions
Contrast-induced nephropathy - increase of >25% or >0.5 mg/dl / >44 micromol/L in pre-PCI serum creatinine at 48 h after PCI.

Anemia - baseline hematocrit value <39% for men and <36% for women.

Hypotension - systolic blood pressure <80 mm Hg for at least 1 h requiring inotrophic support with medications or intra-aortic balloon pump (IABP) within 24 h periprocedurally.

Congestive Heart Failure - NYHA III or IV or prior pulmonary edema
Risk CIN with PCI

• $\leq$5 risk of CIN 7.5%, risk of dialysis 0.04%
• 6-10 risk of CIN 14%, risk of dialysis 0.12%
• 11-15 risk of CIN 26.1%, risk of dialysis 1.09%
• $>$16 risk of CIN 57.3%, risk of dialysis 12.6%

• No validated risk calculators in intravenous contrast
Bottom Line

• Risk benefit ratio
• Patient risk factors
• Probably overly cautious given the literature quotes low risk in GFR >30
  – when pt presents acutely, don’t know the true GFR
• In ambulatory pts no benefit shown for using preventative strategies
• In hospitalized/sick pts
  – Use safe pattern of practice
  – IVF
  – Optimize the diagram
  – ?? Hold ACEI (I do in inpts, and outpts going for arterial procedures)
Case 1

- Pt is given IVF before procedure and after
- ACEI held
- Monitored Cr and urine output

- CT showed diverticulitis
- Abx started, ramipril and amlodipine held
- BP remained 100-110 systolic
- Given more IVF (total of 6 L)
- Lactate came down to 2.9
- Cr the next day is 140, urine microscopy comes back with granular casts
Case 1

- The trend in Cr over next few days
  - Day 1: 95
  - Day 2: 187
  - Day 3: 257

- The trend in U/O
  - Day 1: 800 ml/d
  - Day 2: 750 ml/d
  - Day 3: 400 ml/d

- Positive 5 L balance approximately

- Few crackles on exam and o2 sats 94% on RA (previously 98%)
- BP 110 syst
- No other indication for dialysis
- Now Stage 3 KDIGO
CASE 1

- Questions to ask at this point??
CASE 1

- Do I have the right etiologic Diagnosis?
- Should I diurese the patient?
- Should I consider initiation of dialysis?
- ??need for ICU (according to KDIGO guidelines should consider more invasive monitoring in stage 3...)

• **Etiology**
  – Consider repeating the work up (hx, exam, bw, urine studies)
  – Still in keeping with natural history for ATN

• **Clinical rationale for giving lasix: fluid management**
Diuretics

• Role is uncertain and controversial. No study of diuretics vs dialysis
• In studies, furosemide did not reduce the risk of needing RRT and hospital mortality
  – (CCM 2009;37 533-8, EJCS 2008;33 370-6)
• Experimental animal studies show that furosemide reduces renal medullary injury during ischemia (KI 2005;67 531-42)
  – May improve prostaglandins and renal bloodflow if pt is not volume depleted
• AKI is very complicated and pts tend to not die from AKI itself, therefore unlikely that furosemide study would lead to decreased mortality
• Clinical role in diuresis in volume overload and elyte management (works better in mild AKI than severe AKI)
• Oliguric AKI is a more severe AKI than nonoliguric
  – The severity of the AKI is what will dictate if a pt responds to lasix, its not the lasix that determines the severity of AKI
  – Lasix doesn’t change the severity of the AKI
  – Lasix can improve urine output without improving the GFR
• Repeated High doses of lasix associated with high risk ototoxicity (decreased clearance of lasix)
RRT initiation

- Acute indications

- Fluid overload in AKI is associated with higher mortality (mostly ICU literature)

- If anticipate that there won’t be recovery soon and fluid and electrolyte problems consider RRT

- Consider if in positive fluid balance despite diuresis and especially if o2 needs going up

- Risk/benefit ratio analysis
RRT initiation

- Early vs late initiation: conflicting results mostly ICU literature
  - Big picture: the trend, the expected recovery
  - NEJM article this week October 11
    - Pts with septic shock and severe AKI
    - No difference in overall mortality in 90s
Case 1

- Back to the case
- Cr plateaued at 290 day 4-6 then started to come down, by day 10 Cr 120
- Given lasix for 2 days and diuresed
- ACEI held throughout
- BP remained 140-150 in hospital off meds
- Questions for later:
  - What are her risks and how should she followed?
  - How to prevent AKI (ATN) the next time?
Case 2

- 24 yo male from Vancouver Island
- Transferred to St Paul’s Hospital in Vancouver for PLEX
- 6 day history of fatigue, low energy, vomiting several times a day, decreased exercise tolerance, decreased urine output for past week
- O/E: BP 200/100, P120, proptosis of eyes, JVP 3 cm, chest crackles at bases, no peripheral edema
Case 2

- Cr 550, K 5.0, HCO3 18
- HgB 75, plt 45, positive markers for hemolysis
- Peripheral smear: schistocytes
- U/A: 2+ prtn, microscopy: 20-50 RBC/HPF
- CXR: normal
Case 2

- Prerenal
- Renal
- Postrenal

- DDx
Case 2

• Prerenal
  – Likely decreased po intake

• Renal
  – Vascular: TMA
  – Glomerular

• Postrenal
Case 2

• TMA and schistocytes
  – Secondary to HTN vs TTP vs other TMA
  – Very important to make the distinction as different emergency treatments

• What clinical features will help you?
• What lab features help you?
### TMA syndromes and other systemic disorders associated with microangiopathic hemolytic anemia (MAHA) and thrombocytopenia

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical features</th>
<th>Laboratory findings</th>
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<tbody>
<tr>
<td><strong>Thrombotic microangiopathy (TMA) syndromes</strong></td>
<td></td>
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</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura (TTP)</td>
<td>May have severe neurologic abnormalities. Inherited; may present in a newborn infant, a child with thrombocytopenia, or, less commonly, an adult. Among adults, a common presentation is during a first pregnancy. Acquired autoimmune: Uncommon in children.</td>
<td>Severe MAHA and thrombocytopenia; acute kidney injury is rare. Severe deficiency of ADAMTS13 (activity &lt;10%). Acquired cases often have a detectable ADAMTS13 inhibitor (autoantibody). Inherited TTP has ADAMTS13 gene mutation.</td>
</tr>
<tr>
<td>Complement-mediated TMA</td>
<td>Inherited and acquired disorders may present in children or adults.</td>
<td>Renal failure is prominent. Inherited disorders usually have a heterozygous mutation in a gene encoding a regulatory protein in the alternate complement pathway (eg, C5, CFH, CD46/HF, C3, CFI, CFB, C1q). Acquired disorder has antibodies to complement factor H or I.</td>
</tr>
<tr>
<td>Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)</td>
<td>Abdominal pain, diarrhea (often bloody); possible history of outbreak or exposure to livestock or contaminated food, although most cases are sporadic.</td>
<td>Renal failure is prominent. Stool may be positive for the organism (Escherichia coli or Shiga-like enterotoxin or Shiga toxin.</td>
</tr>
<tr>
<td>Drug-induced TMA</td>
<td>History of exposure to quinine or other implicated medication. Immune-mediated forms have an abrupt onset with fever, chills, abdominal pain, nausea, anorexia, acute kidney injury. Toxic, dose-related etiologies may arise gradually, or onset may be sudden with an intravenous toxic agent (eg, opiate-ER).</td>
<td>Immune-mediated: Severe acute kidney injury; drug-dependent antibodies to platelets and/or neutrophils can be demonstrated. Toxic, dose-related: May have gradual or sudden onset of renal failure and hypertension.</td>
</tr>
<tr>
<td>Coagulation-mediated TMA</td>
<td>Inherited, typically presents in children &lt;1 year old.</td>
<td>DGIF, thrombomodulin, or plasmogen gene mutation.</td>
</tr>
<tr>
<td>Metabolism-mediated TMA</td>
<td>Inherited, typically presents in children &lt;1 year old, but may also present in adults.</td>
<td>Elevated serum homocysteine and methylmalonic acid, and low methionine levels; increased urinary methylmalonic acid, MMA/HC gene mutation.</td>
</tr>
<tr>
<td><strong>Systemic disorders that may present with MAHA and thrombocytopenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated intravascular coagulation (DIC)</td>
<td>May be caused by infection, malignancy, postpartum hemorhage with hypotension, or a vascular abnormality such as a giant hemangiomata (eg, Kasabach-Merritt syndrome).</td>
<td>Thrombocytopenia, decreased fibrinogen, and elevated D-dimer are typical with acute or chronic DIC. MAHA may occur. Prolongation of the PT and aPTT are seen in acute DIC.</td>
</tr>
<tr>
<td>Systemic infection</td>
<td>May include bacterial, viral, rickettsial, or fungal organisms. High fever and chills are common.</td>
<td></td>
</tr>
<tr>
<td>Systemic malignancy</td>
<td>May occur with solid systemic malignancies. Breast, prostate, lung, pancreatic, or gastrointestinal tumors are often responsible.</td>
<td>Depends on specific tumor.</td>
</tr>
<tr>
<td>Pregnancy-related syndromes (eg, severe preeclampsia, HELLP)</td>
<td>Typically present in third trimester or postpartum. Severe hypertension and liver involvement are often present. Abnormalities resolve with delivery.</td>
<td>Elevated hepatic transaminases. Acute kidney injury is uncommon.</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>Typically, systolic BP &gt;200 mm Hg and diastolic BP &gt;100 mm Hg. Neurologic features including PTA may be present. Hypertension may also occur in primary TMA with severe renal involvement, so the temporal relationship is important. Abnormalities resolve with control of the BP.</td>
<td>Often associated with severe renal failure. Renal biopsy demonstrates TMA identical to the primary TMA syndromes.</td>
</tr>
<tr>
<td>Systemic rheumatic diseases (eg, SLE, SS, APS)</td>
<td>SLE may be associated with hypertension, renal insufficiency, and autoimmune complications. APS typically presents with arterial and/or venous thrombosis but can also produce a TMA.</td>
<td>Serologic testing may show autoantibodies characteristic of the underlying condition; APS may have prolonged aPTT. Renal biopsy may demonstrate TMA identical to the primary TMA syndromes.</td>
</tr>
<tr>
<td>Hematopoietic cell transplant</td>
<td>May occur with autologous or allogeneic transplant. May be associated with exposure to cetuximab chemotherapy, radiation, systemic infection, or a calcineurin inhibitor.</td>
<td>No specific findings.</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>May be associated with calcineurin inhibitor administration. May be associated with infection such as CMV in the setting of immunosuppression. In patients receiving a kidney transplant for a primary TMA syndrome, the syndrome may recur in the transplanted kidney.</td>
<td>Renal biopsy may have features of rejection.</td>
</tr>
</tbody>
</table>

Therapy for primary TMA is directed at the underlying pathophysiology; therapy for other systemic disorders associated with MAHA and thrombocytopenia is focused on the underlying disorder. Refer to UpToDate topics on evaluating patients with suspected TMA and on specific syndromes for additional information on presentation/diagnosis and management.

TMA: thrombotic microangiopathy; ADAMTS13: a Disintegrin and Metalloprotease with a Thrombospondin type 1 motif, member 13; DGKe: diacylglycerol kinase epsilon; HELLP: hemolysis, elevated liver function tests, and low platelets; BP: blood pressure; PTAH: posterior reversible encephalopathy syndrome; SLE: systemic lupus erythematosus; SS: systemic sclerosis (scleroderma); APS: antiphospholipid syndrome; CMV: cytomegalovirus; PT: prothrombin time; aPTT: activated partial thromboplastin time.

Case 2

- On further History
  - 8 month history of progressive fatigue
  - stopped being able to work out at the gym 4 months ago
  - Decreased appetite and weight loss of 8 lbs
  - Went to GP for complaints and was told that he’s probably reacting to life stressors (exams and recent breakup)
  - BP was checked and he was told it was “high” but that the GP will monitor it
  - 5-7 days of worsening sx
Case 2

• On further exam in ER:
  – Retinal exam showed AV nicking (chronic change) and cotton wool spots (acute change)
• Called GP: BP in the office 3 months ago was 160/94
Case 2

• Don’t want to miss a diagnosis of TTP

• Clinical reasoning through the case, need to justify decision to PLEX (lot’s of side effects) vs to not PLEX (high mortality in TTP, don’t want to miss it)
TTP

- TMA
- Decreased activity of vWF cleaving protease ADAMTS13
  - Acquired due to an autoantibody inhibitor
  - Hereditary mutations in ADAMTS13
- Small vessel platelet rich microthrombi
- TCP could be <10,000, MAHA, AKI usually not severe
- Tx: PLEX, steroids and ritux until platelet count normalized for 2 days
## Presenting features of 78 consecutive patients with acquired TTP

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Number affected*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microangiopathic hemolytic anemia (MAHA)</td>
<td>78 (100 percent)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>78 (100 percent)</td>
</tr>
<tr>
<td><strong>Neurologic abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Severe (coma, stroke, seizure, focal signs)</td>
<td>41 (53 percent)</td>
</tr>
<tr>
<td>Minor (confusion, headache, etc)</td>
<td>21 (27 percent)</td>
</tr>
<tr>
<td>No neurologic abnormalities</td>
<td>16 (20 percent)</td>
</tr>
<tr>
<td><strong>Renal abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Acute renal failure†</td>
<td>4 (5 percent)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>37 (47 percent)</td>
</tr>
<tr>
<td>Normal renal function</td>
<td>37 (47 percent)</td>
</tr>
<tr>
<td>Fever</td>
<td>8 (10 percent)</td>
</tr>
</tbody>
</table>

Refer to UpToDate topic on the clinical manifestations and diagnosis of acquired TTP for additional details.

TTP: thrombotic thrombocytopenic purpura; MAHA: microangiopathic hemolytic anemia.

* Data are from the day of diagnosis, defined as the day of the first plasma exchange treatment. ADAMTS13 activity was <10 percent of normal in all cases.

† Acute renal failure was defined as an increased serum creatinine of \( \geq 0.5 \text{ mg/dL/day} \) for two consecutive days or a serum creatinine of \( \geq 4.0 \text{ mg/dL} \) with hemodialysis.

Refer to UpToDate topics on diagnosis of TTP for details of the evaluation, including the use of the PLASMIC score and other criteria for confidence in the diagnosis of TTP (which is based on clinical criteria rather than solely on ADAMTS13 activity). Refer to topics on treatment of TTP for the timing of central venous catheter removal (typically, five to seven days) and the dosing of glucocorticoids and rituximab.

TTP: thrombotic thrombocytopenic purpura; PEX: therapeutic plasma exchange; TMA: thrombotic microangiopathy.

* Glucocorticoids are given to all patients based on the potential benefits in reducing inhibitor production. A typical dose for a patient who is awake and alert without neurologic abnormalities is 1 mg/kg per day orally; for a more seriously affected patient, intravenous methylprednisolone at a dose of 125 mg two to four times daily may be appropriate.

† Rituximab is used as part of initial therapy unless there is a contraindication. This is based on emerging evidence that rituximab may reduce the risk of exacerbation and relapse and may hasten the response to therapy.

a Refer to UpToDate for options if TTP does not respond to PEX, high-dose glucocorticoids, and rituximab.
Case 2

- HTN more likely dx for MAHA
  - BP 200/100
  - Platelets not too low
  - Cr too high

- ER on day 1 treated for HTN acutely and Hgb and Plt improved
Case 2

• Now with more history from pt and GP, what is the likely etiology of the kidney impairment?
Case 2

• AKI vs CKD vs AKI on CKD

• Prerenal
  – Likely decreased po intake

• Renal
  – Vascular: malignant HTN
  – Glomerular: ?? RPGN

• Postrenal: less likely
Case 2

- 24 yo male with undiagnosed HTN, elevated Cr and RBC in urine
- Likely 4-8 months of progressive uremic symptoms (chronic anemia may be contributing as well) and 1 week of acute symptoms (which could all be progression of underlying uremic sx from CKD vs due to an AKI)
GLOMERULAR DISEASE

**clinical**

**Nephritic**
- HTN
- AKI
- hematuria
+/- systemic illness

**nephrotic**

**Urine sediment**

**Active**
- RBC casts
- dysmorphic RBC

**bland**

**pathologic**

**Proliferative GN**
- Mesangial cell
- endothelial cell
- Epithelial cell

**Non proliferative GN**
Immunofluorescence patterns

Pauci immune  Linear  Granular or starry sky
**NEPHRITIC approach by IF**

**Pauci immune**
- granulomatosis with polyangitis (GPA)
- eosinophilic GPA
- microscopic polyangitis

**Linear**
- anti GBM
- Goodpastures

**Granular**
- MPGN
- Hep C
- SLE
- cryoglobulins
- PSGN
- PIGN
- IE

**Normal complements**
- IgA
- HSP

**Low complements**

**ANCA**

**Anti GBM**

**Hep C, cryo, ANA, ASOT, BC, Hep B, HIV, SPEP**

**Know your illness scripts and renal ROS**
RPGN

• Features of glomerular disease in the urine and rapid loss of renal function over a short period of time (days, weeks or months)
• Most commonly crescent formation
• 3 types
  – Anti GBM ab disease
  – Immune complex disease
  – Pauci immune disease
Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).

*Courtesy of Helmut G Rennke, MD.*
High-power light micrograph in crescentic glomerulonephritis. The hypercellular circumferential crescent (arrows) is compressing the glomerular tuft in the center of the glomerulus and closing the capillary lumens.

Courtesy of Helmut Rennke, MD.
Case 2

- Likely RPGN
- No clinical features to suggest pulmonary or URT problem
- No Risk factors for Hep C, Hep B, HIV (and tests came back negative)
- No hx or exam to suggest SLE, IE
- Work up sent off
- Hemodialysis started given no improvement in Cr and unlikely to recover in the short term
- Several runs of dialysis and then Renal Biopsy
Case 2

• Working diagnosis?
Case 2

- Serology work up all negative
- Working diagnosis is IgA nephropathy
  - Most common GN in developed countries
  - Peak in 20s-30s
- Prognosis: Cr, HTN, prtn >1 g/d

- Different presentations
  - Synpharyngitic hematuria
  - Microscopic hematuria (+/- mild prtnuria)
  - CKD
  - HTN
  - RPGN
  - Nephritic with nephrotic range prtnuria
  - Rarely malignant HTN
Case 2

- Biopsy showed:
  - Crescentic GN and IgA nephropathy
  - No TMA

- Tx for severe disease:
  - Immunosuppression: steroids, cyclophosphamide (not great studies)
    - pros and cons in this pt
  - Maybe PLEX??

- Less severe disease
  - ACEI, fish oil, consider steroid if cr and prtnuria worsens
Case 2

• Clinical course
• No renal recovery after 3 months
• Off immunosuppression
• Ended up getting a renal transplant

• His proptosis and tachycardia
  – TSH undetectable and he also had hyperthyroidism which may have accelerated his BP on presentation
Back to Case 1

• 58 yo female with HTN, admitted to hospital with sepsis and diverticulitis

• AKI likely secondary to ischemic ATN with episode of severe AKI in hospital

• What are her risks and how should she be followed and how should AKI (ATN) be prevented the next time?

• Why do we care?
Post AKI

• After an episode of AKI
  – Full recovery of renal function
  – Incomplete recovery, some CKD
  – Worsening preexisting CKD, new baseline
  – No recovery, ESRD

• Short term outcomes
  – Increased length of stay, healthcare resources/dollars
  – Inpatient mortality

• Long term outcomes
  – CKD after AKI (systematic review and meta-analysis (KI 2012;81)
  – Recurrent AKI
  – mortality
• Increased incidence of recurrent AKI therefore need strategies to reduce poor outcomes among pts who had AKI

• 1/3 of elderly pts with in-hospital AKI are rehospitalized with recurrent AKI within 12 months
  – Each episode of recurrence is associated with an increased risk for advanced CKD

• First step: identify pts at highest risk

• Study in JASN 27 2016 1190-1200 Predictors of recurrent AKI
  – During index AKI hospitalization:
    • Known comorbid risk factors (DM, IHD, CKD)
    • Longer AKI duration and more severe AKI episode
    • Discharge dx:CHF, decompensated CLD, cancer, ACS, volume depletion
  – Guide patient referral to internal medicine or nephrology
AKI risk factors and prevention

• Move towards identifying high risk pts for ATN and then implementing “prevention” methods

• autoregulation
  – Major surgery (cardiac, major abdominal)
  – Shock
  – Sepsis, severe pancreatitis
  – Prerenal risk factors
  – Atherosclerosis and its risk factors
  – CKD
  – malnutrition
Risk prediction score

- A risk prediction score for AKI in ICU
  - NDT 2017;32(5):814
- CKD- 2 points
- CLD- 2 pts
- CHF 2 pts
- HTN 2 pts
- CAD 2 pts
- pH <7.3 3 pts
- Nephrotoxin exposure 3 pts
- Severe infectious process 2 pts
- Mechanical ventilation 2 pts
- Anemia 1 pt
- With 5 being threshold, 95% negative predictive value and 32% positive predictive value of developing AKI in 48 hours
Prevention when hospitalized

- Identify high risk pts before develop AKI
- Proper but not over resuscitation (extrapolated from CIN literature)
- Avoidance of nephrotoxins: risk/benefit ratio
- If hemodynamic compromise or anticipate compromise hold ACEI (no evidence)
- Follow drug levels
- Prehydrate with chemo/acyclovir, contrast
- Optimize cardiac function, optimize the diagram
- Postop hemodynamic monitoring in high risk pts
- HAU or ICU in high risk medical pts (no evidence, resource, $$)
SHIFTING THE PARADIGM TO PREVENTION OF AKI

A new study shows for the first time that early recognition of Acute Kidney Injury (AKI) risk combined with clinically guided treatment reduces the occurrence of moderate to severe AKI by more than 33 percent.¹

WHY AKI MATTERS:

1. STRIKES IN 1/3 OF CARDIAC SURGERY PATIENTS²
2. 2-3x INCREASE IN HOSPITAL COSTS³
3. LONGER HOSPITAL STAYS +5.7 days³
4. 10-fold RISE IN HOSPITAL MORTALITY⁴
5. 9x HIGHER RISK OF CHRONIC KIDNEY DISEASE (CKD)⁶
6. 2-3x GREATER READMISSION RISK⁶

Prognosis

- 75% of pts post MI follow up with cardiologist
- 10% of pts post AKI follow up with nephrologist
  - Need to follow these pts and monitor renal function, urine ACR, BP
  - No studies to say that monitoring will reduce CKD or recurrent AKI, no cost effectiveness analysis in Canada (CSN)
Prevention as an Outpt

• Post AKI admission KDIGO suggests
  – Evaluate pts 2-3 months after AKI for resolution, new onset, or worsening CKD (KI 2012;81 442-448, 477-485 (cost effectiveness not studied, and risk can go until 3 years)
  – Even AKI <24 hours is associated with adverse outcomes in cohort and prospective EARLYARF study

• CSN statement on KDIGO: need more studies for cost effectiveness of monitoring all pts
• Need better tools to identify high risk pts
• CSN agrees with monitoring very high risk pts who needed RRT and persistent renal impairment
Outpt follow up

• Monitor Cr, proteinuria, BP
• Self management strategies when sick
• ??change outcomes
Challenges

• Clinical use of AKI definitions
  – Estimate the degree of renal impairment from baseline
  – Need earlier detection: Cr too late, missed opportunity for prevention and management
• Differentiation between AKI and CKD using Cr and urinalysis
• Identifying severity of AKI and who will have adverse outcomes (renal recovery, dialysis need)
• Do preventative strategies and outpt monitoring change outcomes?
Biomarkers

• Markers of GFR:
  – Cystatin C

• Markers of tubular injury:
  – urinary LMW proteins, NGAL, UKIM-1, IL-18, ILGF-BP 7

• Early detection of AKI
  – Urinary tubular enzymes, urinary LMW proteins, NGAL, UKIM-1, cystatin c
  – Panel of biomarkers

• Prognostic biomarkers
  – Urinary angiotensinogen may predict the severity of AKI
  – Urinary IGFBP7 and TIMP-2 may predict AKI and long term dialysis or death
Take home

- Early recognition
- Identify etiology
  - Hx, Context (prerenal/CKD RF), exam, Urinalysis and microscopy, CK, Ca, CBC, give fluid if can, R/O postrenal (PVR/foley/US)
  - Know your illness scripts, if not following natural history, rethink the diagnosis
- Management principles
  - Appropriate IVF, avoid nephrotoxins/hyperglycemia, monitor Cr, urine output
  - Treat underlying cause
    - monitor for RRT need
- Intravenous contrast not as high risk for CIN as arterial contrast
- Recognize who is at risk for future AKI/CKD
  - Monitor Cr, urine ACR, BP as outpt (not validated)
  - Sick strategies (not validated)
  - Preventative strategies when hospitalized
- Future
  - Early detection of AKI and severity of disease with biomarkers
  - ?? “curative” treatments down the road
• Questions?
Other topics

- AKI in the ICU
- AKI post cardiac surgery: where lots of prevention is being done
- AKI in post op setting, similar literature
- Emerging treatments of AKI
  - Research/experimental models trying to achieve a “cure” for AKI
  - Mesenchymal stem cells, alkaline phosphatase, catalytic Iron
A new study shows for the first time that early recognition of Acute Kidney Injury (AKI) risk combined with clinically guided treatment reduces the occurrence of moderate to severe AKI by more than 33 percent.¹

**WHY AKI MATTERS:**

- **STRIKES IN 1/3** of cardiac surgery patients²
- **2-3x INCREASE IN HOSPITAL COSTS³**
- **LONGER HOSPITAL STAYS +5.7 days³**
- **10-fold RISE IN HOSPITAL MORTALITY⁴**
- **9x HIGHER RISK OF CHRONIC KIDNEY DISEASE (CKD)⁶**
- **2-3x GREATER READMISSION RISK⁶**


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## WHO Classification of Lupus associated Glomerular disease

### WHO Classification of Lupus Nephritis

<table>
<thead>
<tr>
<th>CLASS</th>
<th>Description</th>
</tr>
</thead>
</table>
| CLASS I | Minimal Mesangial Glomerulonephritis  
- histologically normal on light microscopy but with mesangial deposits on electron microscopy |
| CLASS II| Mesangial Proliferative Lupus Nephritis  
- typically responds completely to treatment with corticosteroids |
| CLASS III| Focal Proliferative Nephritis  
- often successfully responds to treatment with high doses of corticosteroids |
| CLASS IV| Diffuse Proliferative Nephritis  
- mainly treated with corticosteroids and immunosuppressant drugs |
| CLASS V | Membranous Nephritis  
- characterized by extreme edema and protein loss |
| CLASS VI| Glomerulosclerosis |

The flowchart illustrates the proposed classification of MPGN (membranoproliferative glomerulonephritis). It starts with immunofluorescence microscopy, which can show Ig ± C3 deposits in the capillary wall and mesangium, leading to immune complex-mediated MPGN. Further analysis can determine the source of circulating Ig or immune complexes, leading to different subtypes:

- Monoclonal gammapathies
- Autoimmune/rheumatologic diseases
- Infections
- Idiopathic

For complement-mediated MPGN, dominant C3 or C4 staining with little or no Ig or C1q* follows, indicating C3 glomerulopathy or C4 glomerulopathy, respectively. Electron microscopy then identifies C3-DGGN, C3-DGS, C4-DGGN, or C4-DGS, with dysregulation of the alternative pathway of complement. Mutations or antibodies to complement factors or complement-regulating proteins are also considered.

For MPGN showing no staining for Ig, C3, or C4, endothelial injury followed by reparative changes is noted, including thrombotic microangiopathy (TTP, HUS), anti-phospholipid antibody syndrome, nephropathy associated with bone marrow transplantation, chronic renal allograft nephropathy, radiation nephritis, and malignant hypertension.

* In rare cases, patients with MPGN caused by monoclonal gammapathy may present with isolated C3 deposits with no staining for immunoglobulins by routine immunofluorescence staining. Immunofluorescence of formalin-fixed paraffin embedded tissue after protease digestion may reveal the presence of masked glomerular monoclonal immunoglobulin deposits.

Data from:

Algorithm created by Sanjeev Sethi, MD, PhD.
<table>
<thead>
<tr>
<th>Type of CRS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 (acute CRS)</td>
<td>Rapid worsening of cardiac function leads to acute kidney injury</td>
</tr>
<tr>
<td>Type 2 (chronic CRS)</td>
<td>Chronic abnormalities in cardiac function lead to progressive chronic kidney disease</td>
</tr>
<tr>
<td>Type 3 (acute renocardiac syndrome)</td>
<td>Acute, primary worsening of kidney function leads to acute cardiac dysfunction</td>
</tr>
<tr>
<td>Type 4 (chronic renocardiac syndrome)</td>
<td>Primary chronic kidney disease contributes to decreased cardiac function, left ventricular hypertrophy, diastolic dysfunction and increase risk of cardiovascular events</td>
</tr>
<tr>
<td>Type 5 (secondary CRS)</td>
<td>Acute or chronic systemic disorders (e.g. diabetes mellitus) cause combined cardiac and renal dysfunction</td>
</tr>
</tbody>
</table>

*Cavalier King Charles Sp*#2AA3C1
Pathophysiology of cardiorenal syndrome

Right heart dysfunction
- Pericardial constraint
- Activation of vasopressin, RAAS, SNS
- Vasopressin, sodium and water retention
- Decreased renal perfusion/ischemia
- Reduced GFR

Left heart dysfunction
- LV EDP
- SV → CO
- Release of natriuretic peptides, bradykinin, prostaglandins
- Vasodilation, natriuresis
- Intrinsic renal disease

Other causes: NSAIDs, ACEI, ARBs, contrast

ACEI: angiotensin converting enzyme inhibitor; ARBs: angiotensin II receptor blockers; CO: cardiac output; CVP: central venous pressure; LV EDP: left ventricular end-diastolic pressure; ETs: endothelins; NO: nitric oxide; NP: natriuretic peptides; NSAIDs: nonsteroidal anti-inflammatory drugs; RAAS: renal angiotensin aldosterone system; SNS: sympathetic nervous system; SV: stroke volume; GFR: glomerular filtration rate.
Rhabdomyolysis Rx

- Early and aggressive volume repletion
- Lack of trials comparing different fluids
  - Sodium bicarbonate
    - Minimizes precipitation of myoglobin:TH protein
    - Inhibits redox cycling of myoglobin, lipid peroxidation
    - May minimize vasoconstriction
    - BUT may worsen hypocalcemia
  - Normal saline
    - Disadvantage: hyperchloremic metabolic acidosis
- Diuretics (only after volume repletion)
  - Mannitol: antioxidant, may relieve tubular obstruction, may help improve hypovolemia due to osmotic gradient with injured muscle cells
  - Loop diuretics: not well studied, frequently used
Rhabdomyolysis treatment guidelines

- Normal saline 400 ml/h
  - If urine pH < 6.5, alternate each NS liter with 1L of D5W / ½ NS plus 100 mmol bicarb
- Target urine output ~ 200 ml/h
- Frequent K checks
- Correct hypocalcemia only if tetany, seizures, or if severe hyperkalemia occurs
- Consider mannitol up to 200 g/d, cumulative 800 g
  - Discontinue if diuresis not established
  - Check plasma osms and gap if used, stop > 55 mosm/kg
- Hyperkalemia management (usual)
- Loop diuretics
- Hemodialysis for rising hyperkalemia, anuria, volume overload

Adapted from Bosch NEJM 2009
Rhabdomyolysis and AKI

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (continuous)</td>
<td>0.022</td>
<td>...²</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50 to ≤70</td>
<td>...²</td>
<td>1.5</td>
</tr>
<tr>
<td>&gt;70 to ≤80</td>
<td>...²</td>
<td>2.5</td>
</tr>
<tr>
<td>&gt;80</td>
<td>...²</td>
<td>3</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.404</td>
<td>1</td>
</tr>
<tr>
<td>Initial creatinine, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4 to 2.2</td>
<td>0.589</td>
<td>1.5</td>
</tr>
<tr>
<td>&gt;2.2</td>
<td>1.083</td>
<td>3</td>
</tr>
</tbody>
</table>

Initial calcium <7.5 mg/dL: 0.933, Score: 2
Initial CPK >40 000 U/L: 0.805, Score: 2
Origin not seizures, syncope, exercise, statins, or myositis: 1.301, Score: 3
Initial phosphate, mg/dL:
- 4.0 to 5.4: 0.565, Score: 1.5
- >5.4: 1.221, Score: 3
Initial bicarbonate <19 mEq/L: 0.811, Score: 2

Rhabdomyolysis Risk Calculator

A Risk Prediction Score for Kidney Failure or Mortality in Rhabdomyolysis
Gearoid M. McMahon MB BCh², Xiaoxi Zeng MD¹, and Sushrut S. Waikar, MD, MPH¹

Online calculator developed by Karandeep Singh, MD³

¹Renal Division, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA
²National Heart, Lung and Blood Institute’s Framingham Heart Study and Center for Population Studies, Framingham, MA
³Department of Nephrology, West China Hospital of Sichuan University

Age (years): ≤50, >50 to ≤70, >70 to ≤80, >80
Gender: Male, Female
Initial Creatinine (mg/dL): ≤1.4, 1.4 - 2.2, >2.2
Initial Calcium (mg/dL): ≤7.5, >7.5
Initial CPK (u/L): >40,000, ≤40,000
Etiology is myositis, exercise, statins or seizure: Yes, No
Initial Phosphate (mg/dL): ≤4.6, 4.6 - 5.4, >5.4
Initial CO2 (mmol/L): ≤19, >19

Calculate

McMahon et al. JAMA Int Med 2013

www.brighamandwomens.org/research/rhabdo
Obstructive uropathy

• Early phase
  – Elevated intratubular pressure increases $P_{BS}$, thereby reducing single nephron GFR
  – Compensatory hyperemia (afferent vasodilation) that serves to increase GFR

• Later phase
  – Vasoconstriction, reduced renal perfusion
  – Reduction in $K_f$ (ultrafiltration coefficient)

• Recovery after obstruction
  – Dependent on duration, severity (partial/complete)
  – Complete obstruction: relatively complete recovery even after 1 week; little or no recovery after 12wks

• Tubular dysfunction during recovery
• Progressive interstitial fibrosis following severe obstruction
Acute interstitial nephritis

- Timing of onset is variable
  - 3 to 5 days after second exposure, several weeks with first exposure to drug
  - 1 day following rifampin exposure
- Classic triad: fever, rash, eosinophilia
  - Seen in only 10%
- Can see:
  - WBCs, RBCs, WBC casts; rarely RBC casts
  - Subnephrotic proteinuria
  - Fanconi’s syndrome (glucosuria, aminoaciduria, phosphate wasting), Type 2 RTA
- Gallium scan: conflicting reports regarding sens/spec
- Kidney biopsy: interstitial edema, infiltrate with T cells, monocytes; also eosinophils, plasma cells, neutrophils

AIN

• Make dx
• ??Methylpred 1 g IV for 1 day then prednisone 60 mg /d
• Associated with
  – Nsaids, abx, rifampin, PPI, 5-ASA, sulfa drugs
  – Infections, cmv, streptococcal infection, Autoimmune disorders
Acute interstitial nephritis

- Treatment approach
  - Careful review of medication list, OTCs
  - Discontinuation of offending agent
  - +/- steroids
    - No definitive study has ever been (perhaps never will be) performed
    - Some suggestion that early steroid therapy speeds recovery
      - Largest study to date:¹ retrospective, N = 61 only 9 of whom were not treated with steroids

¹Gonzalez et al. Kidney Int 2008
• Indications for work up if plans to intervene
  – Progressive kidney impairment thought to be secondary to RAS
  – AKI thought to be secondary to RAS
  – Recurrent flash pulmonary edema
  – Refractory HTN
• Kidneys most susceptible to hypoperfusion when autoregulation is impaired
• Failure to decrease arteriolar resistance
  – Structural changes in renal arterioles
    • Advanced age, atherosclerosis and RF, CKD
  – Decreased vasodilatory PG
    • NSAIDS, COX-2
  – Afferent arteriolar vasoconstriction
    • Sepsis, hyperCa, HRS, CSA/tacrolimus, contrast
• Failure to increase efferent arteriole resistance
  – ACEI/ARB
• RAS
Risk of ischemic nephropathy

• Recurrent hypoperfusion
  – RAS
  – Chronic volume depletion
  – Anorexia nervosa/bulimia
  – High output ostomies
  – Chronic prerenal risk factors

• Renal tissue hypoxia
  – Increased renin/ang II, increased reactive oxygen species, TGF beta, endothelin all leads to interstitial fibrosis and glomerulosclerosis
• Repetitive episodes of renal hypoperfusion can produce irreversible renal parenchymal damage
  – Increased renin and angII → increased endothelin-1 and TGF beta
• If RAS is hemodynamically signif, GFR preserved by afferent vasodilation and efferent vasoconstriction (autoregulation)
• Acei block ang II, and unable to autoregulate → decrease gfr
  – Usually first few days after acei, still could happen 30 days later
  – So check day 5 and day 30 n high risk pts
• After starting diuretics after acei, higher risk of aki therefore monitor