**REMANT NEPHRON THEORY:**
1. Initial kidney injury
2. Response to injury and misdirected repair
3. Structural consequences
4. Nephron loss
5. Nephron hypertrophy in an attempt to maintain homeostasis
6. Increased metabolic activity
7. Ischemia, acidosis & generation of reactive oxygen species (ROS) → kidney damage

**HOW TO APPROACH AKI:**
- Kidney is a robust organ – can tolerate several insults w/o suffering significant structural or functional change
- Any change in kidney function = severe systemic derangement and predicts poor prognosis.
- Early detection and treatment of AKI may improve outcomes
- Treatment depends on etiology
- Optimize medicines and drug dosing in patients with, or at risk, of AKI

**DRUG-INDUCED NEPHROTOXICITY (DIN):**
- Drugs = common source of acute and chronic kidney failure
  - Cause 20% of all community and hospital acquired episodes of AKI
  - Incidence of DIN = 66% in older adults
- Kidneys = vulnerable to DIN because...
  - High exposure to drugs & metabolites (kidneys receive 20-25% of cardiac output)
  - Proximal tubule = large area for nephrotoxin binding & transport into renal epithelium
  - Reabsorption of glomerular filtrate progressively increases intraluminal nephrotoxin concentrations
- Pathogenic mechanisms of DIN
  - No standard classification scheme for DIN, but most drugs found to cause nephrotoxicity have one or more common pathogenic mechanism
    - Pre-renal: altered intraglomerular hemodynamics
    - Intrinsic: ATN, AIN, glomerulonephritis, rhabdomyolysis, thrombotic microangiopathy
    - Obstructive CKD

**AKI IN ACUTE CARE PROGNOSIS:**
**Mortality:**
- AKI alone (unusual in ICU) 20-30%
- AKI with 2 organs down 50%
- AKI with 3+ organs down 90%

**Outcome (ICU discharge) % on long-term RRT:**
- Normal kidney function before 5-10%
- Abnormal kidney function before 30%

**GENERAL RULES TO PREVENT ACUTE DIN:**
1. Use the least nephrotoxic drug possible
2. Use the lowest effective dose of a drug
3. Avoid combinations that have synergistic nephrotoxicity (ex// NSAIDs + ACEI)
4. Where applicable, adjust dose for kidney function
5. If a nephrotoxic drug is used:
   a. Ensure adequate hydration before and during therapy
   b. Expose the pt to the drug for as short as possible
   c. Be vigilant (is Scr:BUN ratio < 12?)

> These rules don’t apply to all conditions (ex// autoimmune causes of AKI)

**GENERAL RULES TO MANAGE ACUTE DIN:**
1. Discontinue nephrotoxic drug if possible (weigh pros and cons)
2. Ensure patient is adequately hydrated
3. Ensure appropriate monitoring (Scr, BUN, U/O)
4. Supportive renal replacement therapy may be required in some cases. Other times it may be required to remove the nephrotoxic drug.

> The care plan should be patient specific and alternative drug recommendations will depend on the clinical case

**ALTERED INTRAGLOMERULAR HEMODYNAMICS (pre-DIN):**
> Kidney autoregulates intraglomerular pressure by modulating afferent & efferent arterioles to preserve GFR and urine output
- Prostaglandins vasodilate afferent arterioles
- ACEI and ARBs inhibit ATII (vasodilate afferent arterioles)
- NSAIDs anti-prostaglandin activity (vasoconstrict afferent artery)
- Calcineurin inhibitors (cyclosporine, tacrolimus) Dose-dependent vasoconstriction of afferent arterioles

<table>
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<tr>
<th>Drugs</th>
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<tbody>
<tr>
<td>ACEi and ARBs</td>
<td>Inhibit ATII production = vasodilate afferent artery</td>
<td>Check Scr 1-2 weeks after initiation, then repeat in 2-4 weeks</td>
<td>See general rules</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Anti-prostaglandin activity = vasoconstrict afferent artery</td>
<td>Use alternative analgesia, esp. in pts with CKD stage 3+ (egFR &lt; 60 mL/min) or in pts with ↓ IVF</td>
<td>See general rules</td>
</tr>
<tr>
<td>Calcineurin inhibitors (cyclosporine, tacrolimus)</td>
<td>Dose-dependent vasoconstriction of afferent arterioles</td>
<td>Monitor serum drug concentrations (up to 2-3x during first week)</td>
<td>Try reducing the dose before considering discontinuation</td>
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<tr>
<td></td>
<td></td>
<td>Monitor Scr and BUN (accept a 30% rise in Scr)</td>
<td>In kidney transplant pts, differentiate between CNI-induced renal dysfunction and acute rejection</td>
</tr>
</tbody>
</table>

**RHABDOMYOLYSIS:**
> **Pathogenesis:** skeletal muscle injury leading to lysis of myocyte, releasing myoglobin and creatinine kinase
  - Myoglobin = oxygen binding protein in muscle; directly toxic to renal tubules and causes obstruction
> **Drugs:** > 150 drugs implicated
  - Many drugs of abuse (cocaïne, heroin, ketamine, methadone, meth)
  - Statins (risk increased when given with gemfibrozil, niacin, CYP3A4 inhibitors)
> **AKI management:**
  - Hydration adjusted to maintain urine output of 200-300 mL/h, continue until myoglobinuria stops and CX < 5,000 units/L
  - Optimal rate of repletion not compared for efficacy or safety
  - No evidence for preference of one type of fluid replacement
  - CX levels < 5000 do not require IV fluid, as risk of AKI is low
  - Hyperkalemia management is critical (10-40% of cases)
  - Other metabolic abnormalities: hypercalcaemia, hyperphosphataemia, hyperuricaemia
> **Prognosis:** most pts will recover to baseline or near baseline renal function

**GLOMERULONEPHRITIS:**
> **Pathogenesis:** inflammatory changes in glomerulus, renal tubular cells, and surrounding interstitium → fibrosis and renal scarring
  - Caused by immune mechanisms; often associated with necrotic syndrome
  - Membranous nephropathy most often reported with drugs but minimal change disease has also been seen
  - Diagnosis made by renal biopsy and electron microscopy
> **Drugs:** Lithium, gold, interferon-alfa. NSAIDs, penicillamine, hydralazine, captopril, propylthiouracil, pamidronate, zoledronate, heroin
> **AKI management:**
  - Discontinue the drug
  - Optimize conservative therapy
  - If membranous nephropathy: consider immunosuppression after 6-12 months if no recovery
  - If minimal change disease: corticosteroid x 3-4 weeks
**Acute Tubular Necrosis:**
- Drugs cause direct tubular toxicity by impairing mitochondrial function, interfering with tubular transport, increasing oxidative stress, forming free radicals, causing heme tubular toxicity, and abnormal phospholipid metabolism
  - Aminoglycosides; amphotericin B; contrast dye; antiretrovirals (adefovir, cidovir, tenofovir); cisplatin; foscarnet; vancomycin; zoledronic acid

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| Aminoglycosides        | - Bind to megalin (saturation dependent endocytic receptor at brush-border membrane)  
- Taken into proximal tubular cells (concentration of AMGs 10-100x higher than in plasma)  
  - At this concentration, AMGs interfere with protein synthesis in proximal tubular cells \( \rightarrow \) ATN  
- Toxicity related to cationic charge of AMGs - facilitates binding to negative charge of epithelial membrane  
  - Neomycin > gentamicin, tobramycin > amikacin, streptomycin  
- Presentation:  
  - Gradual ↑ Scr after 5-10 days  
  - Generally non-oliguric (> 500 mL/day)  | - Use extended interval dosing where possible (not in enterococcus endocarditis)  
  - Rational: megalin is saturation dependent; AMGs have concentration-dependent bactericidal activity; significant post-antibiotic effect  
  - Evidence: modest and conflicting  
  - Monitor serum drug levels if extended interval dosing used for > 48h or if multiple daily dosing used for > 24h  
  - Extended interval dosing trough target = undetectable  
  - Multiple daily dosing trough target depends on AMG and indication  
  - Limit duration of therapy (< 10 days) and avoid repeated courses (- cumulative dose), if possible  
  - Administer during active periods of the day (chronotherapy) – theoretical  |
| Amphotericin B         | - Direct tubular epithelial cell damage by binding to cell wall and increasing tubular permeability and necrosis  
- Incidence 80% when cumulative dose of 2g is reached | - Monitor Scr, BUN, lftes q1-2 days (↓ Mg/K = wasting)  
  - Use liposomal formulation \( \rightarrow \) enhances delivery to fungi instead of other cholesterol containing cells (like kidney)  |
| Vancomycin             | - Damage to proximal tubules through oxidative stress  
- Dose-dependent effect is suggested | - Monitor Scr weekly  
  - Monitor trough levels and adjust dose when required  
  - Take levels when: deteriorating or unstable renal function, obese (BMI > 40), anticipated therapy > 7 days, severely ill, require trough of 15-20, altered Vd (children, elderly, burns), select dialysis patients  |
| Contrast dye (3-25%)   | - Risk of requiring dialysis:  
  - 1% if normal renal fxn before  
  - 3% if underlying renal impairment  
  - 12% if DM and advanced renal impairment  
- Presentation:  
  - Within 48-72 h: 25% increase in Scr from baseline or 44 umol/L absolute increase in Scr  
  - Scr usually peaks b/w 2-5 days \( \rightarrow \) normal in 14 days  | - Minimize dose of contrast & avoid closely spaced repetition  
  - Use low or iso-osmolar nonionic agents  
  - Avoid volume depletion and NSAIDs  
  - Give IV hydration (better than PO) – one of:  
    - NS IV 1 mL/kg/h x 12 h pre and post  
    - NaHCO₃ IV 150 mEq/L D5W 3 mL/kg/h x 1 hr pre, then 1 mL/kg/h x 6 hrs post  
  - May be role for statins (dose, agent unknown, give 24-48 h pre and post??)  
  - NOTE: many disproven therapies for prevention  
  - N-acetylcysteine  
  - Dialysis  
  - Diuretics (may increase risk slightly)  
  - Theophylline  
  - Mannitol  
  - Dopamine  
  - Fenoldopam  
  - AOX  
  - Ascorbic acid  |

**Acute Interstitial Nephritis** (3-15% of AKI cases)
- Pathogenesis: Unusual allergic response to a drug that is NOT dose-dependent
  - Drugs bind to antigens in the kidney, or act as antigens that are deposited into the interstitium \( \rightarrow \) immune reaction \( \rightarrow \) inflammation & edema of interstitium
- Classic triad: eosinophilia (>75%), fever, rash (50%) \( \rightarrow \) < 10% of patients with AIN display all 3 components of triad
  - With NSAIDs, there’s an absence of classic symptoms; onset delayed 2-3 months (on average 6 months); presence of nephrotic syndrome (protein excretion usually mild for other drugs)
- Onset: 2 weeks after drug exposure, 3-5 days if previously sensitized
- Drugs: allopurinol, antibiotics (β-lactams, cephalosporins, tetracyclines, quinolones, rifampin, sulfonamides, vancomycin), antivirals (acyclovir, indinavir), diuretics (loop, thiazides), NSAIDs, phenoxytoin, PPIs, H₂RAs
- AKI management:
  - Immediately discontinue offending agent \( \rightarrow \) recovery of normal or near-normal renal function within few weeks (60% pts recover)
  - If no significant improvement in renal function within 3-7 days after withdrawal of suspected agent, initiate corticosteroid
    - Prednisone 1 mg/kg/day (max 60 mg) x min 1-2 weeks \( \rightarrow \) once Scr nears baseline, taper therapy for a total duration of 2-3 months
### Drug Induced Kidney Disease

#### OBSTRUCTIVE NEPHRITIS

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<tr>
<td>Acyclovir</td>
<td>• Rapidly cleared from plasma, high concentrations in distal tubular lumen cause crystallizations</td>
<td>• Avoid rapid bolus infusions (max infusion rate 1h for every 500 mg)</td>
<td>• Induction of diuresis with furosemide to wash out obstructing crystals</td>
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<td>• Risk greater with IV but can happen with PO</td>
<td>• Adequate hydration with NS to induce a urinary output of 100-150 mL/hr</td>
<td>• KDIGO doesn’t recommend unless fluid overload</td>
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<td></td>
<td>• Highly insoluble at physiological urine pH</td>
<td>• Dose adjust for pre-existing renal failure</td>
<td>• Hemodialysis for acyclovir removal, but not shown to reverse or reduce duration of AKI</td>
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<td>• Rapid rise in SCr in 12-48h</td>
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<td>• Consider in severe cases where neurotoxicity develops</td>
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<tr>
<td>Methotrexate</td>
<td>• MTX and metabolites precipitate in renal tubules</td>
<td>• Hydration: maintain urine of 100-200 mL/h x 24h post-high dose</td>
<td>• Check MTX level but don’t wait for results to start leucovorin rescue (to treat bone marrow toxicity, especially if &gt; 500 mg/m² was given)</td>
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<td>• Seen with high-dose continuous infusions</td>
<td>• Urinary alkalization: urine pH of 7 increases MTX solubility by up to 10x</td>
<td>• Glucarpidase: bacterial enzyme that inactivates extracellular MTX</td>
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<td>• Dose-dependent</td>
<td>• Prevention: 75 mEq of Na bicarb per liter of NS IV at 125 mL/hr starting 12 hrs before and continued for 24-48h after MTX</td>
<td>• o 50 units/kg IV over 5 mins can reduce MTX levels by 95% in 15 mins</td>
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<td></td>
<td>• Non-oliguric presentation</td>
<td>• Treatment: 100-150 mEq of Na bicarb per liter of D5W IV at 125-150 mL/hr until MTX level &lt; 0.05</td>
<td>• o Health Canada Special Access</td>
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<tr>
<td></td>
<td>• Usually reversible</td>
<td></td>
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<tr>
<td>Ciprofloxacin</td>
<td>• Insoluble in alkaline or neutral pH, rare when pH &lt; 6.8</td>
<td>• Avoid alkalizing urine</td>
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<td>• Oliguric, usually within 2-14 days</td>
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<tr>
<td>Oral Sodium Phosphate Purgatives</td>
<td>• Acute phosphate nephropathy: presumably transient hyperphosphatemia leads to increased precipitation of calcium phosphate salts in distal tubule, causing luminal obstruction</td>
<td>• Prevention is key – poor prognosis, complete recovery rare</td>
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</tr>
<tr>
<td></td>
<td>• Increases in SCr but asymptomatic (days to months later)</td>
<td>• Avoid in renal dysfunction, elderly, volume depletion, ACEI/ARB users</td>
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<tr>
<td>Anticoagulant-related nephropathy</td>
<td>• Glomerular hemorrhage with intratubular obstruction by RBC casts</td>
<td>• Restoration of INR to therapeutic range</td>
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<td>• Increased mortality</td>
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#### THROMBOTIC MICROANGIOPATHY (TMA):

| Pathogenesis: kidney damage is caused by platelet thrombi in afferent arteriole and glomerulus, which is caused by either: |
| a) Toxicity-mediated: direct endothelial toxicity and activation of platelet aggregation |
| b) Immune-mediated: formation of autoantibodies to metalloproteinase that cleaves vWF → activation and adhesion of platelet (ex/ ticlopidine, clopidogrel) |
| Drugs: calcineurin inhibitors (cyclosporine, tacrolimus), mitomycin C, gemcitabine, bleomycin, cisplatinum, daunorubicin, vincristine, quinine, ticlopidine, clopidogrel, estrogen-containing OCPs, cocaine |
| Presentation: |
| o Macroangiopathic hemolytic anemia, thrombocytopenia, AKI |
| o Immune-mediated: sudden onset of severe systemic symptoms, such as chills, fever, GI disturbances, abrupt onset of anuria, neurological changes (mild confusion to coma); usual drug exposure is less than 2-3 weeks |
| o Toxicity-mediated: usually gradual onset over weeks to months of weakness, fatigue, headache, progressive kidney injury |
| AKI Management: |
| o Discontinue offending drug and supportive care |
| • Immune-related drug-induced TMA: implicated drug must be avoided for life as subsequent exposures can be severe and even fatal |
| • Quinidine-induced TMA: warn pts that even low concentrations of quinine in beverages such as tonic water can cause recurrent, severe episodes |
| o Role of plasma exchange (PLEX) with fresh frozen plasma is controversial in drug-induced TMA |
| • Risks of PLEX: infections, thrombosis, plasma-associated transfusion reactions |
| • Recommendations: |
| o Ticlopidine: PLEX first line |
| o Clopidogrel: calcineurin inhibitors: optimum role of PLEX not established |
| o Gemcitabine, quinine: PLEX not recommend (ineffective or harmful) |
| Prognosis: renal function often doesn’t recover completely |
CHRONIC KIDNEY DISEASE:
> **Pathogenesis:** generally presents as tubulointerstitial disease and is called medication-related chronic interstitial nephritis
  > o Slow progressive elevation of creatinine w/ or w/o tubular dysfunction syndromes (renal tubular acidosis, potassium wasting, concentration defects)
  > o NO systemic symptoms (fever, rash, etc)
> **Drugs:** chronic analgesic use (ASA, NSAIDs, acetaminophen), lithium, cisplatin, cyclosporine, Chinese herbs (ex// aristocholic acid)

ANALGESIC NEPHROPATHY:
> **Pathogenesis:** toxic metabolites of various analgesic compounds build up in the renal medulla (medullary loops of henle, vasa recta, collecting ducts) due to the countercurrent mechanism → vasoconstriction, ischemic injury, cortical atrophy, and eventual interstitial changes
> **Clinical pearls:**
  > o Difficult to diagnose and controversy exists regarding risk, prevention, and cause
  > o Use analgesics for shortest duration possible; chronic use should be under supervision of a physician to monitor kidney function
  > o Commonly seen in females in 60s or 70s who have chronic pain syndromes (ex// headaches, joint pains, back pains)
  > o Ingestion of 1g of analgesics per ay for more than 2 years = minimum dosage required
  > o No risk of analgesic nephropathy from regular use of low-dose ASA for CV prevention
  > o Acetaminophen = analgesic of choice in patients with underlying kidney disease
  > o Avoid combination products (acetaminophen with ASA or caffeine)
> **Management:** supportive
  > o Discontinue analgesic
  > o Monitor for gross hematuria (as increased risk of uroepithelial tumors)

LITHIUM NEPHROPATHY:
> **Pathogenesis:**
  > o Nephrogenic diabetes insipidus: lithium enters collecting tubule cells via sodium channels and interferes with ability of ADH to increase water reabsorption; also reduces expression of aquaporins in collecting tubules
  > o Chronic interstitial nephritis: long-term exposure can also lead to chronic interstitial nephritis and eventually interstitial fibrosis and CKD
> **Clinical pearls:**
  > o Positive correlation with duration of treatment and impairment of urinary concentrating ability (average 6.5 – 10 years)
  > o Elevations in Scr → appropriate dose reduction or discontinuation of drug
    > ▪ If Scr > 220 umol/L at presentation, patient is likely to progress to ESRD despite discontinuation of lithium