Slides prepared by the NephMadness Executive Committee

- Anna Burgner
- Samira Farouk
- Pascale Khairallah
- Matt Sparks
- Joel Topf
- Tim Yau
- Bracket submission March 1 - March 31
- Earn MOC and CME credits
- Open to individuals and/or groups
- Details available at AJKDblog.org
- Free to enter
AJKDblog.org

NephMadness.com

[This will direct to the Tourneytopia bracket submission site]
- Review the Regions & Teams on AJKDBlog
  - Register for the game on Tourneytopia
  - Submit your picks by filling out your bracket
  - Discuss on social media using #NephMadness
Ready to fill out your bracket?

31 decisions to make

2,147,483,648 possible bracket combinations
The BRP Has Chosen the Winning Bracket

To win, predict what the BRP thinks will bring the most practice change to nephrology!
To use Zoom to fill out your group bracket, use the next 2 slides

[Pro Tip: You can submit individual & group brackets – and 3 brackets per email address]
Brackets are now closed! The round of 32 has wrapped up with three go-winners: **A**, **B**, and **C**.

**A** has advanced to the Sweet 16 in the **ANIMAL HOUSE** category with a 91.46% win margin.

**B** has advanced to the Sweet 16 in the **ANEMIA** category with a 60.76% win margin.

**C** has advanced to the Sweet 16 in the **ARTIFICIAL KIDNEY** category with a 76.01% win margin.

**Nephrology Bracket Challenge**

- Bracket submission March 1 - March 31
- Earn MOC and CME credits
- Open to individuals and/or groups
- Details available at AJKDblog.org
- Free to enter
How to Fill Out Your NephMadness Bracket with Zoom Polls

**Step 1.** Start a new Zoom meeting *(as Host)*
Click "Polling" then "Add a Question"

**Step 2.** Create 1 question with options A & B.
Click "Save" and check "anonymous"

**Step 3.** Click "Polling" again in your meeting → "Launch Poll". After all have voted, click "End Poll"

**Step 4.** Fill in the matchup winner based on the results. Click "Re-Launch"

**Step 5.** Click "Continue"

**Step 6.** Repeat steps 4-5 until all 31 matchups are completed.
Crown your NephMadness Champion!
Liquid Biopsy Region

Region Writer: Caitlyn Vlasschaert
Region Expert: Florian Buchkremer
Microscopy Techniques

- Cells, casts, lipids, crystals, & microorganisms in the urine can serve as real-time biomarkers of underlying pathology

- Light microscopes illuminate specimens from below to highlight their magnified properties

- **Bright-field (BF), phase-contrast (PC), & polarized light microscopy** are variants of light microscopy

- BF microscopy relies on differences in transparency to visualize a specimen, while PC transforms light path traveling through an object to enhance contours
Figure 2. An assortment of unstained bright-field images: muddy brown granular cast (Juan Carlos Velez), red cell rouleaux (José Poloni), mixed cellular cast containing calcium oxalate stone (Jay Seltzer).

Figure 2. Crisp definition of acanthocyte edges, blebs and all, by phase contrast microscopy. Image by Florian Buchkremer.

Figure 3. Lipid cast in a patient with nephrotic proteinuria by phase contrast (left panel), bright field (upper right) and polarized light (lower right) microscopy. Image by Florian Buchkremer.
Assessment of interobserver reliability of the urine sediment examination

Prospective diagnostic test study

- July 2018 to March 2019
- 10 Surveys
- 76 Study questions
- Adult patients, n = 10
- Urine samples
- 21 Nephrologists, 67% completed the survey

* Nephrologists were unaware of clinical history

Overall % agreement

<table>
<thead>
<tr>
<th></th>
<th>Percentage</th>
<th>95% CI</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casts</td>
<td>59%</td>
<td>(50-69)</td>
<td>0.52</td>
</tr>
<tr>
<td>Other urine sediments</td>
<td>69%</td>
<td>(61-77)</td>
<td>0.65</td>
</tr>
<tr>
<td>Mixed Cellular Casts</td>
<td>0.13</td>
<td>(0.10-0.17)</td>
<td></td>
</tr>
<tr>
<td>Squamous Epithelial Cells</td>
<td>0.90</td>
<td>(0.87-0.94)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: In this study, substantial variability occurred in the interpretation of urine sediment findings, even among expert nephrologists. Educational or technological innovations may help improve the urine sediment as a diagnostic tool.


Visual abstract by Edgar Lerma MD FASN
Staining Techniques
Staining Techniques

- The **Sternheimer-Malbin (SM) stain**, developed in 1948 by Richard Sternheimer and Barney Malbin, is the most widely used for urine sediment analysis.

- The SM stain is composed of crystal violet and safranin, similar to the Gram stain. It is **supravital**, meaning it is applied to live sediment, fresh out of centrifuge!

- Endogenous pigments, including hemoglobin, myoglobin, and bilirubin, can color urinary casts and yield clues to underlying systemic pathology.

- The Sudan stain can be used to detect fat globules in urine.
Figure 4. **Unstained** and **stained** mixed cellular casts by Jay Seltzer.
Figure 6. Nature’s powerful pigments. The left panel shows bilirubin coloring renal tubular epithelial cells (image from a RFN post by José Poloni). The right panel shows free hemoglobin coloring the supernatant after centrifugation (image courtesy of Samira Farouk).
Microscopy Techniques (A)

Pick one

Staining Techniques (B)
Urine Microscopy for GN
Urine Microscopy for GN

- Glomerular bleeding with acanthocyturia commonly occurs in various glomerulonephritides, inherited GBM disorders like Alport syndrome, & in non-GN syndromes like membranous & diabetic nephropathy.

- Acanthocytes (a subset of dysmorphic RBCs) are RBCs that develop arm-like projections (or “blebs”) after passing through the GBM

- Acanthocyturia (> 5% urinary RBCs) are fairly specific but poorly sensitive for GN

- RBC casts, formed in the distal nephron, indicate intraluminal bleeding that has occurred somewhere upstream—at the level of the glomerulus or in the tubules.

- RBC casts can also occasionally be found in acute interstitial nephritis
Figure 8. SM-stained RBC cast under bright-field microscopy (Jay Seltzer). The right panel is a schematic showing that all urinary casts are formed in the distal nephron (created with BioRender).
Urine Microscopy for ATN
Urine Microscopy for ATN

- Acute tubular necrosis (ATN) is the most common cause of AKI in hospitalized patients

- ATN can lead to the sloughing of renal tubular epithelial cells (RTECs) & casts in the urine

- Granular casts = cellular debris + plasma proteins trapped in a Tamm-Horsfall protein matrix within the distal nephron. In general, the darker & coarser the cast → more likely that it represents ATN

- A urinary sediment scoring system for AKI predicted the likelihood of a final diagnosis of ATN using the pretest probability and the number of RTECs and granular casts on initial microscopy
Figure 10. From the RFN post on granular casts by Juan Carlos Velez:
A. Finely granular cast
B. Slightly coarser granular cast
C. “urine poker quads” showing a fine (f), coarse (c) and muddy brown (mb) granular cast accompanied by a waxy (wx) cast
D. “Muddiness” of mb granular casts is better appreciated at low power field compared to high power field (inset).
Is urine microscopy associated with severity and worsening of AKI in hospitalized patients?

**Cohort**
- Prospective study
  - n=249
  - Yale-New Haven Hospital
  - July 2008-March 2009

**Methods**
- A urinary sediment scoring based on number of RTE and granular cells was created:

<table>
<thead>
<tr>
<th>RTE cells/ HPF (points)</th>
<th>Granular casts/ LPF (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1-5 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>≥6 (2)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

**Results**
- n=197 (Prerenal AKI or ATN)
  - Adjusted relative risk: 7.3; 95% CI (4.5-9.7) (For AKI worsening with urinary score of ≥3 vs 0)
  - Urinary Score was **more predictive** for worsening of AKI than AKIN stage
  - No. of granular casts (p=0.01) and RTE (p=0.03) was associated with AKI stage

**Conclusion:** The urinary sediment's score may be a useful tool to predict worsening of AKI due to either ATN or prerenal AKI during hospitalization.


Visual abstract by Priti Meena MD DNB
Urine Microscopy for GN (A)  

pick one  

Urine Microscopy for ATN (B)
Now pick your Liquid Biopsy Region Champion

Microscopy Techniques

Urine Microscopy for GN

Staining Techniques

Urine Microscopy for ATN
Animal House Region

Region Writer: Tiffany Truong
Region Expert: Kelly Hyndman
Illustrator: Corina Teodosiu
Evolution of the VERTEBRATE NEPHRON

Early development in the sea

Later evolution of marine teleosts

Abbreviations:
AL - ascending limb of Henle's loop
CT - collecting tubule
DS - distal segment (distal convoluted tubule in amphibians and mammals)
IS - intermediate segment
N - neck
PC - pars convoluta of the proximal tubule
PR - pars recta of the proximal tubule
PS - proximal segment
PT - proximal tubule
TL - thin limb of Henle's loop

Infographic by Corina Teodosiu, MD
@CTeodosiu
Hopping Mouse
Hopping Mouse

- Lives in dry conditions - needs to conserve every drop of water available
- Highest urine concentration recorded in a mammal (9,370 mOsm/kg)
- Kidney adaptations
  - Longer water permeable segments of descending thin limbs
  - Higher vasopressin levels
  - Large osmolality gradient in the inner medulla
    - Countercurrent multiplication
    - Enhanced ability to reabsorb sodium in thick ascending limb (longer and more transporters)
- Urea concentrated into interstitium via transporters
- ? pelvic peristaltic contractions
**Aquaporins in Desert Rodent Physiology**

**Water conserving mechanisms**
- Very dry feces
- Minimization of evaporative water losses
- Highly concentrated urine

**AQP-related urine concentration mechanisms in desert rodents**
- Expression of AQP 1-7 in the PT
- Longer AQP-1 (+) segments in the DTL
- AQP-2 expression in the CD
- Vasopressin
- TonEBP
- Basolateral AQP-2 expression
- Hypertonicity

**Abbreviations:**
- AQP: Aquaporin
- DTL: Descending thin limb of Henle
- PT: Proximal tubule
- CD: Collecting duct
- TonEBP: Tonicity-responsive enhancer binding protein

**Conclusion:** Future research on the pathways of transmembrane and/or transepithelial water flows across medullary collecting duct cells is likely to offer new insights into cellular roles and regulation of AQPs as well as the urine concentrating mechanism.


Visual abstract by Corina Teodosiu MD
Marine Iguana
Marine Iguana

- Lives in saltwater environment
- Reptiles do not have a loop of Henle – thus, cannot concentrate urine
- Have developed extrarenal salt-secreting organs
- Iguana salt gland located above orbit and connected to nasal passage
How do marine birds and reptiles, like the marine iguana, that drink sea water, eliminate salt?

**Challenges**
- Most of life spent on or in sea
- Drinks sea water
- If relied on kidneys; 2 quarts of urine excretion required for every quart of sea water consumed

**Nasal Salt Gland**
- Secretions
  - 5% NaCl
  - 5x as salty as serum

**Countercurrent & tubule structure**
- Branching tubules radiating from a central duct with parallel capillaries
- Resembles a cylindrical stack of pies with a hole in the middle
- Each pie contains 5-7 cells
- NaCl pumped against an osmotic gradient

**Conclusion:** Nasal salt glands are a special organ which eliminates salt with great efficiency, enabling marine birds to meet their fluid needs by drinking sea water. Similar organs have been found in marine reptiles, like the Galapagos marine iguana.

Visual abstract by Sophia Ambruso DO

@sophia_kidney
Pick one:

Hopping Mouse (A)

Marine Iguana (B)
Seahorse
Seahorse

• The seahorse lacks glomeruli!! Oh my

• How can a “tubule only” kidney function?
  -Controversy
    -Can tubules do more that reabsorb filtrate?
      Turns out urine composition is similar to fish with glomeruli *(yes, tubules CAN)*
    -Aglomerular kidneys more selective for what exogenous substances can be excreted (more like a gland)

• Important advances in kidney physiology come from research in agglomerular fish (the goosefish from Homer Smith)
  -Inulin *(no* tubular secretion) to measure GFR
  -PAH *(both* tubular section and glomerular filtration) to measure renal blood flow

• Loss of glomerular filtration here does not mean kidney failure. Some glomerular fish do not even use their glomeruli at times, called glomerular intermittency.
Kidneys Sans Glomeruli

Of the 45,000 vertebrate species...

...only 30 species of fish have agglomerular kidneys

No glomerular filtration = Less body water lost

Advantageous in hyperosmotic environments

The osmotic challenge

Seawater
~1000 mOsm/kg

Water lost by osmosis

NaCl gained by diffusion

Plasma
~350 mOsm/kg

Urine formation in agglomerular kidneys

Tubular water secretion into proximal tubules favored by:

- NaCl secretion via secondary active secretion of Cl
- Transepithelial secretion of organic & inorganic solutes:
  - Mg
  - P
  - SO4

Conclusion: Challenging basic assumptions in renal physiology, tubular secretion mechanisms in agglomerular vertebrates provide the basis for urine formation and homeostasis.


Visual abstract by Corina Teodosiu MD
Hagfish
Hagfish

- Considered the most primitive vertebrate (evolutionary bridge between vertebrates and invertebrates)

- Hagfish are osmoconformers
  - Meaning serum osmolarity is similar to surrounding seawater (>1,000 mOsm/L)
  - Hagfish plasma is seawater
  - **DO NOT** regulate monovalent ions Na$^+$, K$^+$, Cl$^-$, Br$, \text{HCO}_3^-$
  - **DO** regulate divalent ions Mg$^{2+}$, Ca$^{2+}$, SO$_4^{2-}$
Hagfish

- Low metabolic requirement - little energy required for osmoregulation
- Can excrete ammonia through the skin instead of just gills like most fish
- Have glomeruli that are 10X larger than mammals
Is one of the oldest living craniates, the hagfish, representative of the evolutionary transition between invertebrate and vertebrates?

**300-million-year-old fossil shares same morphological features with modern hagfish**

**Tissue bears a closer resemblance to marine invertebrates**

**Exclusive marine osmoconformers**

### Link to Invertebrates

- Hagfish plasma and red blood cell (RBC) ion concentration is same as sea water.
  - Only divalent ions regulated
  - \( \text{Mg}^{2+}, \text{Ca}^{2+}, \text{SO}_4^{2-} \)

### Unique Hagfish Characteristics

- **Plasma devoid of trimethylamine oxide (TMAO)**
- **Lack electrolyte exchange mechanisms to regulate RBC volume**
- **RBC Volume maintained through high intracellular \( \alpha \)-amino acid concentrations**

### Link to Modern Fish

- **Sharks maintain osmotic equilibrium through high organic osmolytes like TMAO & urea**
- **Like sharks, the hagfish’s liver and muscle are isosmotic to sea water & bridge the osmotic gap with amino acids and TMAO**

**Conclusion:** The hagfish have a vertebrate pattern of organization but possess distinct ‘invertebrate’ characteristics. Akin to marine invertebrates, the hagfish is an marine osmoconformer where inorganic ions make up the osmotic concentration of plasma and RBCs. These findings suggest the modern hagfish may represent the evolutionary transition between invertebrate and vertebrate organism.


Visual abstract by Sophia Ambruso DO

@sophia_kidney
Seahorse (A)

Hagfish (B)

pick one
Now pick your Animal House Region Champion

Hopping Mouse  Marine Iguana

Seahorse  Hagfish
COVID-19 Region

Region Writers:
Debbie Chen & Christin Giordano

Region Expert:
Maria Jose Soler Romeo
COVID in Dialysis
COVID in Dialysis

• In-center hemodialysis represents a high risk for exposure to SARS-CoV-2
  - A large UK dialysis center went from 1 infected patient to >20% of patients infected in 6 weeks.
  - In New York City COVID-19 prevalence
    - 14% in patients on dialysis
    - 2.6% of general public

• High risk for morbidity and mortality in patients with ESKD
  - Mortality rates in different studies: 25-31%

• SARS-CoV-2 infection has been shown to occur much less frequently in patients using home dialysis modalities
High risk of hospitalization and mortality seen in COVID-19 positive maintenance HD patients from a large national not-for-profit dialysis center in the United States.

Older age, heart disease, and markers of frailty were associated with an increased risk of mortality in this study.
COVID in Transplant
COVID in Transplant

• What to do with immunosuppression in patients with kidney transplants and COVID-19?
  • No clear right answer, should be decided on a patient-by-patient basis
  • Need to balance controlling infection and preventing rejection
  • Many centers continue calcineurin inhibitors (CNI) and decrease or stop the anti-metabolite
COVID in Transplant

• Is it safe to continue performing kidney transplants during the COVID-19 pandemic

• During first several weeks of the pandemic DDKT dropped by 24% and LDKT dropped by 87%
  - Many barriers including concern for patient/donor safety (see next slide)

• One single center study demonstrated higher mortality and risk of hospitalization for patients on the kidney transplant waitlist vs patients who had kidney transplants.

• Other studies demonstrated similar mortality between patients with kidney transplants and patients receiving dialysis.
Barriers reported to Living Donor Kidney Transplant during the COVID-19 Pandemic

US state-reported COVID-19 cumulative incidence, week of 5/14/20
- High: ≥500 cases/100K
- Moderate: ≥200-<500 cases/100K
- Low: <200 cases/100K
COVID in Dialysis (A)

pick one

COVID in Transplant (B)
Glomerular Injury in COVID
Glomerular Injury in COVID

• ACE2 protein located on the podocytes

• Multiple reports of collapsing glomerulopathy in patients of African ancestry and high-risk APOL1 genotype → Led to term COVID-19 Associated Nephropathy (COVAN)

• Case reports of other GN’s exist: Membranous Nephropathy, Crescentic IgA nephropathy, Lupus Nephritis, and Anti-GBM disease (unclear if these are 2/2 COVID-19)

• Thrombotic microangiopathy also seen in biopsy series and contributes to glomerular injury
Diffuse Tubular Injury, interstitial edema and collapsing FSGS

SARS-CoV-2

Hypovolemia
Fever
Insensible losses

ACE2

Cytokine release
Interleukins
Interferons

Medication-induced

Direct viral infection

Collapsed glomerular tuft with marked activation/hypertrophy of the overlying podocytes

Collapsed glomerular basement membranes

Prerenal azotemia
Acute tubular injury
Myoglobin cast nephropathy
Thrombotic microangiopathy
Collapsing glomerulopathy
Crescentic glomerulonephritis
Membranous nephropathy
Minimal change disease
Oxalate nephropathy
Interstitial nephritis

2 APOL1 risk variants
Tubular Injury in COVID
Tubular Injury in COVID

• ATN is the predominant lesion seen in path series (even seen in patients without clinical AKI on autopsy)

• Ischemic insults – hypoxia hypotension

• Toxic insults
  - complement activation (terminal C5b-9 complex deposition in tubules)
  - direct viral infection
  - rhabdomyolysis (ACE2 protein also expressed on skeletal muscle)
Diffuse tubular injury present in this kidney biopsy sample from a patient with COVID-19 & AKI
Glomerular Injury in COVID (A)

Tubular Injury in COVID (B)

pick one
Now pick your COVID-19 Region Champion

COVID in Dialysis

COVID in Transplant

Glomerular Injury in COVID

Tubular Injury in COVID
ICU Nephrology

Region Writer: Ryann Sohaney
Region Expert: Ashita Tolwani
Dialysis Timing in Surgical ICU
Dialysis Timing in Surgical ICU

- AKI affects nearly half of critically ill surgical patients

- HEROICS study enrolled 224 patients with severe shock requiring pressors within the first 24 hours post-cardiac surgery.
  - Randomized to early high dose (80 mL/kg/hr) vs traditional start
  - No difference in survival, ICU length of stay, ventilator freedom

- ELAIN trial randomized patients to early (within 8 hours of AKI stage 2) or delayed (within 12 hours of AKI stage 3) initiation of CKRT.
  - Early intervention had lower 90-day mortality
  - Shorter duration of mechanical ventilation
  - Shorter hospital stay, improved kidney recovery
**Conclusion:** Among critically ill patients with acute kidney injury, an accelerated renal-replacement strategy was not associated with a lower risk of death at 90 days than a standard strategy.
Dialysis Timing in Pediatric ICU
Dialysis Timing in Pediatric ICU

- ICU mortality >40% in children with AKI requiring KRT.
- Fluid overload was also associated with longer ICU LOS, prolonged mechanical ventilation and increased mortality.
- Compared to adults, provision of acute KRT in children can be more technically challenging.
- Desperately need more randomized clinical trials to advise optimal therapies in this vulnerable population.
Is fluid overload associated with mortality in children receiving continuous kidney replacement therapy (CKRT)?

**13 centers**
Prospective pediatric CKRT registry

- Fluid overload: Mortality At ICU discharge
  - <10%: 29.4%
  - 10-20%: 43.1%
  - ≥20%: 65.6%

N = 297
Mean age: 8.5 yr

1% increase in Fluid overload
3% increase in mortality

aHR for mortality vs <20% fluid overload: 8.5 [95% CI 2.8, 25.7]

**Conclusion:** Critically ill children who develop greater fluid overload before initiation of CKRT experience higher mortality than those with less fluid overload.


Visual abstract by Divya Bajpai MD DM
@divyaa24
Dialysis Timing in Surgical ICU (A)

Dialysis Timing in Pediatric ICU (B)

pick one
Dialysis with ECMO
Management of Dialysis during ECMO

CKRT can be delivered independently from ECMO.

The main advantage is that issues with the CKRT circuit will not interfere with the ECMO circuit.

The major downside is the need for an additional large bore access. This method also fails to preserve venous access sites should an additional ECMO cannula be required for sufficient ECMO blood flow.

CKRT can be delivered in-line with the ECMO circuit through the use of a CKRT machine.

The advantages to a CKRT machine in-line approach include having accurate control of ultrafiltration rate, and having the ability to monitor and respond to changes in transmembrane pressure.

Access pressure complications may require disabling the CKRT pressure alarms or adding additional tubing to the CKRT device.
<table>
<thead>
<tr>
<th>CKRT-ECMO Circuit</th>
<th>Circuit Design</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>In parallel</td>
<td>CKRT is performed independent of the ECMO circuit through a separate venous catheter</td>
<td>Filter clotting and hemocircuit interruptions do not require assistance from the ECMO team or interfere with the ECMO circuit. Precise control of ultrafiltration rate. No restriction in CKRT modality.</td>
<td>Requires an additional venous access, increasing the risk of access complications (bleeding and thrombosis). The presence of two separate circuits increases extracorporeal blood volume.</td>
</tr>
<tr>
<td>In-line hemofilter</td>
<td>The filter inlet is connected after the ECMO pump or after the oxygenator and returns blood to the proximal portion of the ECMO circuit. Infusion pumps are incorporated into the circuit to control dialysate, replacement and ultrafiltration fluid rates.</td>
<td>Simple and inexpensive.</td>
<td>Requires use of several external infusion pumps. Difficult to control ultrafiltration volume. Inability to control blood flow rate through the hemofilter. No hemofilter pressure monitoring, resulting in diminished ability to detect early filter clotting.</td>
</tr>
<tr>
<td>In-line hemocircuit</td>
<td>Multiple potential circuit configurations: CKRT circuit connect to luer locks on the inlet and outlet ports of the oxygenator. CKRT inlet connected post-blood pump and outlet connect to pre-blood pump (venous drainage limb).</td>
<td>Precise control of ultrafiltration rate. Ability to monitor transmembane pressure. Does not require external infusions pumps. Less priming volume compared to parallel circuit.</td>
<td>May require disabling pressure alarms.</td>
</tr>
</tbody>
</table>
AKI Etiology with ECMO
AKI Etiology with ECMO

• The initiation of ECMO itself may contribute to the development of AKI through several mechanisms.

• Hemolysis is a common complication of ECMO that induces AKI via:
  - Reduction in kidney blood flow
  - Tubular obstruction
  - Direct cytotoxicity

• ECMO may contribute to AKI through alterations in perfusion and by activation of pro-inflammatory mediators.
Adapted from Figure 1 in Khalighi et al in AJKD, 2015. The hemoxylin and eosin stain (panel A) demonstrate distal tubular casts which are periodic acid–Schiff reagent positive (panel B) in a patient with intravascular hemolysis.

Adapted from Figure 1 in Qian et al. AJKD 2010. Prussian blue iron stain demonstrating that these are hemosiderin deposits with the tubular epithelial cells.
Dialysis with ECMO (A)

pick one

AKI Etiology with ECMO (B)
Now pick your ICU Nephrology Region Champion

Dialysis Timing in Surgical ICU

Dialysis Timing in Pediatric ICU

Dialysis with ECMO

AKI Etiology with ECMO
Workforce Region

Region Writer: Bethany Roehm
Region Expert: Yusra Cheema
What are the factors influencing specialty choice in nephrology among medical students and residents?

**Reasons to Choose ✓**
- Subject Interest: 92%
- Suitable Work-Life Balance: 73%
- Access to Mentors: 70%
- Subject Exposure: 66%

**Reasons to forgo ✗**
- Lack of Interest: 79%
- Remuneration Concerns: 43%
- Not Suitable Work Life Balance: 39%
- Subject Exposure: 32%

**Key Driving Factors:**
- Having a Mentor
- Interest in Physiology

**Conclusion:** Incorporating novel educational tools and broadening the scope of the nephrology elective, highlighting ongoing areas of clinical and research innovation, expanding opportunities for interdisciplinary collaboration and procedural skills, and strategies to reduce burnout may be useful areas on which to focus future recruitment efforts.


Visual abstract by Verner Venegas MD MHA
Medical Student Interest
Medical Student Interest

- 2/3 of graduating residents develop their ultimate career choice prior to starting residency
- Mentorship and networking opportunities targeted to medical students
- ASN TREKS (Tutored Research and Education for Kidney Scholars)
- Advocacy example spearheaded by medical students:  
  - Race-based GFR discussions
- Other areas of advocacy
  - Dialysis coverage for undocumented immigrants
  - Social inequities in kidney care
Resident Interest
Resident Interest

- 68% of nephrology fellows made their decision to pursue nephrology during residency.

- Many programs (e.g., ASN KidneySTARS) provide mentorship to both medical students and residents.

- Important to display the diversity of our field to residents rather than the traditional “inpatient-only” side.

- Student loan debt forgiveness programs exist via ASN (for underrepresented minority groups) and NIH (for future physician scientists).
Why not Nephrology?
A survey of fellows not choosing Nephrology as a future career

Belief that patients were too complicated
35%

No role model or mentor for guidance
33%

Not enough procedures
26%

Too difficult of a subject matter
26%

Conclusion: A majority of the internal medicine non-nephrology fellows never considered nephrology as a career choice. A significant proportion were dissuaded by several factors, including a complicated nephrology patient population, a perceived lack of role models or mentors, a sense that nephrology does not offer enough procedures, and difficult-to-understand subject matter.


Visual abstract by Omar Taco MD Msc
Medical Student Interest (A)

Resident Interest (B)

pick one
Academia

• Provides multiple career path opportunities:

  - **Physician scientist** – path usually starts during/prior to fellowship with research and application to T32 training grants
  
  - **Clinician educator** – med ed and leadership opportunities at medical student, resident, fellowship level
  
  - **Expert subspecialist** – academic centers provide the referral base and multidisciplinary services needed
Private Practice
Private Practice

• Provides more direct patient care, flexibility depending on your practice model

• Opportunities for teaching and mentorship still exist but often need to be forged by the individual

• Financial compensation is better than academics (20-100K depending on the source)

• Fellowship programs should be incorporating the business aspect into their curriculum as the majority of graduates plan to go into practice
Academia (A)

Private Practice (B)

pick one
Now pick your Workforce Region Champion

Medical Student Interest

Resident Interest

Academia

Private Practice
Anemia Region

Region Writer: Arun Rajasekaran
Region Expert: Nupur Gupta
Oral Iron
Oral Iron

- Oral iron formulations are cheaper and easier to administer than IV formulations. Newer formulations are well-tolerated and have better efficacy compared to older ones.
  
  - Ferric citrate vs ferrous sulfate x 12 weeks resulted in higher Tsat and ferritin increase in the citrate group.

- Newer oral iron formulations may be as effective as IV iron formulations for treatment of anemia in patients with CKD.
  
  - In patients on dialysis receiving oral ferric citrate for 52 weeks, 85% of patients required no additional IV iron.

- RCT of patients with iron deficiency anemia and CKD stage 3-5 not on dialysis showed
  
  - Short course of oral sucrosomial iron was as sufficient as IV ferrous gluconate in correcting anemia.
What is the effect of ferric citrate vs ferrous sulfate on iron & phosphate parameters in patients with CKD & iron deficiency?

**Participants:**
- 60 participants

**Interventions:**
- **Ferrous sulfate:** 325 mg PO TID (195 mg elemental Fe/day)
- **Open-label Randomized**
- **Ferric citrate:** 2 g PO TID (1260 mg elemental Fe/day)

**Outcomes: Difference in mean change at 12 weeks**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ferrous sulfate</th>
<th>Ferric citrate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSat %</td>
<td>+8 (1-15)</td>
<td>+37 (10-64)</td>
<td>+69</td>
</tr>
<tr>
<td>Ferritin ng/mL</td>
<td>+8 (1-15)</td>
<td>+37 (10-64)</td>
<td>+69</td>
</tr>
<tr>
<td>Hepcidin pg/mL</td>
<td>+8 (1-15)</td>
<td>+37 (10-64)</td>
<td>+69</td>
</tr>
<tr>
<td>Hemoglobin g/mL</td>
<td>+8 (1-15)</td>
<td>+37 (10-64)</td>
<td>+69</td>
</tr>
<tr>
<td>iFGF23 pg/mL</td>
<td>+8 (1-15)</td>
<td>+37 (10-64)</td>
<td>+69</td>
</tr>
</tbody>
</table>

**No difference** in incidence of adverse events between treatment arms

**Conclusion:** Compared to ferrous sulfate, ferric citrate for 12 weeks resulted in a greater mean increase in TSat and ferritin concentration in individuals with moderate to severe CKD and iron deficiency.


Visual abstract by Eric Au MBBS MPH FASN
<table>
<thead>
<tr>
<th>Iron Formulation</th>
<th>Dose Prescribed (per tablet)</th>
<th>Elemental Iron</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional Oral Iron Formulations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous Sulfate (generic)</td>
<td>325 mg</td>
<td>65 mg</td>
<td>3 tablets a day</td>
</tr>
<tr>
<td>Ferrous Fumarate</td>
<td>325 mg</td>
<td>106 mg</td>
<td>2 tablets a day</td>
</tr>
<tr>
<td>Ferrous Gluconate (Fergon)</td>
<td>325 mg</td>
<td>37.5 mg</td>
<td>5 tablets a day</td>
</tr>
<tr>
<td><strong>Novel Oral Iron Formulations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferric Citrate (Auryxia)</td>
<td>1000 mg</td>
<td>210 mg</td>
<td>3 tablets a day</td>
</tr>
<tr>
<td>Ferric Maltol (Ferracru)</td>
<td>30 mg</td>
<td>30 mg</td>
<td>2 tablets a day</td>
</tr>
<tr>
<td>Liposomal Iron (Ferrolip)</td>
<td>30 mg</td>
<td>30 mg</td>
<td>1 tablet per day</td>
</tr>
<tr>
<td>Sucrosomial Iron (Sideral Forte)</td>
<td>100 mg</td>
<td>30 mg</td>
<td>1 tablet per day</td>
</tr>
</tbody>
</table>
IV Iron
IV Iron

- Advantages of IV iron include greater potential for bone marrow delivery, less concern for adherence and absorption.

- Rare side effects of IV iron formulations include transient hypotension, abdominal symptoms, risk of infections, and hypophosphatemia among other.

- New IV iron formulations permit a relatively large quantity of iron to be given during a short time period, and in a single session.

- Faster and more consistent improvement in hemoglobin levels with
  - Proactive *over* reactive IV iron in patients receiving dialysis
  - IV iron *over* oral iron in patients with CKD
FIND-CKD: Is IV ferric carboxymaltose (FCM) better than oral iron in treating iron deficiency anaemia in patients with CKD?

<table>
<thead>
<tr>
<th>Methods</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>193 centers 20 countries Open label RCT</td>
<td>2:1:1</td>
<td>Over 56 weeks</td>
</tr>
<tr>
<td>n = 626</td>
<td>Oral iron</td>
<td>Primary endpoint</td>
</tr>
<tr>
<td>n = 317</td>
<td>31.8%</td>
<td>Mean hemoglobin increase (g/dL)</td>
</tr>
<tr>
<td>n = 154</td>
<td>IV Ferric carboxymaltose</td>
<td>Mean hemoglobin increase &gt;1g/dL</td>
</tr>
<tr>
<td>n = 155</td>
<td>Low ferritin target (100-200 μg/L)</td>
<td>32.2%</td>
</tr>
<tr>
<td>n = 155</td>
<td>IV Ferric carboxymaltose</td>
<td>23.5%</td>
</tr>
<tr>
<td>n = 155</td>
<td>High ferritin target (400-600 μg/L)</td>
<td>P = 0.026 Compared to oral iron</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = 0.014 Compared to oral iron</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; 0.001 Compared to oral iron</td>
</tr>
</tbody>
</table>

**Conclusion:** Compared with oral iron, IV FCM targeting a ferritin of 400-600 μg/L quickly reached and maintained Hb level, and delayed and/or reduced the need for other anemia management including ESAs.


Visual abstract by Krithika Mohan MD
Oral Iron (A)

IV Iron (B)

pick one
ESAs
ESAs

- ESAs alleviate anemia-related symptoms, improve QoL measures, reduce transfusions.

- Side effects include adverse cardiovascular, cerebrovascular, and cancer-related events.

- KDIGO guidelines suggest
  - considering ESA use only if hemoglobin < 10 g/dL
  - addressing all potentially correctable etiologies of anemia first
  - replete iron stores if iron deficient.

- Generally, hemoglobin levels are maintained between 10 and 11.5 g/dL in patients on dialysis treated with ESA.
Erythropoietin stimulating agents

**Benefits vs. Risks**

**Benefits**
- Improvement in Hgb resulting in:
  - Better QOL
  - Fewer BT
  - Less LVH

**Risks**
- Hypertension
- Malignancy
- Thromboembolic events
- Vascular access thrombosis
- CV and all-cause mortality

QOL: Quality of life, BT: Blood transfusion, LVH: Left ventricular hypertrophy

Infographic by Priti Meena MD DNB

@priti899
HIF Stabilizers
What is HIF?

• Hypoxia inducible factor (HIF) is present in nearly all tissues. HIF gene activation results in enhanced red blood cell synthesis via various pathways.

• HIF stabilizers are small-molecule oral formulations that result in the enhancement of HIF-regulated gene expression.
HIF Stabilizers

• Currently, 3 HIF stabilizers are under development in the United States:
  - Roxadustat
  - Vadadustat
  - Daprodustat

• Studies suggest that HIF stabilizers improve hemoglobin levels when compared to placebo and to ESA in patients with CKD and ESKD.
Is Roxadustat efficacious and safe for the treatment of anemia in patients with CKD?

Phase 3, Double-Blind, Multicenter, Randomized, Controlled Trial

- **29 Sites in China**
- **2:1 Randomization**
  - **Placebo**: n = 51
  - **Roxadustat**: n = 101

**Primary Endpoint**: Mean Change in Hb from baseline
- **Placebo**: Decrease of $0.4 \pm 0.8$ g/dL
- **Roxadustat**: Increase of $1.9 \pm 1.2$ g/dL

**Secondary Endpoint**: Mean reduction in baseline hepcidin level at week 9
- **Placebo**: $15.10 \pm 48.06$ ng/mL
- **Roxadustat**: $56.14 \pm 63.40$ ng/mL

**Adverse Events**
- **Placebo**: 75% (38/51)
- **Roxadustat**: 68% (69/101)

**Conclusion**: CKD patients in roxadustat group had a higher mean hemoglobin level than those in the placebo group after 8 weeks. During the 18-week open-label phase of the trial, roxadustat was associated with continued efficacy.

Chen, Nan et al. Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis. NEJM 2019; 381:1001-1010

Visual abstract by Dhwanil Patel MD
ESAs (A)

pick one

HIF Stabilizers (B)
Now pick your Anemia Region Champion

- Oral Iron
- IV Iron
- ESAs
- HIF Stabilizers
Primary Care

Region Writer: Racquel Holmes

Region Expert: Clarissa Diamantidis
Transplant Primary Care
Transplant Primary Care

- More patients are living longer with kidney transplants (KT)
- People with KT most often die with a functioning graft rather than on dialysis
- Major causes of death are
  - CV disease – need risk factor mitigation: BP, lipids, aspirin
  - Infection – use inactivated vaccines, pneumococcal, influenza, covid-19 mRNA, recombinant varicella vaccine
  - Malignancy – standard cancer screening: c-scope, low dose CT, mammograms, and pelvic exams. Plus: dermatology evaluation
- Watch for drug-drug interactions with immunosuppression
CKD Primary Care

- 37 million people in the US have CKD, but only 30,000 nephrologists

- 14% of patients in a primary care doctor’s office have CKD → This is a primary care problem!

- Two major clinical practice guidelines:
  - ACP
  - KDIGO

- Both guidelines are from 2012 and are old and out of date
ACP guidelines for CKD stage 1-3

• Short and Simple

• Screen people for CKD if they have risk factors: Age, Obesity, Native American, Hispanic, or Black, Family history, Diabetes, Hypertension

• Patients already on an ACE inhibitor or ARB don’t need additional testing for proteinuria

• ACE inhibitors or ARB for patients with CKD and hypertension regardless of albuminuria

• In patients with CKD and elevated low-density lipoprotein (LDL) levels, use a statin
KDIGO Guidelines on the Diagnosis and Management of CKD

- Long and comprehensive

- 130 plus pages

- Covers all aspects of kidney care, often goes well beyond scientific certainty and provides opinion based recommendations.
Transplant Primary Care (A)

pick one

CKD Primary Care (B)
GFR in CKD
GFR in CKD

• Glomerular filtration can be measured but it's complicated.

• Labs can’t measure inulin. Iohexol and iothalamate clearances are considered gold standard but there is no accepted standard methodology.

• Creatinine based GFR estimates are plagued by demographic differences in creatinine production (and possibly renal handling).

• Validated for predicting death and hospitalization.

• Use of race systematically raises the GFR of Black patients → Delays referral to specialists and listing for transplant.
Proteinuria in CKD
Proteinuria in CKD

- Proteinuria is the oldest sign of kidney disease
- Urine protein is not standardized and varies from hospital to hospital
- Urine albumin uses an immune assay and is much more reliable and standardized
- Urine albumin predicts adverse kidney outcomes as well as cardiovascular complications
- Increased urine albumin is a more powerful risk factor for cardiovascular disease than estimated GFR
GFR in CKD (A)

Proteinuria in CKD (B)

pick one
Now pick your Primary Care Region Champion

Transplant Primary Care

CKD Primary Care

GFR in CKD

Proteinuria in CKD
Artificial Kidney Region

Region Writer: Krishna Agarwal
Region Expert: William Fissell
WAK – Wearable HD
WAK – Wearable HD

• Portable battery operated, worn via belt/vest.
• Push-pull mechanism to optimize blood and dialysate flow.
• Dialysate regenerated via sorbent technology
• Human studies demonstrated mean CrCl of 20.7 mL/min over 24-hours
• CONS
  - bulky (5 kg)
  - requires heparin to prevent clotting
  - urease to degrade urea generates CO2 which can impede flow
AWAK – Wearable PD
AWAK – Wearable PD

- Battery operated, small purse-size, < 2 kg

- 1-1.5L dialysate instilled into peritoneal cavity
  - 500 cc drained
  - filtered
  - regenerated via sorbents
  - returned to the peritoneum (similar to tidal exchanges)

- 8 exchanges/hour, cumulative dialysate flow of 96 L/d

- Study of 20 human patients over 24 hours demonstrated urea clearance of 31.4 mL/min

- CONS
  - sorbent cartridge required change 3 times/day
  - long-term effects on peritoneum
  - long-term infections remain unknown
WAK – Wearable HD (A)

pick one

AWAK – Wearable PD (B)
Implantable Bioartificial Kidney
Implantable Bioartificial Kidney

- Combines high-efficiency filter with bioreactor of cultured renal tubule epithelial cells
- Uses arterial pressure as blood pump, negates need for electrical pumps (similar to CAVH)
- Filter made using silicon nanotechnology with microchips mimicking the glomerular slit diaphragm
- Cultured kidney tubule epithelial cells approximate neutral fluid balance and concentrate toxins, no need for dialysate regeneration
- Toxin-rich concentrate then routed to the bladder as artificial urine
Implantable Bioartificial Kidney

CONS
- Farther from real life implementation compared to WAK/AWAK
- Thrombus potential with low flows
- Cell culture stress and degradation
Scaffolded Bioartificial Kidney
Scaffolded Bioartificial Kidney

- Kidney derived from 26 different cell types (epithelial, endothelial, mesangial, tubular, etc)
- Technology for 3D printing a scaffold for a kidney is not here yet
- "Decellularizing" a kidney (post-mortem, or potentially even other animal species) can also create a scaffold that retains the protein structure
- "Recellularizing" with iPSCs or cultured tubular epithelial cells regenerates the organ
Implantable Bioartificial Kidney (A)

Scaffolded Bioartificial Kidney (B)

pick one
Now pick your Artificial Kidney Region Champion

WAK – Wearable HD

AWAK – Wearable PD

Implantable Bioartificial Kidney

Scaffolded Bioartificial Kidney
From your Effluent 8, pick your Filtered 4
From your Filtered 4,
Pick your Left & Right Kidneys...

...Since you only need 1 kidney,
crown your NephMadness 2021 Champion
Thanks for playing & good luck!

Now, participate in the social media discussion #NephMadness