#BCMKidneyHealth

Cool Beans

The Nephrology Fellowship Survival Guide

For the fellows, by the fellows

Baylor College of Medicine
June 2019 | 1st Edition

Chapters

Chapter 1: Navigating Your Way

THE METHODIST HOSPITAL

Places to Know

- Start your rounds on Dunn 4 West Transplant Unit Physician Dictation Room – **be ready by 8:30AM**. All units have work-rooms, but we usually work from Dunn 4W (transplant floor). Okay to leave purse/bag there, but I do not advise to leave valuables
- You need to print a copy of the list for Dr. Adrogue before rounds. If there are any new consults to see that day, please add the names of the patients to the list before you print. This will save you the trouble of finding patients' labels from their charts. Dr. Adrogue also likes a name sticker for any patient that is being staffed that day in addition to three diagnoses for each new patient that he will write down on the list.
- Hemodialysis Unit is on Fondren 4th Floor
- Pre-Transplant Clinic is Out-Patient Tower 26th Floor (cross over on the skybridge)
- Biopsy conference is in the same place; Outpatient (OPC) 26th Floor in front of the clinic- EVERY Monday at noon, lunch provided
- Physician Services Lounge is on 1st Floor Main Building near the main elevators

Rounds

Surgeon rounds begin at 8:30am on the 4th floor conference room (Dunn 431)

- Very informal rounds, but this is your chance to figure out and confirm your plan with the surgeons, the surgeon PA, the social worker, the transplant coordinator, and the transplant pharmacist. You will go with Dr. Adrogue to these rounds
- If you are on time, you can ask that they discuss your patients first so you can leave to finish work. We must present any of our transplant

patients (within past 3 years) including new transplants. There is a new transplant surgeon each week.

- Dr. Adrogue tends to agree with this group of individuals, so have your plan nailed down here and you will have an easier time during rounds with him.
- The surgery PA (Laura), transplant pharmacist, and surgery transplant fellow are very important to know. The transplant protocol is on our shared drive.

Dr. Adrogue formal rounds following table surgery rounds

- Tuesday-Thursday: pre-transplant clinic with Dr. Adrogue on 26th floor of Outpatient Center. You usually see around 2 patients per day. They will either be dialysis patients who are on the transplant list and just need an updated physical, or patients being seen for the 1st time to be placed on the transplant list, or normal/healthy people being evaluated to donate a kidney. Get a workspace on wheels and log-in to the clinic (HMH renal transplant) and take that into each room with you. You will evaluate the patients together and then you will write the clinic note. Please get the smart phrases for clinic notes from the fellow rounding before.
- ****Noon on Mondays Only:** Pathology conference you have to attend in conference room on 26th floor of Outpatient Center. Lunch is provided. If one of your patients had a renal biopsy that week, expect that patient to be discussed (often times by the fellow) and be prepared to answer any questions about that patients care.
- **It's helpful to put dialysis orders in the night before. Just remember to change the date to "tomorrow."
- ***Any new admissions that are going to require dialysis, you have to notify the dialysis unit that they are here. Also, run the list of HD patient's with the charge nurse each morning to confirm the patients on the schedule for the day to avoid delays.

Phone numbers

- Hemodialysis unit: 713-441-3042
- Methodist Operator: 713-790-2201
- To call a page back from external site: 713-441-****
- Nila: 713-798-8350
- Laura, surgery PA: 281-777-0399
- Dr. Adrogue: 713-416-7786

Additional Info:

- EPIC Electronic Medical Record. Remote access for use at home: apps.houstonmethodist.org. Please call tech support to set this up on your home computer
- Weekend sign out: done via IPASS in EXCEL document
- Answering service will contact you with Baylor Nephrology patients that show up at Methodist (make sure it is Dr. Horacio J. Adrogue Sr – not Horacio E. Adrogue Jr. - his son who also works at Methodist with Methodist Nephrology Fellowship, but we don't see their patients). We also see patients of Dr. Abdellatif and Dr. Workeneh.
- For after hours (after 5pm), the charge nurse at the dialysis unit should be contacted to arrange for dialysis. They have fourth shift on most days in the dialysis unit and if stable, patients may receive dialysis in the dialysis unit. However, if the dialysis unit is closed or a patient is too sick to be in the dialysis unit, they should receive dialysis in the ICU.
- The on-call fellow will be contacted by the pre-transplant coordinator and should see all pre-emptive transplant patients for medical clearance. Ensure appropriate induction orders are being placed (either by you or the surgery team). Sometimes PD/HD, and/or PLEX needs to be performed in the middle of the night for which the dialysis nurse or the pathology/blood bank needs to be contacted, respectively.

CHI Baylor St. Luke's Episcopal Hospital

Places to know

Orient yourself to the elevators first

- Yellow = "Towers" (i.e. Floors 7 Tower – 25 Tower)
- Purple = "ICU/CCU" (i.e. 7 South 1-6, 6 S 1-2)
- Green = CV Recovery/Cooley Building (2nd Floor CVR, 7 Cooley A/B)
- Hemodialysis Unit (purple) 7 South 6
- CV Recovery (green): where the sickest patients in the hospital are especially on ECMO or post transplant
- 7 South 1-5 (purple): Medical /Neuro ICUs
- 6 South 1-2 (purple): CCU

Rounds/Two Nephrology Services (that we rotate on)

St. Luke's Baylor Nephrology

1. Rounds usually start around 10am. (Please check with attending on service to confirm)
2. Usually have one resident and one neurology intern with the fellow
3. ***Need consents (paper) for each admission. Place "verify consent" order on EPIC and get HD nurse to print out consent and you may sign this afterwards
4. ***Any new admissions that are going to require dialysis, you have to notify the dialysis unit that they are here and also run the list of HD patient's with the charge nurse each morning.

St. Luke's Renal Specialists of Houston (largest group in Houston) and Dr. Murthy (Baylor Transplant Patients)

1. One SL fellow will be on this rotation
2. Rounds with Dr. Murthy start promptly at 8AM. Fellows are in charge of seeing all of his ICU patients and chart checking others. Mauricio, NP, is there to assist with other patients
3. Rounds with Renal Specialist start around 10:30AM. Contact them once you are done pre-rounding to start rounds with them.
4. **You will attend Renal Specialist transplant clinics on Tuesday and Thursday afternoons from 1:30pm-5pm at O'Quinn Medical towers

14th floor during this rotation. Please ask the Renal Specialist attending/other fellows if you have any additional questions

Phone numbers

- Hemodialysis Unit: 832-355-6760
- SLEH Operator: 832-355-4146
- To call page back from external site: 832-355-****
- Dr. Murthy: 832-978-6745
- Mauricio, Dr. Murthy's NP: 713-320-5571
- Dr. Timmins 713-417-4026 / Dr. Etheridge 713-417-4027 / Dr. Finch: 713-501-0807 / Dr. Yao: 832-549-4686 / Dr. Pandya: 713-585-6905

Additional Info:

1. EPIC Electronic Medical Record. Remote access for use at home-rasportal.sleh.com
2. Weekend sign out: done via IPASS within the EPIC EMR
3. Multiple nephrology groups round at SLEH (>70 nephrologists are credentialed at SL!) so please check that a patient is 'ours' before seeing! Do not accept any consult on a patient that has been seen by a private nephrologist in the past at SLEH in the medical center.
4. The dialysis unit staff lounge has a LOCKER (#16) that is reserved for our fellows for your personal items. There is a padlock and the code is on the back of the lock.
5. After hours hemodialysis for inpatients may only be performed in the ICU and on-call nurse/dialysis unit must be contacted.
6. The on call fellow will be contacted by the pre-transplant coordinator and Dr. Murthy, and should see all pre-emptive transplant patients for medical clearance. Ensure appropriate induction orders are being placed (either by you or the surgery team). Sometimes PD/HD, and/or PLEX needs to be performed in the middle of the night for which the dialysis nurse or the pathology/blood bank needs to be contacted, respectively.

Women's Pavilion and TCH West Pavilion

- Occasionally will have patients to see here (1-2 / month). SLEH fellow is responsible for these patients.
- Typically interesting cases; all pregnant patients
- Please communicate very well with the OB/GYN department
- Staffed by BCM St. Luke's attending
- EPIC Electronic Medical Record. Remote access for use at home-remote.texaschildrens.org/my.policy
- TCH password expires if not used monthly. If you can remember, try to log in monthly to avoid password reset
- IT department is VERY helpful and will reset it immediately if needed

Discharges to SNF / Communication with Faculty

- Please notify Nila if any patient is discharged to a SNF as often times our BCM Nephrology faculty (Without fellow!) will see the patient
- Please call or text the BCM faculty if their patient is admitted so they are aware and possibly can give you additional info about the patient

Ben Taub General Hospital

Places to Know

- 6th Floor (6C) Hemodialysis Unit
- Renal Office in the HD Unit.
- Medical ICU (6E). Surgical ICU (4E).
- Emergency Center: 1st floor behind the main elevators
- Interventional Radiology: 1st floor near the ER

Hemodialysis Orders

- Order sets tab → Search for "dialysis" → Fill in order template → Need consents (paper) for each admission (dialysis nurses will most of the time ask you for your "autograph")
- SLED available with the same machine; can do CRRT with the same machine but SLED preferred

ER HD Patients: not eligible for chronic hemodialysis (some refer to as "emergency-only" HD)

- There are criteria to meet to receive emergent dialysis (K>6.0, hypoxia, severe anemia / uremia / acidosis)
- PA/NP in EC will assess patients first. Will usually start paging/calling you at 6AM for orders.
- EC physicians will also call you for patients needing HD
- Make sure you inform EC to place nephrology consult order.
- There is a NP/PA on call at night to see patients and write orders for emergent dialysis. They will page you for approval and to discuss orders if the patient meets criteria. You need to see the patient only if not a routine presentation (i.e. ICU admission, sepsis, etc.).
- When you get paged:
- Open the patient's chart, review the POC labs including Hemoglobin
- Check iron stores, ferritin
- Check last time patient received iron (if needed) or aranesp
- Place HD orders, and give iron or Aranesp if needed
- You can save time and increase efficiency by having saved order sets (ask another fellow to show you)
- Do not need consents each time – if so, it is done by EC
- Attendings will see while on HD and write a progress note; BT-ESRD fellow will follow if inpatient. Sometimes patients are admitted post treatment.

Admissions

- NEVER admit to your own service! BTGH is too busy for that!
- Call the case manager 713-873-4434 to have a patient admitted to a medicine team
- Once the case manager assigns the patient to a team, call that team to give the admission

Rounds/Overview

3 teams (each with 1 fellow and 1 attending):

- BTGH 1: AKI/ACUTE Renal Fellow
  - Usually with one resident +/- medical student.
- BTGH 2: ESRD/ER HD patients
  - Please run dialysis schedule with HD nurse at the beginning of the day to assess how many slots are available to be allocated to ER emergent HD patients
- BTGH 3: Outpatient Clinic / Procedure/ Biopsy fellow
- Rounding starts ~9:30 to 10AM for BT1 and BT2 fellow (please check with attending on service)

Phone numbers

- Hemodialysis Unit: 713-873-2381
- SLEH Operator: 713-873-2010
- To call page back from external site: 713-873-***

Additional Info:

- EPIC Electronic Medical Record. Remote access for use at home: citrixaccess.harrishealth.org. Please contact IT Service Desk 713-566-HELP with any questions or issues you may have.
- Weekend sign out: done via IPASS through EPIC
- No primary patients, even if for kidney biopsies
- PD: rare to have Peritoneal dialysis patients at BT; 2-3 of our nurses are trained.
- After hours hemodialysis for inpatients may only be performed in the ICU and on-call nurse must be contacted after consent is obtained, orders placed. Emergent dialysis patients are dialyzed in the ER.

Veterans Affairs Medical Center

Places to Know

- Hemodialysis Unit 3rd Floor (near 3A, blue section)
- VA 1 Fellow Room in dialysis suite, VA 2 Fellow Room outside dialysis suite next to bathroom. Access code: 4570
- MICU/CCU: 3rd Floor (red section). SICU: 5th Floor (red section). Human resources/badging: 4th floor (red section)

Teams

- VA1 primarily covers SICU, transplant, 50% of AKI/ESRD, and MWF CLC patients
- VA2 primarily covers MICU/CCU, 50% of AKI/ESRD, and TTS CLC patients
- The resident/anesthesia intern can switch between services halfway through the rotation

Rounds

- Typically start at 9:30 to 10am Monday-Friday (but check with your attending)
- Please run the dialysis schedule with the dialysis charge nurse at 7AM (for current day), 5PM (to plan 1st shift for the next day), and prior to leaving for conferences

Phone Numbers

- VA HD unit-24907
- VA Operator-713-791-1414
- To call page back from external site: call VA operator then dial 2****
- VA On Call Nurse Pager- 281-567-1500

Hemodialysis Orders

- All patients need a consent (using iMedConsent) for hemodialysis or peritoneal dialysis and will be valid for 1 year through multiple admissions. Consenting is the responsibility of the fellows and must be done electronically (as per VA policy) utilizing a laptop or workstation on wheels. These are available in the ICUs and dialysis unit. Scanning

consents is against VA policy and some units may make you redo the consent if it is not done electronically.

- Dialysis order sets are located in the medical specialty clinic orders -> renal/dialysis section. Please ensure dialysis access is correct in the order and do not forget to check the time.
- Notify the charge dialysis nurse of patients needing HD. **Please do consent for patient first, place order, then document that you have called the nurse.**

CLC

- CLC patients need to be seen monthly and PRN. MWF is seen by VA1 and TTS by VA2
- For each CLC patient, please write with a comprehensive monthly note and fill out the excel CLC patient flowsheet.
- **New** dialysis orders have to be placed during the 1st week of each month (please do not renew them)
- IV iron should be given with HD, please inform HD nurses when you place order
- Aranesp should be ordered for Sunday's to be given by CLC unit
- Please update CLC flowsheet by the 15th, update sign-outs weekly, and notify medical director of new transfers to CLC.

Admissions (from renal clinic)

- Call x23789 (bed control) and tell them you have an admission and give them diagnosis
- Bed control will give you a medicine team and you should call the resident and give a summary. The team will place admission orders. Then, please tell the nurses (either in HD Unit or in Renal Clinic) that patient needs to be sent to that unit for admission (if you have time, you can walk them yourself)

Additional Info

- CPRS is the electronic medical record use. Home access is available on request, but an application is needed to be filled out for this. Contact Dr. Maulin Shah for additional Info
- Primary patients for consulting services are very rare but do happen in special circumstances (I.e. Transplant when requested by Drs. Ramanathan or Pan)
- Weekend sign out: done via IPASS in EXCEL document
- When one of the fellows on VA1 or VA2 is on vacation, the attending/resident on that service will follow up to 10 patients from the original service. These patients should be non-ICU and non-transplant patients. The remaining patients will be seen by the other service.
- After hours dialysis may only be performed in the step down unit or ICU and on-call nurse must be contacted after consent and orders done.

All call is HOME call. Notify your attending about call day, so that post-call rounds begin early so you can leave by 12p!

Ben Taub – call room information:

- Go to security office located across the hall from "Concierge" desk in the entrance on parking garage side.
- Ask for H8 or H9 (these are the only reasonably good ones).
- Rooms are mislabeled – H8 is actually H9 and vice versa.
- H9 (on the left) door handle will not open unless you aggressively turn the handle and hold before pulling on door

St. Lukes – call room information

- Take the yellow service elevators to the 8th floor and go to this room (see picture)
- The code to this and all other rooms is 3155*
- This room may be used by

Urology-if occupied, find another vacant room; same code

VA

- Take the red elevator to the 4th floor. Turn right and keep walking past the old library. Just as you merge onto the main hallway, on your right is the "Medicine Call Rooms" |Use the code 7291*

Chapter TWO:
Acute Kidney Injury and CRRT

KDIGO guideline define AKI as any of the following:
- Increase in SCr by ≥0.3mg/dl (≥26.5lmol/l) within 48 hours; or
- Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5ml/kg/h for 6 hours.

AKI Staging

Stage	Serum Creatinine	Urine output
1	1.5-1.9 x baseline OR ≥0.3 mg/dl (≥26.5µmol/l) increase	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 x baseline	<0.5 ml/kg/h for ≥ 12 hours
3	3.0 x baseline OR Increase in sCr to ≥ 4.0 mg/dl (≥353.6 µmol/l) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m²	<0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

Type AKI	Urinalysis	U Na	FeNa	FeUrea	Bun:Cr
Pre-renal	High specific gravity; Normal or hyaline casts	<20	<1	<35	>20:1
Intrinsic	ATN: low specific gravity, muddy brown casts, renal tubular epithelial cells Vascular: normal or hematuria GN: Proteinuria, hematuria, RBC casts, dysmorphic RBCs Interstitial: Mild proteinuria, hematuria, WBCs, WBC casts, eosinophils	>20	>1	>50	<20:1
Post-renal	Normal or hematuria	>20			>20:1

	WBCs, occasional granular casts				

FeNa = (UNa x SCr / SNa x UCr) x 100
FeUrea = (Uurea x SCr / BUN x UCr) x 100

Continuous and Prolonged Renal Replacement Therapy (CRRT/PIRRT)

CRRT is primarily employed in the ICU with critically ill patients that have a more delicate hemodynamic status and less capacity to accommodate large volume and solute removal in a short period of time. It has practical advantages for volume control in dynamic patients and has been associated with lower length of stay in the ICU. Modes of continuous renal replacement therapy vary depending on whether convection or diffusion (or a combination of both) is primarily utilized for solute clearance. Convection is the hydrostatic force across a membrane while diffusion is the movement of solute across a concentration gradient. While there are theoretical and practical reasons to prefer one modality over another, there are no proven benefits for one modality over another regarding mortality or renal recovery. Continuous veno-venous hemodialysis (CVVHD) is the work-horse of CRRT in the medical center, and as the name implies is continuous solute clearance via diffusion.. We mostly use CVVHD at the medical center except BT. We also have the ability to do SLED/ SHIFT therapy at all of the centers (St. Luke's, Methodist, BT and VA). There are two commonly used machines for CRRT, namely Prismaflex and NxStage. NxStage is utilized at all pavilions in the medical center except Texas Children's Hospital..

Modalities of CRRT:

1. SCUF – Slow Continuous Ultra filtration: This mode of CRRT uses the principle of ultrafiltration purely to remove excess fluid from the body and therefore is used to safely treat fluid overload. For this reason, fluids removed are generally not replaced. It works by pumping the patient's blood through a filter which separates the fluid and molecules according to the size of the

filter pores. These are generally very small in this mode so as not to lose different solutes. Convection does also occur in this mode, however, is restricted by the filter pore. This mode offers less in terms of solute clearance, and therefore can limit abrupt falls in plasma osmolality (before equilibration) that induce further decreases in extracellular volume.

2. Continuous veno-venous hemofiltration (CVVH) uses convection. Hydrostatic force is applied across the membrane and with this fluid removal there is some accompanied 'solvent drag' that brings solute along-side. Therefore, CVVH requires larger (than other modalities) volume removal in order to achieve adequate clearance. Replacement fluid serves to maintain hemodynamic stability. Replacement fluid can be given pre-filter or post-filter. Pre-filter dilutes solute and reduces efficiency of clearance, but has the advantage of reducing filter clotting. Post-filter has the opposite effects. Calculating a filtration fraction can help you determine where to place replacement fluid with an ideal filtration fraction around 15%. We do not regularly prescribe CVVH in the medical center though our NxStage Machine can do
3. CVVHD – Continuous Veno-Venous Hemodialysis: This mode of CRRT is driven by diffusion of molecules across a semi-permeable membrane along a concentration gradient. A dialysate with similar chemistry to normal blood is pumped counter-current to the blood through the filter. Any molecules that are in greater concentration in the blood are drawn across into the dialysate and removed from the body. Molecules which are low in the blood are also replaced by the normal levels in the dialysate. Generally diffusive principles are more effective for removing small sized molecules. In this mode replacement fluids are not administered.
4. CVVHDF – Continuous Veno-Venous Hemodiafiltration: This mode utilizes both diffusion and convection. Some portion of

solute clearance is achieved with diffusion via counter-current dialysate flow while another portion of solute clearance is attained with hydrostatic force and solvent drag. Thus, both a dialysate flow and replacement fluid rate are needed in this therapy.

Modalities of PIRRT:

1. SHIFT – This therapy utilizes the NxStage machine and is performed over the course of a nursing shift (hence, the name). Typically it runs for 6 to 12 hours. Dialysate flow rates are typically ~double that of CRRT (3.5-6 L/hr for a 12 hour therapy) given the abbreviated treatment time. Blood flow rates are largely 200-300 mL/hr.
2. SLED – Sustained Low Efficiency Dialysis: These therapies use conventional hemodialysis machines with lower blood-pump speeds and dialysate flow rates to provide solute and fluid removal slower than IHD but faster than conventional CRRT. Typically, SLED requires lower blood flows of 150-200 mL/min and low dialysate flow rates of 200-300 mL/min for 6 to 12 hours daily. It is an advantageous intermediate therapy that does not require continuous connection to a machine and can help avoid the hemodynamic instability that might ensue with IHD.

Dialysate fluids:

The dialysate fluid is standardized/ pre-prepared and packaged ready to use typically in 5 L bags which are hung on the machine. Dialysate fluids are designed to mimic normal blood chemistry as closely as possible so as to encourage the correct amount of diffusion in the system if that technique is being used, but also to ensure that as a replacement fluid it does not cause imbalance in the blood chemistry. Therefore to create the correct therapeutic action the chemistry of dialysate fluid does not differ all that much apart from the buffer agent used. There are typically 2 different potassium concentrations, 2 mEq/L and 4 mEq/L. The majority of CVVHD done

without anticoagulation would be with either RFP 400 or RFP 404 (or their B Braun/Duosol counterpart). Additionally, there are 0 calcium solutions that should only be used with regional citrate anticoagulation (RCA). The table below shows a summary of the chemical differences:

	K (meq/L)	Ca (meq/L)	Na (meq/L	Bicarb (meq/L)	Glucose	Use with RCA/ACDA
NxStage: RFP 400	2	3	140	35	100 mg/dL	NO
NxStage: RFP 401	4	2.5	140	35	100 mg/dL	NO
NxStage: RFP 402	0	3	140	35	100 mg/dL	NO
NxStage: RFP 403	2	0	140	35	100 mg/dL	YES
NxStage: RFP 405	4	0	140	35	100 mg/dL	YES
NxStage: RFP 404 (401)	4	2.5 (3)	140	35	100 mg/dL	NO
NxStage: RFP 453	2	0	130	25	100 mg/dL	YES
NxStage: RFP 454	4	0	130	25	100 mg/dL	YES
Duosol: 4552	2	3	140	35	1 g/L	NO
Duosol: 4555	4	3	140	35	1 g/L	NO
Duosol: 4553	2	0	136	25	0	YES
Duosol: 4556	4	0	136	25	0	YES

At Methodist, the dialysate compositions available are RFP 400, 401, 402, 403 & 405.
At St. Luke's, the dialysate compositions available are B Braun Duosol as listed above.
While at the VA, the dialysate compositions vary between both NxStage and B Braun Duosol.

Access:

Recommended Length in cm of temporary catheter:

Right IJ: Height (cm)/10 adequate for 90% of patients
Left IJ: [Height (cm)/10] + 4 adequate for 94% of patients
Femoral access should be between 19-24 cm

Right IJ quinton/mahurkar catheter preferred in acute setting due to less contact with vessel wall and less kinking. KDIGO has weak recommendation of femoral over Left IJ, but patients with higher BMI may have more colonization. Thus, body habitus should be considered.
Catheter recirculation ~5-15% in acute non-tunneled catheters. Femoral catheters have higher recirculation, ranging from 5 to 38% (avg. 20%). Inverting lines or switching ports increases recirculation up to 20-30%.
Can jump to tunneled dialysis catheter (TDC) if expecting 2 or more weeks of use.

Access Alarms:

Elevated Venous/Return Pressure: Kinked blue line or catheter, clot in venous port of catheter, catheter hubbed against vessel wall
Low Venous/Return Pressure: Return line disconnected
Low (High Negative) Access Pressure: Kinked red line or catheter, clot in catheter, catheter hubbed against vessel wall, another catheter aspirating blood from the same site
High (positive) access pressure: arterial cannulation

Ordering Therapies

For CVVHD, you need to specify a blood flow rate/ BFR (typically 200-300 ml/min), an hourly UF rate, dialysate flow rate/DFR (typically 25-35

ml/kg/hr) and dialysate fluid component. Along with lab monitoring, electrolyte replacements and blood pressure management.
A reference dose of 25 ml/kg/hr can be reasonably chosen as the default prescription for CRRT dose in critically ill patients. However, a higher dose than 25 ml/kg/h may be indicated if the target level of a specific solute cannot be achieved. Similarly, a higher dose of CRRT may be required to maintain the acid–base homeostasis or to correct evolving acid–base disturbances. While the default initial CRRT dose recommendation of 25 ml/kg/h applies to the majority of critically ill patients, the CRRT prescription may need individualization and reassessment with appropriate adjustments to achieve adequate fluid, electrolyte and metabolic balance. Early on, septic and post-operative patients are hyper-metabolic and may require more clearance, while later on in the course as treatment progresses.

Prescribed therapy often varies from delivered therapy. Due to interruptions in treatment from alarms, diagnostic testing, procedures, etc. the delivered dose is frequently not the same as the prescribed dose. The monitor can provide you with information regarding the parameters of the therapy without changing any of the prescription. The prescription can only be changed on the machine itself.

A typical order for the different therapies would be:

ORDER	CVVHD	SLED	SHIFT
BFR	200-300 ml/min	100-200 ml/min	200-300 nl/min
DFR	20-35 ml/kg/hr (usually 1.5-3 L/hr)	200-300 ml/min (Ben Taub)	Typically varies between 5-6 L/hr
NET UF	Total net fluid balance goal per hour	Total net fluid balance goal/total amount / est UF goal	Goal number of liters to be removed over the course of treatment (2-4L)
Tx TIME	Continuous	Can range from 6-12 hours/day	Ranges from 6-12 hours/day
MACHINE	NxStage	Standard machine	NxStage

		utilized for IHD	

Electrolyte replacement protocols should be in place with each order along with lab checks. These are protocolized per institution with slight variability. It is important to pay particular attention to phosphorus levels as patients can frequently become hypophosphatemic on continuous therapy. CRRT-induced hypophosphatemia can cause secondary hypoventilation in ventilated patients induced by muscle weakness.
Catheter Packing: heparin (1000 units/ml injection for acute catheter and 5000 units/ml injection for chronic catheter) vs anticoagulant citrate dextrose solution A (ACD-A) injection for patients that cannot tolerate heparin.

Estimating creatinine clearance and drug dosing during CRRT
CRRT clearance = unbound fraction x effluent rate
To estimate creatinine clearance, simply sum the average hourly effluent (UF + delivered therapy fluid dose) and divide by 60 to get estimation in ml/min. For example, a patient with an hourly UF (not net UF) of 200 mL/hour and delivered dose of 2 L/hr has on average 2,200 mL of effluent. Divided by 60 minutes, this comes out to 36.67 mL/min.
For each antibiotic that is primarily cleared by renal route of elimination, take the estimated creatinine clearance and multiply by (1-protein binding capacity (a percentage)) of that antibiotic. Take antibiotic X with a PBC of 20%. In the above example, we would multiply 36.67 mL/min x 0.8 = 29.33 mL/min. Thus, antibiotic X should be dosed for a creatinine clearance of 29.33 mL/min.
Methods for estimating drug clearance for prolonged intermittent renal replacement therapies (like SLED and SHIFT) is not uniformly standardized. Please refer to the practice pattern for that particular institution. Please note that certain antibiotics are not compatible with SHIFT and likely SLED due to difficulties maintaining within therapeutic index. For SHIFT, the VA has a guideline for antibiotic administration. As always, please communicate antibiotic recommendations with primary ICU team and pharmacy.

Anticoagulation

Continuous renal replacement therapy (CRRT) should ideally run with little to no interruption to provide volume control, metabolic (acid-base and electrolyte) control and adequate solute clearance. Typically, CVVHD can be run with no anticoagulation but there are instances where anticoagulation may be required. Two options available to anticoagulate during CRRT are heparin (anticoagulates both filter circuit AND patient) and citrate (anticoagulates only the filter circuit, but NOT the patient).

Heparin anticoagulation is less than ideal due to difficulties maintaining within therapeutic index. Patients on CRRT are dynamic with highly variable pharmacokinetics and critically ill patients often have low antithrombin creating resistance. Acute phase proteins and necrotic cells can bind up heparin. The systemic anticoagulation results in increased bleeding risk and the possibility of HIT. No universally agreed upon protocol exists. Some programs have described using a loading dose of 500-2000 units an additional 500 units/hr targeting an aPTT of 45 seconds.

Regional citrate anticoagulation with ACDA is used to avoid the unnecessary risks of systemic anticoagulation, limit blood loss from premature filter clots, and reduce interruptions in therapy. Many post-operative patients are anemic and at high risk for filter clots. Consider RCA in patients who are at high risk for premature filter clots or if filter lasts less than 24 hours.

Calcium is a necessary co-factor in the clotting cascade. In conjunction with calcium-free dialysate, citrate works by binding calcium regionally (in the circuit only) to ensure that the blood does not clot. Citrate infusions, like Anticoagulant Citrate Dextrose-A (ACDA), are given into the filter circuit and titrated to achieve a low post filter (ionized) calcium in the filter circuit (goal 1-1.4 mg/dL). Calcium MUST be given back to the patient to avoid low systemic (ionized) serum calcium levels/ hypocalcemia. A calcium infusion (usually Ca gluconate) is given continuously to achieve a normal serum free (ionized) calcium level (goal 4.2-5 mg/dL).

Typically sodium citrate complexes are cleared during CVVHD. However, if clearance is reduced or citrate delivery is increased, sodium citrate complexes can end up in the return line and be delivered to the patient leading to hypernatremia and metabolic alkalosis (if hepatic metabolism is not overwhelmed, as the liver converts citrate to bicarbonate). If hepatic metabolism is overwhelmed (as can be the case in a cirrhotic patient or a patient with massive transfusions) metabolic acidosis or citrate toxicity can occur as a result of insufficient metabolism of the sodium citrate complexes. Caution and vigilance should be exercised in patients with liver failure, extreme lactic acidosis, and massive transfusions. Monitoring total calcium to ionized calcium levels (should not be >2.5) can help determine if a patient is experiencing citrate toxicity.
It is important to communicate with nursing if planning to start regional citrate. Ensure that patients have an adequate access for calcium gtt and a line (preferably art line) for systemic ionized calcium draws, and confirm that nursing understands where these infusions are placed.

Ordering Regional Citrate at VA:
INITIAL INFUSION RATES:

Blood Flow Rate (mL/min)	Dialysate Flow Rate (mL/hour)	ACDA (mL/hour)	Calcium Rate (mL/hour)
150	2000	225	75 (1.5 g/hr)

Note: Increasing the blood flow rate necessitates a proportional increase in the ACDA rate. ACDA and calcium are titrated per protocol.

Chapter THREE: Chronic Kidney Disease

Percentage of US Population by eGFR and Albuminuria Category: KDIGO 2012 and NHANES 1999–2006				Persistent albuminuria categories Description and range			
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30mg/mmol	
GFR categories (mL/min/ 1.73m^2) Description and range	G1	Normal or high	≥90	55.6	1.9	0.4	57.9
	G2	Mildly decreased	60–89	32.9	2.2	0.3	35.4
	G3a	Mildly to moderately decreased	45–59	3.6	0.8	0.2	4.6
	G3b	Moderately to severely decreased	30–44	1.0	0.4	0.2	1.6
	G4	Severely decreased	15–29	0.2	0.1	0.1	0.4
	G5	Kidney failure	<15	0.0	0.0	0.1	0.1
				93.2	5.4	1.3	100.0

Chronic Kidney Disease (CKD) is defined as abnormalities of kidney structure or function that are present for >3 months and have health implications. CKD is classified based on cause, GFR category (G1 to G5), and albuminuria category (A1 to A3).

Prognosis and Prevalence of CKD in the United States by GFR and Albuminuria category. Colors reflect the ranking of relative risk for kidney disease progression and cardiovascular risk. Green: Low risk, Yellow: Moderately increased risk, Orange: High risk and Red: Very high risk. Cells how the proportion of adult population in the United states.

The prevalence of CKD is about 11.5% of the U.S adult population**.** Data from National Health and Nutritional Examinations Surveys from 1999-

2006. **(1). KDIGO 2012 Clinical Practice guidelines for the management of CKD. Kidney int Suppl. 2013; 3:1-150.**

Clinical markers of Kidney damage:
1. Albuminuria and albumin to creatinine ratio (ACR): > 30 mg/g (3.4 mg/mmol) or greater.
2. Abnormal Urinary sediment. Such as white or red blood cell and casts.
3. Electrolyte and other abnormalities caused by tubular disorders.
3. Imaging abnormalities. Such as echogenic small kidneys, polycystic kidneys or hydronephrosis.
4. Pathologic abnormalities: Kidney biopsy can reveal glomerular, interstitial or tubular disease.
5. History of kidney transplantation.

Reduced GFR: Glomerular filtration rate (GFR) is generally considered to be the best available index of overall kidney function. Declining GFR is the hallmark of progressive kidney disease that should be reviewed in every patient visit. Measured GFR varies in normal individuals by age, sex, dietary protein intake, and possibly by race-ethnicity. Based upon clearance measurements in healthy people and in people with kidney disease, the widely accepted threshold defining a decreased GFR is less then 60ml/min per 1.73 m^2. Kidney failure is defined as a GFR<15ml/min per 1.73m^2 or treatment by dialysis. (see figure on previous page)**. GFR<60min/min per 1.73 m persistent for 3 months or more is diagnostic of CKD.**
Some elderly individuals have lower GFR (45-59ml/min per 1.73 m^2) with no other evidence of kidney damage. These people have only moderately increased risk of CKD progression. They likely need no treatment but should be monitored closely.

Etiology of Chronic Kidney Disease:

The most common reported causes of CKD are diabetes mellitus and hypertension, less frequent causes are primary glomerular, tubulointerstitial, and cystic diseases.

Risk factors for CKD development or progression:
Non-modifiable: Old age, male sex, black race, family history of DM or CKD, APOL 1 allele and low birth weight.
Modifiable: Albuminuria, hypertension, episodes of AKI, underlying cause of kidney disease (e.g diabetic nephropathy), obesity, hyperlipidemia, smoking, high protein diet, metabolic acidosis, hyperphosphatemia, hyperuricemia, hyperglycemia and elevated plasma soluble urokinase receptor (suPAR).
1. Hypertension: Hypertension is a known risk factor for progressive GFR decline. Multiple risk factor intervention trial (MRFIT) and African American Study of Kidney Disease (AASK) trial showed elevated blood pressure as a risk factor for progression of non-diabetic kidney disease.
2. Albuminuria: Is an independent risk factor in both diabetic and non-diabetic kidney disease. Modification of diet in renal disease study (MDRD) showed in a population that is predominantly non diabetic, those with albuminuria had the highest risk of progressive kidney disease. The Ramipril Efficacy in Nephropathy (REIN) trial also showed similar results.
3. Recurrent AKI: Multiple studies have shown that in patients with preexisting CKD, AKI is risk factor for development of progressive chronic kidney failure. **(2) JAMA 1997 Dec 17;278(23):2069-74; (3) *JAMA* 2002. 288(19):2421-2431; (4) N Engl J Med 1994; 330:877-884; (5) *Lancet* 1997; 349:1857-1863.**

Management of Chronic Kidney Disease:
Detection: Screening not recommended in general population but accepted in those at high risk. Reasonable approach to CKD testing, at minimum includes, eGFRcr and urine Albumin to creatinine ratio. Test all patients with hypertension, diabetes, CVD, cancer, HIV infection, and before

imaging procedures with iodine based or Gadolinium based contrast. Need for other testing including urine analysis or imaging depends on the nature of risk factors. Limited data on optimal testing frequency for CKD screening in high-risk patients. Annual testing is recommended for patients with hypertension, diabetes and HIV. Until evidence is available, others at increased risk be tested at least every 3 years.

Evaluation: Goals of evaluation are 1) to identify the duration and cause of CKD, 2) to assess severity based on GFR and albuminuria, 3) to identify the complications and risk of progression to kidney failure. Evaluation includes thorough history and physical exam and laboratory testing and imaging studies. Patient with GFR < 60ml/min per 1.73 m^2 should have assessment of *hemoglobin, serum calcium, phosphate, albumin, parathyroid hormone and 25 hydroxy vitamin D levels.* Test for traditional risk factors for CVD, such as lipid panel, insulin resistance and inflammation. Evaluate for symptoms of CVD or detect asymptomatic CVD in patients with multiple risk factors. Some elderly individuals have eGFR <60 ml/min per 1.73 m^2 but no other risk factor or marker of CKD. Extensive evaluation of etiology of CKD may be deferred in these cases but close monitoring is appropriate.

Measure	CATEGORIES		
	Normal to Mildly Increased	**Moderately Increased**	**Severely Increased**
AER (mg/24 hours)	<30	30–300	>300
PER (mg/24 hours)	<150	150–500	>500
Albumin-to-Creatinine Ratio			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
Protein-to-Creatinine Ratio			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Negative to positive	Positive or greater

Evaluation of duration: Per KDIGO, kidney dysfunction of less than 3-month duration is termed as Acute Kidney disease and 3 month or greater is CKD.
Evaluation of cause: A simplified system to classify kidney disease by anatomic location: Glomerular, vascular, tubulointerstitial, and cystic and congenital diseases. Cause may remain unknown (e.g. CKDu).
Evaluation of GFR: KDIGO recommends initial evaluation with eGFRcr, followed by confirmatory test if required. Use CKD-EPI 2009 equation for estimation of GFR. Confirmatory tests include measurement of clearances of exogenous filtration markers or creatinine clearance, or eGFR based on serum cystatin C with or without serum creatinine. Following is the online link to estimate eGFR online using CKD-Epi 2009 equation.
https://www.kidney.org/professionals/kdoqi/gfr_calculator
Evaluation of albuminuria: KDIGO recommends initial evaluation with spot urine ACR, followed by confirmatory test. Alternate initial evaluation can include spot urine total protein-to-creatinine ratio (PCR) and urine dipstick. Early morning specimen is preferred. Confirmatory test: Timed urine collection for measurement of albumin excretion rate.

Albuminuria and Proteinuria Measures:

AER=Albumin excretion rate, PER=Protein excretion rate.
Treatment and Prevention of CKD progression:
Goal of therapy is to slow or reverse the vicious cycle of Renin Angiotensin-Aldosterone system (RAAS) activation, glomerular and systemic hypertension, proteinuria, inflammation and progressive fibrosis. In addition, therapies to target the modifiable risk factors have been developed**.**

1. Antagonism of Renin-Angiotensin-Aldosterone System (RAAS). RAAS blockage by using ACE inhibitors or Angiotensin receptor blockers

dilate the efferent arteriole, lead to glomerular relaxation and subsequent reduction in glomerular hypertrophy and injury. RAAS blockage also mediates improvement in systemic hypertension and impairs the inflammatory and fibrosing effect of various cytokines, including TGF-B. Net effect of RAAS blockage are hemodynamic, antifibrotic and antiproteinuric.

Reno-protective effects of RAAS inhibition have been shown in Diabetes mellitus type 1 and 2 in various clinic trials. The effect of ACE inhibition on diabetic nephropathy, Irbesartan for Microalbuminuria in type 2 DM (IRMA- 2) trial, Irbesartan diabetic nephropathy trial (IDNT) and Losartan (RENAAL) trial. Similar results have been seen in non-diabetic kidney disease: A metanalysis by Jafar etal. In non-proteinuric and nondiabetic nephropathy, the data for use of RAAS blockage are not as strong.
(6) N Engl J Med 1993; 329:1456-1462; (7) N Engl J Med 2001;345: 851-860; (8) N Engl J Med 2001; 345:870:878; (9) N Engl J Med 2001;345:861-869; (10) Ann Intern Med.2003;139:242-252.

2. Blood Pressure Control:

BP goals vary in various guidelines but optimally should be less than 130/80 per most recent ACC/AHA guidelines. In SPRINT trial, non-diabetic patients were assigned to either standard (140) or intensive (120) systolic BP control. Data showed a 27% relative risk reduction mortality in intensive arm. This benefit extended to patients with CKD, although there were more electrolyte imbalance and AKI in intensive arm **(11) Hypertension 2017;71: e13–e115. (12) N Engl J Med 2015; 373:2103-2116**

3. Lifestyle Modification:

A Low (2.4gram) sodium, low fat, and moderately low protein (0.8-1.0g/kg of body weight) diet per day is recommended. Preexisting albuminuria decreases with weight loss. Hyperlipidemia is a risk factor for CKD progression that improves with physical activity and weight loss.

4. Cardiovascular risk reduction:

Leading cause of death in CKD is cardiovascular disease (CVD). CVD has many manifestations in individuals with CKD including atherosclerotic and stiff vessels with resultant ischemic heart disease and heart failure and structural changes like left ventricular hypertrophy and valvular diseases. CVD risk is increased in all stages of CKD. Reduced GFR and albuminuria with or without GFR reduction are strong predictors of CVD risk. *Hypertension, sodium and volume retention, anemia, hyperphosphatemia, DM, vascular disease and electrolyte imbalance including hyperkalemia are all reported risk factors*. Cardiovascular risk reduction with life style modification, *smoking cessation, aspirin use, and pharmacological treatment of hypertension, dyslipidemia, albuminuria and hyperglycemia is recommended.*

5. Nutrition in Chronic Kidney disease:

Protein energy wasting (PEW), a state of decreased body stores of proteins and energy fuels, is common in individuals with CKD. Dietary protein restriction has small but real effect on progression of CKD. (eGFR 0.5ml/min per year benefit). Maintenance dialysis patients have high dietary protein requirement because of increased metabolic stress associated with dialysis therapy. Serum albumin and prealbumin levels are good laboratory markers of nutritional status.

Recommended intakes of Protein, Energy, and Minerals in Kidney Disease

	Protein	Energy	Phosphorus	Sodium
Chronic Kidney Disease				
Stages 1–3	No restriction	No restriction	600–800 mg/day	<2 g/day[a]
Stages 4–5	0.60–0.75 g/kg/day[b]	30–35 kcal/kg/day[c]	600–800 mg/day[d]	<2 g/day
Dialysis				
Hemodialysis	>1.2 g/kg/day	30–35 kcal/kg/day[c]	600–800 mg/day[d]	<2 g/day
Peritoneal dialysis	>1.3 g/kg/day	30–35 kcal/kg/day[c]	600–800 mg/day[d]	<2 g/day
Acute Kidney Injury				
No dialysis	1.0–1.2 g/kg IBW/d	30–35 kcal/kg/day	600–800 mg/day[d]	<2 g/day
Dialysis	1.2–1.4 g/kg IBW/d	30–35 kcal/kg/day	600–800 mg/day[d,e]	<2 g/day

Potassium intake: Stage 1-3: no restriction. Stage 4-5: <2 grams/day.

Foods high in potassium: Fruits: Mango, Orange, Apricots and Bananas. Vegetables: Potatoes, tomatoes, dried beans, Broccoli, kale, mushroom and spinach. Other: Bran, chocolates, milk and milk products and nuts.

Foods high in phosphorous: Colas, beer, milk and mild products, chocolate, dried fruits, beef and calf liver, beef, pork, legumes, nuts with seeds and whole grains.

Vitamins: No vitamin A supplementation. Vitamin E and K not routinely supplemented. Water-soluble vitamins supplementation recommended using CKD specific multivitamins.

(13) Am J Kidney Dis. 2000;35: S1:S140.

6. CKD Mineral and Bone Disease (CKD-MBD)
CKD alters the regulation of calcium, phosphate and vitamin D homeostasis leading to secondary hyperparathyroidism, elevated Fibroblast Growth Factor 23 (FGF23), metabolic bone disease, soft tissue calcifications, and other metabolic derangements that have significant impact on morbidity and mortality.

Pathogenesis: Decrease in GFR leads to decrease phosphorous excretion which increases the FGF23 levels. FGF23 suppresses the renal and extra renal 1,25 (OH)2D (Calcitriol) production and promotes phosphorous excretion by inhibition of sodium-dependent phosphorous absorption.
Parathyroid hormone (PTH) concentration rises in increments as GFR declines. PTH increase calcium reabsorption in the distal tubule of nephron and increase bone resorption to increase efflux of calcium and phosphorous. PTH also increase production of Calcitriol via stimulation of Cyp27b1 enzyme. Net effect is to maintain serum calcium concentration in normal or near normal range.
Calcitriol acts on the vitamin D receptor (VDR) in the intestine and promotes calcium and phosphorous absorption. Serum calcium acts on the calcium sensing receptor (CaSR) located on the Parathyroid gland to suppress PTH secretion.

Histological Classification of Bone Disease in CKD:
Classification adopted by KDIGO focuses on turnover, mineralization and volume (TMV).
1. Secondary hyperparathyroidism (high turnover bone disease or osteitis fibrosa).
2. Osteomalacia. (Defective mineralization).
3. Mixed uremic bone disease. (Mixture of high turnover bone disease and Osteomalacia).

4. Adynamic bone disease (Decreased rate of bone formation without mineralization defect).

Clinical manifestations of bone disease associated with CKD:
1. Musculoskeletal: Fractures, tendon rupture and bone pain, muscle pain and weakness. Incidence of hip fracture 4.4-fold increase in patients undergoing dialysis.
2. Extra skeletal: Coronary and peripheral vascular calcifications, Calcemic Uremic Arteriolopathy (CUA) or Calciphylaxis. Increased cardiovascular and all-cause mortality.

Diagnosis of Bone disease with CKD:
1. Biochemical parameters. Serum Parathyroid hormone level is used as a marker of the bone turnover activity. Defining the target PTH level in CKD remains a challenge. Because of end-organ hypo responsiveness to PTH, the recommended target PTH levels are greater then the upper limit of normal. Acceptable PTH target ranges for intact serum PTH are 35-70 pg/ml, 70-110pg/ml and 150-300pg/ml for CKD stage 3,4 and 5 respectively. Due to lack of standardization of PTH assay, KDIGO prefer to define PTH target as 2-9 time the upper limit of upper limit of normal in ESRD patients.
2. Bone Biopsy: Gold standard is iliac crest bone biopsy with double tetracycline labeling. Consider performing in setting of atraumatic fracture with no clear etiology, suspected aluminum toxicity, before parathyroidectomy in patients with musculoskeletal symptoms and/or hypercalcemia, with intact PTH levels (100-500pg/ml) , and to exclude adynamic bone disease before initiation of antiresorptive therapy.
3. Imaging: Radiographic findings from osteoblast activity due to elevated PTH can cause 'Rugger-Jersey spine' on radiography. Osteoclast mediated bone resorption can cause cortical thinning and subperiosteal, intracortical, and endosteal bone resorption. DEXA scans are recommended to measure the bone mineral density in patients with CKD 3-5 with evidence of CKD-MBD and/or risk factors for osteoporosis.

Treatment of Mineral and bone disorder in CKD:
Treatment is directed toward normalizing serum calcium, phosphate, PTH and metabolic acidosis
1. Controlling serum phosphorus: Dietary phosphorus restriction to (800-1000 mg/day) is difficult to attain but should be initiated in all CKD patients. Per KDIG) 2017 guidelines, serum phosphorus level goal in CKD G3a-G5 is return to normal range (2.5-4.5 mg/dl).
Phosphorus binder's choice depends on binder's efficacy, side effects and cost.
Calcium containing binders: Calcium carbonate and calcium acetate. They are best ingested with food to maximize binding of ingested phosphorous in the gut. Side effects include increase risk of hypercalcemia and vascular calcifications. They are low cost option, but use is out of favor due to calcification risk.
Non-Calcium containing binders:
Sevelamer *(800-3200 mg TID)* contains cross-linked polyallylamine hydrochloride. It is an ion exchange polymer which binds phosphorous in the gut. It also decreases serum cholesterol and LDL levels and increase HDL. It is more costly and causes some gastrointestinal side effects. ***Lanthanum*** *(1500-3000 mg tid)* is a trivalent cation with an ability to chelate dietary phosphate, but low systemic absorption. It can cause mild gastrointestinal side effects.
Aluminum *(Amphogel 300-600 mg PO tid)* containing phosphate binders are most effective binders but increase systemic aluminum absorption that can cause neurologic, hematologic, and bone toxicity. It should be used only for short term (<4 weeks) for sever refractory hyperphosphatemia.
Iron containing binders: **Sucroferric Oxyhydroxide** *(1500-2000 mg/day divided TID)* and **Ferric Citrate** ***(****1gram tab, 6-9 tabs/day divided TID)* have recently become available. They have the dual advantage of phosphate chelation and iron supplementation. Data on patient-centered outcomes are not yet available.

2. Activating the Calcium-Sensing and Vitamin D receptors to suppress PTH hyperfunction:

Vitamin D Analogues: Treatment with 1, 25(OH2)D3 (Calcitriol) or an activated vitamin D analogue (Paricalcitol, Deoxicalciferol, Alfacalcidol, or 22-Oxacalcitrol) is a means of controlling secondary hyperparathyroidism. By binding to VDR on parathyroid tissues, with vitamin D analogue suppress PTH production. These can be administered orally or intravenously. *Current guidelines suggest correcting vitamin D deficiency and insufficiency defined by 25 (OH) D3 levels below 20 and 30 ng/ml, respectively with treatment strategies recommended for general population.*

Use Ergocalciferol 50,000IU q weekly for 8-12 weeks to replete 25(OH)vitamin D levels. Once replete (>30ng/ml). Change dose to q monthly or use OTC Cholecalciferol 2,000IU q daily.

For secondary Hyperparathyroidism in CKD: *Use Calcitriol 0.25-1mcg po once daily if PTH above target replete and serum phosphorus level well controlled*.

Calcimimetics: They are CaSR agonists that act on the parathyroid gland by allosterically increasing the sensitivity of the receptor to calcium. **Cinacalcet,** approved by FDA in 2004 to treat secondary hyperparathyroidism in patients with stage 4 CKD. It decreases serum PTH without increasing serum calcium or phosphorus levels. Recently, another Calcimimetic, **Etelcalcetide**, has been approved by FDA which is an intravenous drug proved to be superior to Cinacalcet in reducing PTH concentrations among patients on hemodialysis.

Cinacalcet 30-180 mg po once daily. Use if PTH above target goal with optimal treatment with phosphorous binders and activated vitamin D.

3. Parathyroidectomy:

Parathyroidectomy should be considered for persistently elevated PTH levels associated with hypercalcemia and/or hyperphosphatemia despite medical management and for CUA or bone pain and fractures in the presence of elevated PTH. Either a subtotal parathyroidectomy or total parathyroidectomy with forearm gland implementation can be performed.

Percutaneous ethanol injection is another option that can be performed if surgical resection not chosen. Hungry bone syndrome is a frequent complication of parathyroidectomy especially with markedly elevated PTH and is characterized by hypocalcemia, hypophosphatemia and hypomagnesemia secondary to increased bone uptake. Treatment with intravenous calcium may be necessary. Concomitant oral calcium replacement before or after surgery reduce the risk.

Patients with stage 3 and 4 CKD:

Phosphate restriction, phosphate binders and calcium supplementation are the mainstays of treatment in stage 3 and 4. Metabolic acidosis cause an efflux of calcium from the bone as bone hydrogen ions with carbonate release. Chronic metabolic acidosis should be treated with sodium bicarbonate supplementation. Stage 3 and 4 CKD patients with vitamin D deficiency should be supplemented with Ergocalciferol or Cholecalciferol. Activate vitamin D analogues in stage 3 and 4 are generally not recommended due to risk of hypercalcemia. KDIGO recommends use of Calcitriol or vitamin D analogues in patients with CKD 4 and 5 be reserved for only severe and progressive secondary hyperparathyroidism. Calcimimetics are not approved for use in CKD 3 and 4 patients. Bisphosphonates are not used in CKD 3-5 as they may exacerbate kidney failure.

7. Anemia of Chronic Kidney Disease:

The incidence of anemia in CKD stage 1 and 2 is less than 10%, 20-40% in CKD 3, 50-60% in CKD 4 and more than 70% in CKD 5 as per population based NHANES and PAERI studies. **(14) N Engl J Med. 1998;339:584-590. (15) N Engl J Med. 2008;358:433-444.**

Pathogenesis: It is multifactorial and important causes include insufficient production of endogenous Erythropoietin (EPO), iron deficiency, acute and chronic inflammation, severe hyperparathyroidism, aluminum toxicity, folate deficiency, decreased RBC survival and RBC loss. The contribution of erythropoietin deficiency becomes greater as GFR declines.

Erythropoietin is produced by kidney in response to hypoxia inducible factor (HIF). HIF is produced in response to low oxygen delivery to the kidneys. In CKD, kidney is unable to increase EPO production in response to anemia.
Hepcidin is a peptide produced by liver which is upregulated by IL-6 and iron overload and downregulated by TNF-alpha and iron deficiency. It inhibits iron transport across cell membrane, trapping it in the macrophages and preventing it from being absorbed across the intestine. Hepcidin contributes more to anemia in patients with CKD when inflammation and infection are present.
Clinical manifestation: Major clinical manifestations are fatigue, decrease cognitive decline, loss of libido, decrease sense of well-being and anginal symptoms in patient with CAD. Symptoms tend to occur with Hgb <10gm/dl. Persistent anemia can lead to left ventricular hypertrophy (LVH) which strongly correlates with increase hospitalization and mortality in CKD patients.
Laboratory Evaluation: KDIGO 2012 clinical practice guidelines recommend at least annual screening for patients with CKD3 and more frequently with advanced CKD. In those with diagnosed anemia not on treatment, Hgb concentration should be measured at least every 3 months in CKD stage 3 to 5 and monthly in patients on dialysis.
Evaluation should include a *complete blood count including RBC indices, reticulocyte count, serum ferritin and transferrin saturation (TSAT) or reticulocyte Hb content (CHr).* Anemia of EPO deficiency is normochromic and normocytic. Serum ferritin correlates with iron bound to tissue ferritin in reticuloendothelial system. Serum ferritin is an acute phase reactant. TSAT is a measure of circulating iron available for delivery to erythroid marrow. In absolute iron deficiency, serum ferritin level is <25 ng/ml in men and <12 ng/ml in women. In functional iron deficiency, TSAT is <16% with normal or elevated serum ferritin levels. Functional iron deficiency is either due to increase iron demand by erythroid marrow or action of hepcidin in setting of inflammation or infection. In CKD, anemia patients often respond to iron supplementation with considerably higher serum ferritin and TSAT levels.

Reticulocyte count can be used to distinguish anemia due to under production or increase RBC loss. Routine testing for EPO level in anemic patients with CKD is not recommended as it is expensive and does not guide in treatment.

Erythropoietin-Stimulating Agents (ESA) available in USA:

1. Epoetin (Epogen, Procrit). *Starting dose: 50 units/kg based on 3 times/weekly doing. 3 times weekly IV in HD patients, every 1-2 weeks SC in CKD-non dialysis and PD patients.*

2. Darbepoetin (Aranesp). *Starting dose 0.45 mg/kg weekly or 0.75 mg/kg every 2 weeks in ESRD patients, 0.45 mg/kg every 4 weeks in CKD-non dialysis.*

3. Methoxypolyethylene glycol epoetin beta (Mircera). *0.6 ug/kg every 2 weeks; monthly when Hb is stable at twice every 2-week dose. IV in HD patients, SC in ND-CKD and PD patients.*

Target Hemoglobin level: 2012 KDIGO clinical practical guidelines for anemia of CKD suggest:

1. For adult CKD non dialysis patient with Hgb <10g/dl, decision to initiate ESA is individualized based on rate of fall of Hgb, previous response to iron therapy, risk of needing transfusion, risks related to ESA therapy, and presence of symptoms attributable to anemia.
2. For adult CKD patients, on dialysis, it is suggested that ESA therapy e used to avoid having Hgb concentration fall below 9 gm/dl by starting ESA when Hgb is 9 to 10 g/dl. Individualization of therapy is reasonable as some patients have improvement in quality of life (QoL) at higher Hb concentration, and ESA therapy may be started above 10gm/dl.
3. In general, it is suggested that ESAs are not used to maintain Hgb concentration above 11.5 g/dal in adult patients with CKD. Individualization of therapy may be necessary as some patients experience improvement in QoL at Hb >11.5 gm/dl and will be prepared to accept the risks.
4. In all adult patients, it is recommended that ESAs not be used intentionally to increase the HB >13gm/dl.

Iron deficiency and treatment: 2012 KDIGO anemia guidelines recommend a trial of IV iron (or 1 to 3 months trial of oral iron in non-dialysis patients) for adult CKD patients with anemia not on iron or ESA therapy if an increase in Hb concentration without starting ESA therapy is desired, TSAT is <30%, and ferritin is <500ng/ml.
For those CKD patients receiving ESA therapy not receiving iron supplementation, a trial of IV iron (or a 1 to 3 months trial of oral iron in non-dialysis patients) is recommended if an increase in Hb concentration or decrease in ESA dose is desired, TSAT is <30% and ferritin is <500ng/ml. Guidelines consider the evidence to be insufficient to recommend a serum ferritin ceiling above which IV iron must be withheld but rather to weight the risks and benefits of IV iron therapy.

Available iron preparations:
Oral preparations should be given 1 hour before or 2 hours after meals. The minimum required dose to iron deficiency is 200 mg of elemental iron daily. The bioavailability of oral iron salts is 1 to 2% only in a patient with elevated ferritin. Common available preparations include ***Ferrous sulfate*** *325 mg (65 mg elemental iron) tablet 3 times per day,* ***Ferrous fumarate*** *325 mg (100 mg elemental iron) tablet 2 times per day,* ***Ferrous gluconate*** *325 mg (30 mg elemental iron) tablet 5 to 6 tablets per day and oral polysaccharide-iron complex 150 mg capsule (150 mg elemental iron) twice per day.*
Intravenous preparation includes *Iron dextran (**Dexferrum**) 1000 mg in 10 divided doses or as 1 single dose IV, Iron sucrose (**Venofer**) 1000 mg in 3-10 divided doses, Iron gluconate (**Ferrlecit**) 1000 mg in 8 divided doses (Hemodialysis only),* ***Ferumoxytel*** *(Feraheme) 510 mg 2 doses and Ferric Carboxymaltose (**Injectafer**) 750 mg 2 doses.*
Iron dextran is least expensive and can be given as 1 large dose of 1000 mg but is associated with fatal anaphylactic reaction leading to black box warning by FDA and require a test dose of 25 mg at time of first administration. Iron sucrose and Iron gluconate are preferred in hemodialysis

patient as they require multiple doses (max 250-300 mg per session) but are not associated with fatal anaphylaxis.

ESA resistance and adjuvant therapy: *ESA resistance has been defined as failure to achieve Hb greater than 11g/dl despite an epoetin dose of greater than 500 units/kg per week or the equivalent of another ESA.*

The causes of ESA resistance are the same as the causes of anemia in CKD except for EPO deficiency and with addition of pure red cell aplasia. After iron deficiency, the most common cause of ESA resistance in patient with CKD is inflammation/infection. For patient who have not responded adequately over a 12-week period of escalating ESA dose, the FDA recommends that increasing the dose further is unlikely to increase response and may increase risk. For CKD patients not on dialysis, the Epoetin dose ceilings of 300 units/kg per week (or the equivalent of another ESA) and for those on dialysis the dose ceiling is 450 units/kg per week. There is insufficient evidence to support the use of adjuvants, such as L-carnitine and vitamin C and Androgens. Blood transfusions are considered last resort and there is no single Hb concentration level that necessitates transfusion. The decision should be made based on patient's individual situation.

Abnormalities of Hemostasis: Include increase bleed tendency secondary to platelet dysfunction. Treatment for bleeding episodes in uremic patients is to provide adequate dialysis and give Desmopressin (DDAVP). Dose is 0.3 ug/kg IV or 3 ug/kg intranasally, repeat 1 to 2 times before tachyphylaxis develop.

8. Acid-Base balance in CKD: Acid-base balance is normally maintained by the renal excretion of the daily acid load (approximately 1 mEq/kg per day, derived mostly from the generation of sulfuric acid during the metabolism of sulfur-containing amino acids). Elimination of this acid load is achieved by the urinary excretion of hydrogen ions, both as titratable acidity and as ammonium. I had not noticed before, but there is no need to number the references. **(16) Kidney Int Suppl. 2005;**

Development of Metabolic acidosis: Metabolic acidosis can develop as a result of one or more of the following pathophysiologic processes. Increased production of nonvolatile acids, increased loss of bicarbonate and decreased renal excretion of acid. As the number of functioning nephrons declines in CKD, acid excretion is initially maintained by an increase in the ammonium excreted per nephron. However, total ammonium excretion begins to fall when the glomerular filtration rate (GFR) is below 40 to 50 mL/min. As a result, CKD leads to retention of hydrogen ions and development of metabolic acidosis. **(17) J Clin Invest. 1965 Apr; 44:495-506.**

Consequences of Metabolic acidosis: Chronic metabolic acidosis in patients with CKD may produce a variety of pathophysiologic changes including bone resorption and osteopenia, increased muscle protein catabolism, aggravation of secondary hyperparathyroidism, reduced respiratory reserve and exhaustion of body buffer systems, resulting in increased severity of acute intercurrent illnesses, reduced Na^+-K^+-ATPase activity in red blood cells and myocardial cells, which could impair myocardial contractility and produce heart failure, endocrine disorders such as resistance to growth hormone and insulin, and hypertriglyceridemia, systemic inflammation and hypotension and malaise.

Association with progression of CKD: Observational studies in patients with non-dialysis dependent CKD have found that lower serum bicarbonate concentrations, higher net endogenous acid production, high dietary acid load, and inability to excrete acid are all associated with a higher risk of progressive renal function loss. **(18) Kidney Int. 2011;79(3):356, (19) Nephrol Dial Transplant. 2009 Apr;24(4):1232-7, (20) Am J Kidney Dis. 2013;62(4):670. (21) Am J Kidney Dis. 2009 Aug;54(2):270-7.**

Potential Mechanism of Progression of CKD: Exact mechanism is unknown**.** it may be due at least in part to the adaptive response of surviving nephrons to the loss of their neighboring nephrons. Metabolic acidosis promotes an adaptive increase in ammonium excreted per nephron, which is associated with activation of the complement system, the renin-angiotensin

system, and with increased renal production of endothelin-1, all of which may produce tubulointerstitial inflammation and chronic damage to the kidney. **(22) Kidney Int. 2009 May;75(9):929-35. (23) J Am Soc Nephrol. 2009;20(9):1869.**

Therapeutic approach: Per 2013 Kidney Disease Improving Global Outcomes (KDIGO) guidelines, in patients with CKD and metabolic acidosis, alkali therapy (usually with sodium bicarbonate) be used to maintain the serum bicarbonate concentration in the normal range (> 22: 23 to 29 mEq/L). Alkali therapy usually consists of sodium bicarbonate or sodium citrate (citrate is rapidly metabolized to bicarbonate), typically in a dose of 0.5 to 1 mEq/kg per day. Sodium citrate should be avoided in patients also taking aluminum-containing antacids. Bicarbonate supplementation appears to slow the progression of CKD. The best evidence come from this trial of 134 patients with CKD 4. (**24) Kidney Int Suppl (2011). 2013;3(1):73. (25) J Am Soc Nephrol. 2009;20(9):2075.**

Choice of Therapy:

1. Sodium Bicarbonate 650-1300 mg 2-4 times/day. Adjust dose based on serum bicarbonate levels. Common side effects: Bloating, flatulence, edema and hypernatremia.

2. Sodium Citrate (Oracit): 10-30 ml 3-4 times/day. (Citrate is rapidly metabolized to bicarbonate). Cause less bloating. May increase aluminum absorption in patients taking aluminum containing antacids.

Other treatment options include calcium citrate, calcium acetate or calcium carbonate. A small study in CKD 4 patients showed dietary modification to increase fruits and vegetables increase serum bicarbonate levels above baseline. A novel met hod to increase serum bicarbonate is the oral administration of nonabsorbable hydrochloric acid binders. However, such diets are high in potassium. The specific regimen should be individualized based upon patient tolerance, affordability, and individual comorbidities and biochemical characteristics. **26. Clin J Am Soc Nephrol. 2013;8(3):371. 27. Clin J Am Soc Nephrol. 2018;13(1):26**

Chapter FOUR: Miscellaneous Topics

Disclaimer: The following is meant as a study guide. Evidence/society-based guidelines/sources should be consulted for decisions on patient care.

Cystic diseases

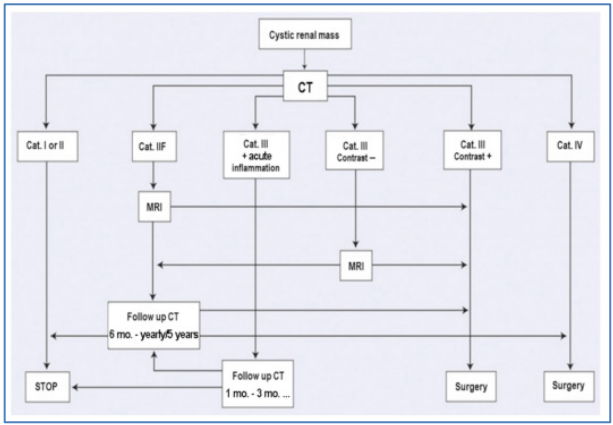
1. Acquired cystic disease in the adult. Defined by involvement of both kidneys, with ≥ 4 cysts, without family history, with normal smooth contour kidneys. No extrarenal cysts.

a. Pathogenesis not well defined. Risk factors include severe chronic hypokalemia, chronic kidney disease, genetic changes (proto-oncogene activation/growth factors leading to tubular hyperplasia/cyst formation).

b. Screening u/s for ESRD pt on HD >3 years without a limited life expectancy is recommended. Involved urology for Bosniak class 3≥ III.

c. Bosniak classification - Diagn Interv Imaging. 2018 Apr;99(4):189-218.

Category	CT features	Diagnosis (risk of malignancy)
Bosniak I	Water attenuation (from −5 to +15 HU) Homogeneous Smooth margins without perceptible wall Non-enhancing (attenuation increase < +10 HU)	Simple cyst (0%)
Bosniak II	A few (1–3) thin septations Thin calcification of the wall or septation Hyperdense cyst (> +50 HU) [a] (small and subcapsular) Non-enhancing (attenuation increase < +10 HU) or moderate enhancement of septations	Complicated cyst (0%)
Bosniak IIF	Multiple thin septations (> 3) Thin (< 1 mm), just perceptible wall (not measurable) Thick calcification Large (> 3 cm) hyperdense lesion [a] or intraparenchymal localization Non-enhancing (attenuation increase < +10 HU) or moderate enhancement of septations or hairline-thin wall	Complicated and multilocular cyst Cystic tumor (cystic cancer, cystic nephroma or MEST) (5–15%)
Bosniak III	Numerous thick septations Uniform grossly (measurable) or slightly irregular thick wall Thick and/or irregular calcifications Enhancement of wall or septations	Complicated cyst Cystic tumor (cystic cancer, pseudocystic necrotic cancer, cystic nephroma or MEST) (50–60%)
Bosniak IV	Thick, very irregular wall Mural nodule(s)/solid tissue elements Enhancement of wall or nodules	"Cystic" cancer Pseudocystic necrotic cancer mixed epithelial and stromal tumor (MEST) (90–100%)



2. APKD

a. 76% of families with ADPKD have mutation on chr 16 (PKD1), others on chr 4 (PKD2) or undefined mutation.

b. Screening recommendations for patients with positive family Hx vary by age and risk – see recommendations.

c. Ultrasound imaging typically first line. For patients with families of unknown genotype:

   i. 15-39 years, ≥ 3 unilateral or bilateral cysts.

   ii. 40-59 years, 2 cysts in each kidney.

   iii. 60 years or older, 4 cysts in each kidney.

   iv. Gene sequencing may be useful when the imaging results are equivocal or when a definitive diagnosis is required.

v. Based on age, total kidney volume, disease progression rate and Cr, vaptan may be used – requires authorized provider and prescribing program.
vi. Google "Mayo image classification ADPKD" for calculator.
vii. TEMPO – Pts with eCrCl > 60 mL/min + TKV >750 mL, tolvaptan reduced: annual increase in TKV, annual decline in eGFR, rate of renal decline at 4 years, and rate of kidney pain.
viii. REPRISE – Age 18-55 with eGFR 25-65, age 56-65 with eGFR 25-44. Tolvaptan lowered eGFR decline at 12 months (-2.34 cc/m/1.73m^2 vs -3.61 cc/m/1.73m^2.

3. Medullary sponge kidney - <1% population, common in patients <20 years of age with recurrent calcium nephrolithiasis.
a. Usually incidental finding on imaging – typically benign, but complications of recurrent obstruction/infection leading to CKD/ESRD. May also have flank pain without stones.
b. Multiple factors for stone formation – hypercalciuria, hypocitraturia, hyperuricosuria and hyperoxaluria (24 hour collection)
i. Forms calcium phosphate crystals in cysts that are seeds for stone formation
ii. Hematuria, nephrolithiasis and nephrocalcinosis.
iii. Decreased concentrating ability and bone mineral density.
c. Definitive diagnosis with either IVP or multidetector-row CT w/ contrast – although not typically done given risks and usual benign course of disease.
4. Various genetic disorders
a. Autosomal dominant tubulointerstitial kidney disease (ADTKD)
i. Rare, 500 families in USA affected. Slow, progressive renal disease starting in teens – prog. To ESRD between 30-50. Bland sediment, minimal proteinuria.
ii. Causes:
1. ADTKD-UMOD mutation (uromodulin), above + gout. 70% of cases.

2. ADTKD-REN mutation (renin). Above + low-norm BP, anemia. 5% of families
3. ADTKD-MUC1 mutation (mucin1). Above no gout or anemia. 30% cases.

b. Autosomal recessive tubulointerstitial kidney disease (ARTKD) AKA nephronophthisis.
   i. Mutations in parts of ciliary apparatus (centrosome, cilia, basal bodies)
   ii. Pts with polyuria/polydipsia, impaired concentrating, bland sediment, and progress to ESRD in childhood.
   iii. 20% have extrarenal manifestations – retinitis pigmentosa, hepatic fibrosis, skeletal defects.

c. Steroid resistant NS/FSGS
   i. European-descent adolescents with sporadic - for genetic screening start with screen for P.R229Q variant of podocin (NPHS2) before sequencing entire gene. Present in 6% of cases, OR for homozygous variant individuals is 7.4.
   ii. Inherited – INF3, inverted formin 2 mutation is autosomal dominant, must have positive family history.

d. Alport Syndrome – hematuria, CKD, lenticonus, bilateral sensorineural hearing loss
   i. Traditionally is X-linked COL4A5 affecting males, female carriers usually with mild disease.
   ii. Autosomal recessive homozygous COL4A3 or COL4A4 mutations
      1. Men and women affected similarly – same disease as X-linked
      2. A single mutation would cause thin basement nephropathy with hematuria, preserved renal function.
   iii. Autosomal dominant heterozygous COL4A3 or COL4A4 mutations
      1. Men and women affected similarly – very mild disease showing in adulthood with great variability among relatives.

e. Autosomal dominant hypocalcemia is due to mutation in calcium sensing receptor.
f. Pendrin – anion exchanger (Cl/HCO3) – mutation leads to autosomal recessive Pendred syndrome with hearing loss, goiter, but no electrolyte abnormalities at baseline.
g. Autosomal dominant DI - accumulation of misfolded ADH precursors in neurons ER -so called toxic gain of function (linked to 40 mutations of AVP-NPII gene). Develops several years after birth. The normal pituitary bright spot on MRI is initially preserved, but eventually lost as the disease progresses over time.
h. Tuberous sclerosis is autosomal dominant mutation of TSC 1 or 2 causing multisystem hamartomas. 80% of TSC cases are de novo.
   i. Angiomyolipomas are most frequent renal finding. May have renin dependent hypertension due to compression of renal tissue by mass.
i. Hypercholesterolemia with lipoprotein X associated with cholestatic or obstructive jaundice is a cause of pseudohyponatremia.
j. TAL - Bartter type 1 NaK2Cl. Type 2 ROMK. Type 3 basolateral chloride channel.
   i. Classic form of Bartter is type III basolateral chloride channel, presents later in life with hypokalemia, met alkalosis and hypercalciuria. Reduced severity due to redundancy in chloride channels.
k. Gitelman (AR mutation in thiazide-sensitive sodium-chloride symporter) hypoK/Mg, hypocalciuria, alkalosis. Usually not diagnosed until late childhood or adulthood - all patients have cramps fatigue, polyuria/polydipsia, and chondrocalcinosis due to chronic low magnesium.
   i. Urinary calcium is normal or high in Bartter (like with loop – calcium reabsorption in TAL requires normal NaCl reabsorption at site).
   ii. Urinary calcium is reduced in Gitelman (like thiazide).

iii. HypoMg may occur with both Gitelman (more common) or Bartter.
iv. Check 24 hour Ca, Mg, etc for both.

l. Fabry's – X-linked defect αgalactosidase-A > accumulation globotraoxylceramide (Gb3) in lysosomes.
i. Hemizygous males more severely affected than females. Female heterozygous have variable disease ranging from no symptoms to severe phenotype (skewed X inactivation).
ii. Limb pain, telangiectasias, abdominal pain, corneal opacities, proteinuria/pu/pd, progressive renal dysfunction

Genetic hypertensive disorders.

m. Glucocorticoid-remediable hyperaldosteronism (GRE, FH type
i. Autosomal dominant chr 8 uneven crossover – chimer of ACTH-driven promoter and aldosterone synthase.
ii. HTN, hypokalemia and met alk. Treat with steroids to decrease ACTH.

n. Apparent mineralocorticoid excess (AME)- Autosomal recessive – deficiency in 11βhydroxysteroid dehydrogenase 2 leads to higher intrarenal cortisol, which has aldo like effect. (licorice also does this)
i. Tx with dexamethasone to suppress endogenous cortisol.

o. Liddle's syndrome- Autosomal dominant mutation on chr 16 > defective ENaC endocytosis > higher expression and activity. Childhood hypertension, hypoK, alkalosis.
i. Treat with amiloride and low salt diet.

p. Pseudohypoaldosteronism Type II (Gordon's syndrome)-Mutation in WNK kinases 1-4> hyporenin, hypertension.
i. Thought due to increased Na-Cl transporter activity.
ii. WNK I inhibits ROMK in vitro, so it may cause decreased K secretion.
iii. WNKs may increase paracellular Cl transport, decrease H and K secretion into the lumen.
iv. Treatment with thiazides.

Exposure, intoxication and meds

q. Star fruit associated with oxalate nephropathy.
r. Ephedra causes hypertension and stones.
s. Glycyrrhizic acid sweetener (licorice) causes excess aldosterone-effect though competitive inhibition of 11-ß-hydroxysteroid dehydrogenase 2 leading to increased intrarenal cortisol
t. Noni juice causes hyperkalemia.
u. Increased ACTH production by lung cancer (more common with SCLC) increases adrenal cortisol production.
v. Ifosfamide induces Fanconi proximal tubule wasting and nephrogenic diabetes insipidus, may occur months after completing chemotherapy.
w. Topiramate inhibits carbonic anhydrase and is associated with renal tubular acidosis and distal RTA with calcium phosphate stone formation.
x. Acyclovir associated with crystals but not stone formation.
y. Atazanavir is associated with stones, most soluble in pH<4.5 urine and requires large volumes to enhance solubility and prevent precipitation.
z. Acetaminophen associated with oxoproline acidosis in alcoholics and pts with poor nutrition due to glutathione deficiencies.
aa. Ketorolac associated with hyporeninemic hypoaldosteronism and type 4 RTA.
bb. Aristochloic acid is represented pathologically by significant IFTA due to tubular injury.
cc. Renal potassium wasting due to inhalation of paint thinner is the result of toluene-induced type 1 distal RTA. Toluene metabolized to hippuric acid => sodium hippurate, a non-reabsorbable anion leading to increased distal sodium delivery, upregulating aldosterone, exacerbating total potassium wasting.
dd. Salicylate ingestion.

i. The key to understand is that higher pH keeps salicylate out of brain. Activated charcoal is useful.

ii. Alkalinization

1. Alkalinization of serum is first line in toxicity not requiring dialysis.
2. Bicarbonate infusion should be titrated to keep the arterial pH between 7.5-7.6.
3. Intubation should be avoided in patients with salicylate toxicity as it usually leads to reduction in pH with increase in CNS salicylate levels.
4. If necessary high tidal volumes should be used to maintain a systemic alkaline pH.

iii. Indications for dialysis

1. Salicylate level is >100 mg/dL.
2. Neurological symptoms.
3. Pulmonary or cerebral edema.
4. Impaired kidney function.
5. Poor response to medical therapy.

ee. KDIGO recommends a low-dose deferoxamine test for patients suspected of having aluminum overload or toxicity.

i. If there is an increase in serum aluminum of >50 mg/L 2 days after infusion, confirms presence of overload.

ii. Deferoxamine is the treatment but it is associated with mucormycosis and neurotoxicity.

ff. Lithium overdose

i. Oral active charcoal <u>does not</u> prevent the absorption of *charged* particles, like lithium.

ii. NO role for charcoal in lithium intoxication. Must do whole bowel irrigation with polyethylene glycol in large acute ingestions or sustained release preparations.

iii. HD is indicated if:

1. Asympatomatic, normal renal function, lithium > 5

2. Lithium >4 with Cr > 2
3. Any level of altered mental status or complications with level of >2.5
4. The above with concern for further GI absorption

iv. Chronic toxicity (NDI) may be ameliorated by amiloride.

gg. Tenofovir causes acute kidney and proximal tubule injury via mitochondrial toxicity.

hh. Rhabdomyolysis is the most common cause of AKI with ecstasy intoxication.

ii. Ciprofloxacin induced crystalline nephropathy – risk is increased in the elderly, with high dose and in setting of alkaline urine.

jj. Phenylephrine is a non-selective alpha agonist that may cause hyperkalemia by blocking cellular uptake.

kk. NEVER start belatacept in a patient without testing for EBV first. Tenfold increased risk of developing posttransplant lymphoproliferative disorder (PTLD) in patients receiving belatacept who are EBV seronegative.

ll. Ranitidine must be adjusted if GFR<30 or it may cause altered mental status.

mm. Rasburicase is contraindicated in G6PD deficiency (e.g. if patient had prior anemia with TMP/SMX use).

nn. Cetuximab, panitumumab, matuzumab, epidermal growth factor inhibitors, causes movement of magnesium TRPM6 channel to apical membrane = >hypomagnesemia.

oo. Interferon associated with minimal change disease and AIN.

pp. NucleoSIDE RTI (stavudine, didanosine) associated with ATN, lactic acidosis and fulminant hepatic failure with rhabdomyolysis.

qq. NucleoTIDE RTI like tenofovir associated with acute tubular necrosis and Fanconi syndrome.

rr. Gadolinium leads to decrease in ionized calcium level – pseudohypocalcemia.

ss. Colchicine toxicity. Tubulin inhibitor – leads to bone marrow and GI tract effects due to targeting sites with high cellular turnover.
   i. Three phases of toxicity:
      1. GI toxicity with colitis and diarrhea. Imaging may show colitis.
      2. Multiorgan failure with AKI, pancytopenia and circulatory collapse.
      3. Recovery phase with persistant neurological deficits.
   ii. Narrow therapeutic index – 7 mg may be fatal.
   iii. Colchicine is metabolized by CYP3A4 in liver, which macrolides inhibit. Co-administration of colchicine and macrolides is <u>contraindicated</u> – half of deaths from colchicine toxicity are due to macrolide admin.

tt. Lactic acid gap – POC lactate very elevated but serum lactate normal or mildly elevated.
   i. POC uses lactate oxidase, which also converts *ethylene glycol* – serum test uses lactate dehydrogenase which does not.

uu. Aristocholic acid causes chronic interstitial nephritis.

vv. Nordihydroguaiaretic acid is an antioxidant compound from creosote bush - extends life of insects, but causes renal cysts and renal cell carcinoma.

ww. Salicin is a willow bark anti-inflammatory compound that causes renal papillary necrosis.

xx. Yohimbine (African tree bark used for erectile dysfunction) causes lupus nephritis which response to steroids.

yy. Anthraquinone - quinone derivative- building block of many dyes and used in bleaching pulp, obtained from rubarb plant. Causes CIN.

<u>Random factoids from studying for board</u>

zz. Plasma free metanephrine levels are the best screening test for pheochromocytoma – also easier than 24 hour urine collection.

aaa. Both immunoglobulin deposition disease and amyloidosis have been associated with cardiac and renal involvement.

bbb. In mild to moderate AS, target goal BP of 130-139/70-89.

ccc. For workup of resistant hypertension, in setting of hypokalemia and ACEI/ARB, aldosterone level can be suppressed and thus lead to a false negative result. Consider rechecking the levels after 2 weeks off of ACEI +/- after replacing potassium.

ddd. RAS - mineralocorticoid therapy for primary hyperaldosteronism is associated with higher risk of developing chronic kidney disease according to observational studies. Surgical adrenalectomy appears to mitigate this risk.

eee. HCV leads to type II cryoglobulinemia and results in type I MPGN.

fff. AA males with collapsing FSGS with HIV+ are typically normotensive - they do not develop edema even in the presence of severe nephrotic syndrome due to renal sodium leak and the presence of significant hypergammaglobulinemia offsetting the loss of oncotic pressure from hypoalbuminemia.

ggg. IRIS can appear as mononuclear infiltration of renal interstitium, essentially a form of acute interstitial nephritis.

hhh. Levaminsole induces leukocytoclastic vasculitis mpo and pr3.

iii. Upper respiratory tract disease (e.g. nasal crusting) highly associated with relapse in GPA. MPO < PR3 relapse risk.

jjj. Findings of hyperemic optic discs and putamen swelling are suggestive of methanol intoxication.

kkk. Abnormalities in factor H, inhibitor of alternative complement pathway, are most important for some pts with MPGN classified as C3 glomerulopathy.

lll. Sacroiliitis associated with HLA-B27 positivity and IgA nephropathy, hematuria with infection tends to be simultaneous-probably chronic IgA nephropathy.

mmm. Overall prevalence of biopsy-proven AIN are 2-5% in biopsies for any reason, and 10-15% of biopsy for AKI.

nnn. Cryoglobulinemia presents with leukocytoclastic rash, often with nephritis and abnormal liver function tests. A hallmark is the ability

of cryoglobulins to depress c4 to undetectable levels with a low-normal c3.

ooo. A urine osmole gap of < -150 [e.g (Na + K) – Cl is a large negative value] predicts a urine ammonium of >75 indicating an appropriate renal response to metabolic acidosis. Positive or low negative values for urine osmolal gap denote a renal tubular contribution to acidosis.

ppp. Correcting acidosis without potassium supplementation for hypokalemia may precipitate symptomatic hypokalemia. Here may be secondary to inherited hypokalemic periodic paralysis not associated with hyperthyroidism, rather with skeletal muscle Ca channel mutation.

qqq. The combination of AKI with severe hypertension and GI bleeding following an invasive vascular procedure strongly suggests cholesterol embolization

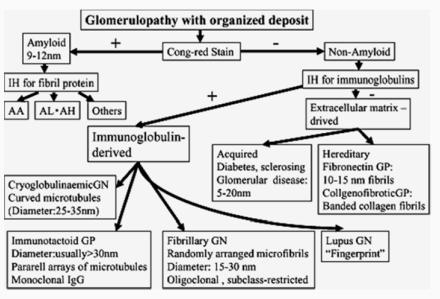
rrr. In preeclampsia, circulating VEGF levels are decreased due to increase in circulating FLT-1, a soluble VEGF receptor that is excessively made, resulting in hypertension and endothelial dysfunction with proteinuria.

sss. The major disadvantage of high flux membranes is back-filtration of dialysate and potential exposure to bacterial endotoxin.

ttt. AA men have greatest risk for dev. of diabetic nephropathy.

uuu. Kidney donation associated with increased risk for adverse outcomes during pregnancy, including preeclampsia.

vvv. Phosphate nephropathy occurs from precipitation of calcium phosphate crystals in medulla. Best stain on biopsy is Von Kossa, which stains phosphate and not oxalate.



www.

xxx. Craniopharyngioma post-surgical - classic triphasic response following injury to pituitary stalk. Initially DI, then unregulated release of stored vasopressin from degenerating neurons, then permanent DI.

yyy. Nephelometric serum free light chain assay has highest s/s and its preferred to confirm paraproteinemia before biopsy.

zzz. Serum immunofixation electrophoresis will miss diseases that only produce light chains.

aaaa. Malaise, fatigue, low-grade fever and pulmonary and renal masses with lymphoplasmacytic infiltrates in kidney and liver suggest IgG4 disease - typically highly responsive to steroids.

bbbb. Sufficient urine collection

i. Men 22 mg/kg

ii. Women 17 mg/kg

Chapter FIVE: Dialysis

Prescription for a stable chronic outpatient dialysis session

Time: 3.5 to 4 hours

Dialyzer: High flux, high efficiency (high urea clearance, high β-2 microglobulin clearance, high KoA, high Kuf)

Blood Flow (Qb): 300-400 ml/min (as fast as access and hemodynamics allow)

Dialysate Flow (Qd): 500-800 ml/min (typically 1.5-2 times the Qb is sufficient)

Dialysate Concentrate:

- Sodium 140 mEq/L, Potassium 3 mEq/L, Calcium 2.5 mEq/L, Bicarbonate 35 mEq/L.
- Dialysate concentrate should be adjusted to fit the patient's needs based on laboratory values.

Heparin anticoagulation: (not always needed)

- Low dose: bolus 2000 Units followed by 1000 Units/hour
- Normal dose: bolus 50-75 Units/kg followed by 5-7 Units/kg/hour

Dry weight goal or ultrafiltration goal

- ideally ultrafiltration is less than 10-13 ml/kg/hour

Prescription for initiation of dialysis

	1st Dialysis	2nd Treatment	3rd
TIME	2 h	2.5 h	3 h
Dialyzer	Smaller, low flux, low KoA	Smaller, low flux, low KoA	
QB	200 ml/min	250 ml/min	300 ml/min
QD	400 ml/min	500 ml/min	600 ml/min
UF	Minimize unless patient severely		

	overloaded		
Dialysate	Vary by lab		
Meds	Mannitol 12.5 g injections for 2 doses with first dose at the beginning of HD and second dose 1 hour after HD initiation.		

Options for anticoagulation

- Saline flushes, 200 ml via circuit every 30 min – 60 min as needed to prevent clotting. Ultrafiltration must be adjusted to remove the extra volume delivered to the patient.
- Unfractionated Heparin: Low dose: bolus 2,000 Units followed by 1000 Units/hour. Normal dose: bolus 50-75 Units/kg followed by 5-7 Units/kg/hour.
-

Medication dosing

Medications should be dosed according to residual kidney function and expected clearance with dialysis. In general, medications with a low volume of distribution and a low level of protein binding will be readily cleared with dialysis whereas medications with a high volume of distribution and a high level of protein binding will not be as readily removed with the dialysis procedure. Medications that are cleared with dialysis should be re-dosed after the dialysis session.

Dialysis Adequacy

spKt/Vurea

This metric is calculated using urea levels before and immediately after dialysis initiation. It assumes that urea is in a "single pool" or compartment. For patients that are dialyzed thrice weekly, the National Kidney

Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) 2015 hemodialysis adequacy guidelines (https://www.kidney.org/professionals/guidelines/hemodialysis2015) recommend a target spKt/Vurea of 1.4 and a minimum "delivered" spKt/Vurea of 1.2. This dose can be reduced in patients with significant residual kidney function provided that the residual kidney function is closely monitored. The following equation is recommended by the 2015 KDOQI hemodialysis adequacy guidelines for calculating spKt/V urea in patients undergoing thrice weekly hemodialysis:

spKt/Vurea = –ln(R–0.008 x T) + (4-3.5 x R) x 0.55 x Weight loss/V

R = postdialysis urea / predialysis urea

T = duration of dialysis treatment (hours)

Weight loss = Postdialysis weight – predialysis weight, converted to L (note 1 kg = 1L)

V = Total body water volume, calculated using Watson equation (L)

ln = natural logarithm

Urea reduction ratio

The fractional reduction of urea during a single dialysis treatment is known as the urea reduction ratio (URR). The URR has the advantage that it is easy to calculate and easy to understand. It is calculated using the following formula:

URR = 1 – (Postdialysis BUN/Predialysis BUN)

Roughly, a URR of 0.65 (or 65% urea reduction) correlates with a spKt/Vurea of 1.2. Target URR for hemodialysis patients is above 0.65

PERITONEAL DIALYSIS

Sample APD prescription

APD refers to the PD sub-type which utilizes an automated cycling machine to perform the bulk of the exchanges. APD is classified as either:

1. NIPD, nightly intermittent PD; using the cycler at night followed by a "dry day" without dialysate in the peritoneum (should only be considered in those patients with significant residual renal function)

2. CCPD, continuous cyclic PD: nightly PD using the cycler, followed by a day dwell (i.e. “last fill”) during which dialysate dwells all the day until the time of reconnection to the cycler at night
3. High-dose APD: nightly PD with the cycler plus a daytime dwell and at least one manual daytime exchange before reconnecting to the cycler at night
4. Tidal PD: nightly APD, each cycle drains a percentage of the infused volume (incomplete draining) before refilling the peritoneum, therefore allowing a constant amount of dialysate to remain in the peritoneum.
“Urgent start PD” refers to truly urgent presentations requiring PD within 72 hours of catheter insertion. **“Early start PD”** refers to the more elective variant, where PD is started between 3 and 14 days after catheter insertion and HD sometimes used initially.

The **typical APD prescription** should take into account the following factors:
1. Absence or presence of daytime dwell
2. Dwell volume: 1500 – 2000mL is the typical starting volume; larger patients or those needing additional solute clearance may require 2500 – 3000mL
3. Total cycler therapy time: Dependent upon lifestyle characteristics and needs, and the amount of solute clearance needed. More time = more clearance
4. Number of cycles per night, typically 3 -5 cycles/night. More than 5 cycles per night should be avoided if possible because each additional cycle causes a greater proportion of the total cycler time to be spent draining and filling, rather than dwelling. Additionally, many overnight short dwells create a sodium sieving effect, leading to morning thirst and increased oral intake.
5. Tonicity of dialysate: This is a dynamic factor, and changes will be made on a daily or weekly basis per the patient’s extracellular fluid status.
6. NIPD modality preferably should be used only in patients who have significant residual kidney function, because short PD exchanges provide

poor middle molecule clearance. Residual kidney function, or a long dwell in the daytime, provides middle molecular solute clearance that NIPD cannot provide.

Sample CAPD prescription

The most common initial CAPD prescription is probably the 4x2L prescription, meaning 4 exchanges per day, with 2L inflow volume for each exchange. The most common variations on this standard prescription take into consideration patient size and residual kidney function (RKF).

Considerations when writing the initial CAPD prescription:

- Smaller patients can usually meet solute clearance targets with smaller inflow volumes of 1,500 – 2000 mL, whereas larger patients typically require inflow volumes of 2,500 mL or more.
- Inflow volumes which are too large for a particular patient can be associated with discomfort (abdominal distension, back pain, decreased appetite from bloated sensation); however, some patients may grow accustomed to the inflow volume with time.
- Larger inflow volumes increase intraperitoneal pressure, and therefore increase the risk of developing a new hernia or peritoneal leak. To decrease the intraperitoneal pressure, larger inflow volumes should be preferentially used at night, while supine; if the patient has large inflow volumes during the day the patient should avoid any activity or position which could further increase intraperitoneal pressure (e.g., Valsalva maneuver, squatting, chronic coughing, heavy lifting, etc.)
- If significant residual kidney function is present, fewer exchanges per day may be sufficient (as long as the total peritoneal + renal K_t/V meets target); in these cases, NIPD (nocturnal dialysis only) can also be considered. In such patients, residual kidney function must be measured frequently (i.e. at least quarterly) to detect any decrement in RKF that would necessitate a change in the PD prescription in order to meet solute clearance targets.
- The term “incremental PD” refers to the process of initiating peritoneal dialysis using fewer exchanges (and often at least one “dry” period during the day without a PD fluid dwell) when a patient has significant residual kidney function, and

subsequently increasing the PD "dose" over time, as needed to meet solute clearance and ultrafiltration targets.

Kt/Vurea calculation in PD

In peritoneal dialysis: total K_t/V_{urea} = peritoneal K_t/V_{urea} + kidney K_t/V_{urea} | K = dialyzer clearance rate (L/day) – in PD the dialyzer is the peritoneal membrane | t = dialysis time | V = volume of distribution of urea (approximately the total body water volume, or TBW) (L) | peritoneal K_t/V_{urea} = [dialysate urea] / [BUN] * (total volume of drained effluent in 24 hours) | V_{urea} (use an estimate of TBW, or use Watson formula)

Example: A 45-year-old well-nourished male is on APD. PD prescription: 4 nocturnal cycles with inflow volume of 2L each, last fill 2L Icodextrin.H is weight is 70kg. 24-hour collection of dialysate produces 12.5L of fluid with a dialysate urea concentration of 65 mg/dL. His BUN is 70 mg/dL.

His daily (24h) peritoneal K_t/V = [(65 mg/dL / 70 mg/dL) * 12.5L] / (0.6 * 70) = 0.27. His weekly peritoneal K_t/V = 0.21 * 7days = 1.93; this is "adequate" peritoneal dialysis

Adequate dialysis should be assessed clinically and not only by measurement of solute clearance. A sufficient dose of peritoneal dialysis is that which is associated with overall sense of well-being, absence of malnutrition, no uremic symptoms, biochemical balance, euvolemia, and erythropoietin-stimulating agent (ESA) responsiveness.

Current International Society of Peritoneal Dialysis (ISPD) guidelines recommend a minimum total (renal + peritoneal) K_t/V_{urea} of 1.7

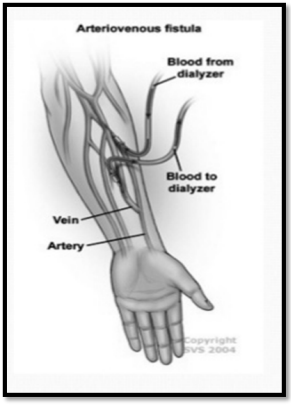
- Initial K_t/V_{urea} should be measured within 1 month of initiating peritoneal dialysis, and thereafter at intervals of no less than every 4 months.

- Patients who rely on residual kidney function to meet the minimum solute clearance target (K_t/V_{urea} of 1.7) should have residual kidney function measurements every 1-2 months if feasible, but no less than every 4 months.

"Incremental PD" refers to the practice of using residual kidney function (RKF) to achieve the total desired solute removal, and initially prescribing only a modest dose of PD. This may take any of several forms: prescribing a smaller total volume of fluid (*e.g.,* only two or three CAPD exchanges daily); using only part of the day (*e.g.,* nocturnal APD with a dry day); or performing PD for fewer than 7 days per week. **(1) Am J Kidney Disease. Review. Dialysis Access, KDOQI Guidelines. (2) ISPD Guidelines Watnick April 2011**

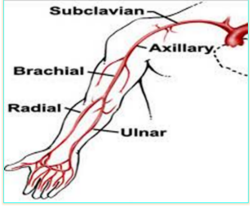
Chapter SIX: Dialysis Access

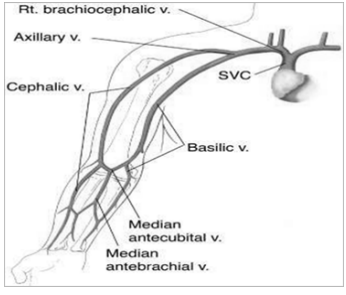
Arterio-Venous Fistula

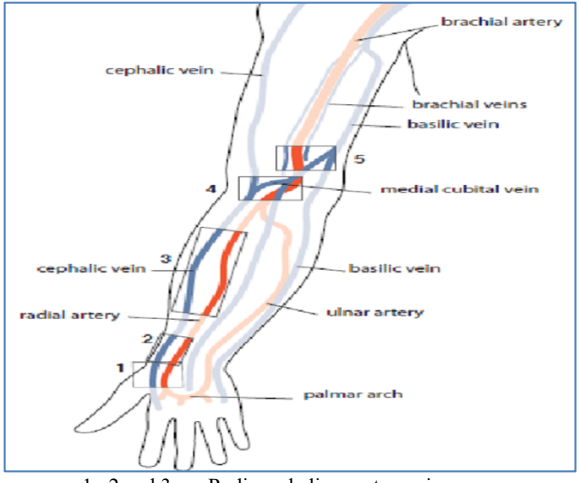


This is an anastomosis created between an artery and a native vein resulting in direct blood flow from artery to vein. An AVF takes about 6-12 weeks to 'mature' before it can be used. During this maturation process blood flow through the AVF increases, resulting in dilation and pressure induced thickening of the venous wall. This in turn helps withstand the shear from repeated cannulation of the venous part of the AVF.

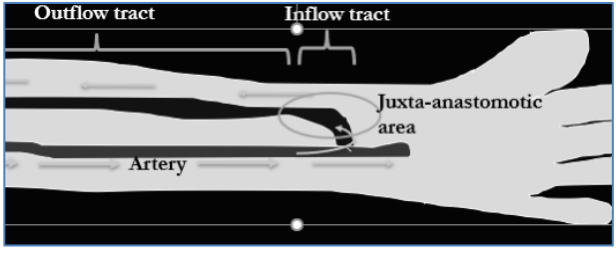
Vascular anatomy of the Upper limb:







-1 , 2 and 3 are Radiocephalic anastomosis
-4 is Brachio-cephalic Anastomosis
-5 is Brachio-basilic anastomosis



Note the direction of the blood flow from the artery to the vein. Blood from the artery flows through the inflow tract into the outflow tract.

Assessment of an AVF:

a. Rule of six in assessing an AVF:

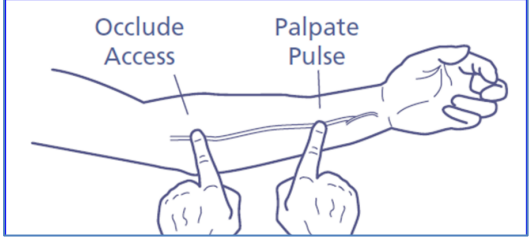
At least **Six** weeks from AVF creation

-Minimum of **six** cm in length (for 2 needle cannulation)
-Blood flow rate of at least **6**00 ml per min

-Depth of no more than **6**mm
-Diameter of the body of the AVF should be at least **6** mm

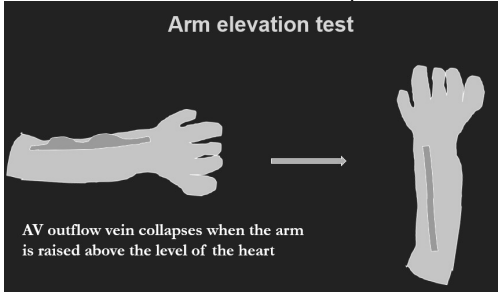
Examining an AVF:

-Observe the skin over the AVF
-Examine for bulges, ulceration, edema, or collateral veins
-Examine the distal extremity for pallor or gangrene
-Listen for the bruit over the AVF using a stethoscope and compare its quality over the length of the AVF.
-Feel the thrill over the AVF along the entire length; feel the warmth of the distal extremity and check for good capillary refill.



b. Augmentation test: Occlude the outflow vein tract, should be able to palpate a strong and bounding pulse if the inflow tract is patent.

c. Arm elevation test:
Raising the arm above the level of the heart, will collapse the AV outflow vein if the outflow tract is patent.



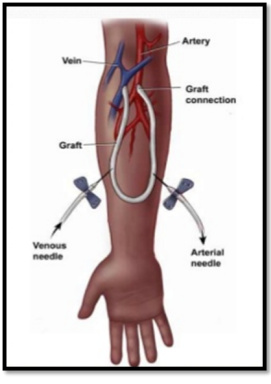
A. Advantages and Complications of the AVF:

a. AVF is considered the preferred access compared to other options because of the low infection rates, high patency rates and overall better patient survival.

b. Complications associated with the AVF include, delayed maturation, thrombosis, Aneurysms, High output cardiac failure and steal syndrome.

Causes of fistula immaturity or early failure

- **Stenosis** → **Angioplasty (PTA/Stent)**
  - Arterial disease
  - Juxta-anastomotic
  - Venous outflow
  - Angioplasty of stenosis
  - Balloon assisted maturation
- **Accessory veins** → **Coil embolization or ligation**
- **Thrombosis** → **Thrombectomy**
- **Deep vein** → **Superficialization**



Steal Syndrome:

This complication of the AVF is seen in about 1-4% of the patients with an AVF, leading to decreased blood flow to the distal extremity resulting in pain, numbness, and gangrene. It is more common with 'Upper arm AVF' rather than Radio-cephalic AVF. Treatment options include the DRIL procedure and the RUDI procedure.

Arterio-Venous Graft:

An AVG is also an anastomosis between an artery and a vein allowing blood to flow directly from the artery to the vein, using a prosthetic material like PTFE (Polytetrafluoroethylene) polymer.

When do you consider an AVG over an AVF?

AVG is considered the first choice in mostly elderly patients with unsuitable blood vessels, that are insufficiently large or poorly distensible. These patients often have poor AVF maturation rates.

Advantages of an AVG over AVF include:
-Larger surface area available for needle cannulation
-Easer cannulation
-Shorter maturation time

Maturation time: It can be used in about 2-3 weeks from placement, when the post-surgical edema and erythema has subsided, and the graft course is palpable. Adhesion of the graft to the subcutaneous tissue prevents any hematoma formation.

a. Early use grafts: Self-sealing PTFE grafts requires more surgical skill for placement but have similar performance as conventional grafts and can be used in about 24 hours after placement, once the surgical edema resolves.

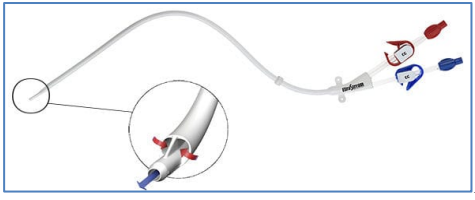
b. Common sites for AVG placement include:
-Brachio-basilic
-Radio-basilic
-Brachio-axillary

Catheters: Tunneled and Non-tunneled

Venous catheters are the least preferable choice for dialysis access when compared to the options listed above, due to the increased risk of infection, poor flow rates (~300 ml/min) and increased morbidity and mortality. Patients with catheters are noted to have higher levels of inflammatory markers and poor survival rates. Based on more recent reports, there is more evidence to think that these poor outcomes are not merely related to catheters alone, but also related to the kind of patient population likely to get a catheter who are acutely sick or have severe vascular disease preventing them from having other long term accesses. Hence, there is renewed interest in choosing venous catheters for specific patient population like the elderly with several comorbidities or those with limited life span, morbidly obese, or those have undergone multiple AV access insertions and do not have any more sites available.

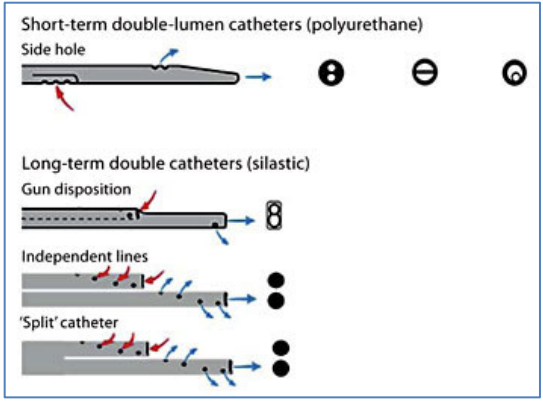
'Fistula first initiative' is being redefined as 'Patient first, fistula second and catheter last' when it comes to optimal dialysis access

a. Types of dialysis catheters:
-Acute vs Chronic dialysis catheters
-Tunneled vs Non-tunneled dialysis catheter
-Cuffed vs non-cuffed dialysis catheters



Acute catheters like Quinton catheters, Shiley catheters or Trialysis catheters are non-tunneled and placed for emergent dialysis access. They are non-cuffed and usually need to be replaced with chronic catheters if the patient will need dialysis for more than 1 week. Advantage is the ease and pace of placement, but with increased risk of infections.

Chronic dialysis catheters are tunneled and cuffed. Tunneled catheter insertion involves creating a subcutaneous tunnel with an exit site lateral to the venotomy site by blunt dissection and using a tunneling device. T**he cuffed end of the catheter sits under the skin of the exit site**, and anchors itself to the subcutaneous tissue holding it in position. These characteristics help in reducing infection related complications and catheter migration.



Dual lumen catheters have a side by side configuration rather than a co-axial configuration, there by having a split tip with different termination points for the inlet and outlet ports. This helps to reduce 'Recirculation' .

Insertion sites: (in order of preference for non-tunneled dialysis catheters)

1. -Right internal jugular (IJ) vein
2. -Femoral vein (Fem)
3. -Left internal jugular (IJ) vein
4. -Subclavian (SC)

   This is often a topic of debate and femoral vein is considered favorable than the left IJ because of its tortuous course to the Right atrium and helps preserve the upper extremity central venous vessels for future AV access creation. Femoral vein catheters need to be at least 20 cm in length so that the tip is in IVC to have higher flow rates.

b. Common complications associated with central venous catheterization:
Arterial puncture
IJ or SC: Pneumothorax, Hemothorax, Pericardial tamponade, cardiac perforation, injury to the brachial plexus or the recurrent laryngeal nerve.
Fem: Femoral vein perforation and retroperitoneal bleed
Delayed complication: include thrombosis, infection, central venous stenosis

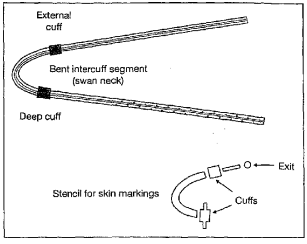
c. Catheter lock solutions:
The dead space within the lumen of the catheter is filled with lock solutions during the interdialytic period. This dead space varies between manufacturers and the length of the catheter. The required volume of lock solution is often noted on the catheter hub.

Heparin: 1000-5000 units /ml concentration is often used as the lock solution. Higher concentrations are discouraged for risk of systemic anticoagulation.

Citrate: 4% solution is often used as a lock solution. 4% solution is comparable to Heparin. Citrate based solution with antibiotics have been shown superior to heparin in preventing CLABSI. Also, high concentration Citrate (30%) are considered more effective than Heparin but are associated with higher risk of systemic hypocalcemia.

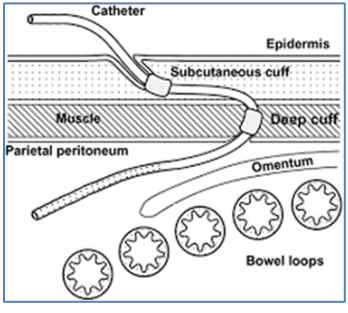
There are other options in development that include lock solutions that not only sterilize the inside of the lumen also prevent biofilm formation. Solutions with glyceryl trinitrate, taurolidine and methylparaben are in various stages of testing.

Peritoneal Dialysis Catheters:



Types of catheter material:
-Polyurethane catheters
-Silicone catheters (silastic) –Most common - barium impregnated for xray identification; breakdown on Iodine exposure

Tenckhoff catheters are arched or swan neck and may have a coiled end. Have 2 cuffs composed of Dacron polyester fiber that irritates local tissue to scar around it. The superficial cuff stays in the subcutaneous tissue and the deep cuff stays in the rectus muscle.



Placement and post-operative care: Placement is done using closed seldinger technique (using an US at bedside), Open, Peritoneoscopic or Laparoscopic.

Post-operative dressing is left in place for 7-10 days with transfer set external to the dressing for flushing. Catheter is flushed in 3-5 days with 1L of 1.5% dextrose in supine position. For urgent start dialysis, catheter may be used immediately (low volume supine PD). Catheter is ready in 2 weeks and may wait about 3-4 weeks if complicated case or hernia repairs were done at the same time.

a. PD catheter related complications:

Immediate complications from placement include Bowel or bladder perforation, Rectus sheath hematoma (from injury to epigastric artery), hemoperitoneum, catheter kinking.
Other complications include:
-Peri-catheter leaks: Seen more frequently with urgent start PD. This risk can be minimized by using lower volume supine PD.
-Intra luminal obstruction: caused by thrombus in setting of hemoperitoneum. Usually presents as a 2-way obstruction. Can be relieved with vigorous flushing, TPA or mechanical thrombus removal.
-Malfunction from adhesions or loculations:
-Omental wrap: Often leads to a one-way obstruction. Needs surgical fixing with omentopexy.
-Catheter tip migration: can be prevented with rectus sheath tunneling.

b. Mupirocin is considered better than placebo for exit site application to decrease episodes of peritonitis. Multiple studies have shown the same (Perez-fontan, Mupirocin study group, Bernardini, Thodis).

c. Exit site infection:
Exit site infection is diagnosed when there is purulent drainage from the exit site; erythema alone may not represent an infection. Tunnel infection is defined as the presence of clinical inflammation or ultra-sonographic evidence of collection along the catheter tunnel.
Diagnosis of exit site infections:
-Culture swab of the purulent material
-Gram stain to help guide initial therapy
Treatment of exit site infections:
Oral antibiotics are enough but needs coverage for MRSA. Bactrim or Clindamycin can be used vs Cephalexin if no concern

for MRSA. Duration of therapy is usually 2 weeks and 3 weeks if treating Pseudomonas.

d. Exit site care:
Wash the exit site in shower with soap and water and its ok to allow water to run over the exit site in shower. Secure the catheter tubing after shower and apply antibiotic cream at the exit site daily. Dressing over the exit site is optional. Regarding topical antibiotics, Mupirocin or Gentamicin cream is considered superior then Polysporin. Screening of nasal Staph Aureus and eradication with Mupirocin is recommended prior to PD catheter insertion.

Chapter SEVEN: Electrolytes

Effective osmolality or tonicity is determined by concentration of osmoles in plasma that do not move freely across cell membranes

Measured Osmolality (laboratory) =number of solutes/Litre of solution

Calculated Osmolality = 2 X Na+ (mEq/L) + BUN(mg/dL) / 2.8 + glucose (mg/dL)/18+ ethanol/4.8 (normal range 275–295 mosm/kg).

Approach

1. Is it hypotonic or non-hypotonic ?
2. Is it acute (<48 hours) or chronic(>48hours).
3. Is it moderate(130-125) or severe (<125)? (when < 110meq/l can be associated with mental status changes and seizures)
4. Is it symptomatic or oligo-symptomatic (previously referred to as asymptomatic?
5. Is it associated with decreased, normal or increased ECF?

Non-hypotonic hyponatremias

Hypertonic or translocational:
Shift of water from intracellular to extracellular compartment due to the presence of solute retained in the ECF (such as in hyperglycemia or retention of hypertonic mannitol, glycine, sorbitol, IVIG)

Isotonic hyponatremia:
Caused by infusion of large volume of isotonic fluid in ECF that does not contain sodium such as mannitol eg irrigation with mannitol during TURP.

Pseudohyponatremia:
Pseudohyponatremia results from reduction in the water content in a given volume of plasma. Sodium content of water phase is not affected but since plasma is measured on the lab BMP, sodium measurement is falsely lowered. Causes include paraproteinemia (check SPEP/kappa lamda light

chain) or hypertriglyceridemia (check lipid panel). It is an iso-osmolar/ isotonic hyponatremia. Currently with ion selective electrodes to measure sodium it is rarely a problem, but can occur with use of diluted plasma samples.

Hypotonic Hyponatremias:
Results from a combination of
1. Inadequate solute intake
2. Excess Free water intake
3.Retention of free water or impaired excretion of free water. (2 + 3 often occur together)

The Physical Exam: Check orthostats, skin turgor, loss of axillary sweat, JVP, edema, New school : IVC collapsibility(higher colpasability index corelates with elevated CVP, IVC diameter < 1.6cm correlates with lower CVP- may be falsely + in pts with severe TR and mech ventilation), Lung ultrasound and bioimpedance analysis.

Approach Hypotonic Hyponatremias by
1. Assessing volume status
2. Urine osmolarity

Labs that can give you a clue…such as
BUN/Cr ratio: low EABV (effective arterial blood volume) and hypovolemia PTC reabsorption of sodium, water and urea will be increased→ BUN: cr ratio > 20:1, Urine sodium concentration < 25mmol/L in hypovolemia and low EABV.
(In volume contraction, urine Cl should be less than 15meQ/L). Diuretic use and impaired conc ability of kidney such as in ATN and CKD may lead to higher urine Na)

I.VOL STATUS:

Hypervolemic Hyponatremia:
Liver cirrhosis, Nephrotic syndromes,
Congestive Heart Failure. Pregnancy.

Euvolemic Hyponatremia: SIADH(CNS lesion, malignancy, meds,MDMA..) Post-op states, pain, nausea→ also cause ADH release. **Cerebral salt wasting** (coined in 1957 before SIADH and popular in neurocrit literature. Likely no difference bw SIADH and CSW. Tx the same : SALT!). **Psychogenic polydipsia. Beer potomania**.
Thiazide diuretics. Hypothyroidism. Adrenal insufficiency (may also be hypovolemic)

Do not forget to order TSH and am cortisol before dx SIADH. A hx of post partum hemorrhage may be indicative of central Adrenal insufficiency.

Hypovolemic Hyponatremia:

- **Renal sodium losses:** diuretics, salt wasting nephropathy, adrenal
  Insufficiency, Salt wasting nephropathy, Bicarbonaturia, ketonuria
- **Extra-renal sodium losses:** Diarrhea, vomiting, blood loss,
- **Third space fluid sequestration:** bowel obstruction, peritonitis, pancreatitis, burns.All GI fluid losses are hypotonic- therefore hyponatremia will only develop if

free water is concurrently being ingested. Patients with GI losses may present with hypernatremia if access to free water is restricted

II. URINE OSMOLARITY:

- Reflects concentration of urine.
- Urine osm < 100-200mOsm/ L→ primary polydipsia, tea and toast diet, beer potomania

- Urine osm > 200-300mOSm/L→ indicative of high ADH state.

Other tests: serum uric acid (low in SIADH and high in vol depletion/CHF/nephrotic sx/cirrhosis).

Most hospitals will require a central line for infusing 3% hypertonic saline and a limit of 20-50mL/hr.
Rules vary for 2% hypertonic saline

II MANAGEMENT
-Hypotonic Hyponatremia with severe hypokalemia: first correct potassium depletion since this correction repairs the hyponatremia
- Hypotonic hyponatremia
I. Fluid restriction is mandatory. If excessive water intake is the cause of hyponatremia, may be the only intervention needed.
II. Indication for hypertonic saline (eg 3% saline): severely symptomatic hypotonic hyponatremia or hypotonic hyponatremia with neurological or neurosurgical conditions.

Target rate of correction:

a. Acute hyponatremia: increase the serum sodium by 4 to 6 mEq/L over a period of a few hours to prevent / reverse cerebral edema.

One guideline recommends giving up to three 100mL boluses of 3% hypertonic saline over 10-15 mins at a time followed by 3% hypertonic saline @ 1mL/kg/hr. However, our preference is to use the Adrogue- Madias formulas in determining rate of fluid administration rather than using hypertonic saline bolus.

b. Chronic hyponatremia or unknown duration (severe ,moderate or mild sx)→target 4-6mEq/24 hrs, limit to 8mEQ/24 hrs. do not exceed 1.5-2meQ/hr .

Formulas for estimating infusate and fluid loss effect on serum sodium

Infusate Formula (Formula 1)	$\Delta[Na^+]_s = \frac{[Na^+ + K^+]_{inf} - [Na+]_s}{TBW + 1}$
Fluid-Loss Formula (Formula 2)	$\Delta[Na^+]_s = \frac{[Na^+]_s - [Na^+ + K^+]_{fl}}{TBW - 1}$

$[Na^+]_s$ = serum sodium, inf = infusate, fl = fluid, TBW = Total Body Water.

The output of these formulas represent the impact of retention of 1 L of infusate or loss of 1 L of fluid (eg urine, NG output). Use of fluid loss formula is necessary when fluid losses are substantial.

-Also useful to think about whether ADH is appropriately or inappropriately elevated. Appropriate ADH high state, such as in hypovolemia, may have rapid correction of sodium once ADH has been turned "off" and you may have to be conservative with initial treatment.

Risk of overcorrection is osmotic demyelination. Greatest in alcoholics patients, malnourished patients, concurrent hypokalemia, liver disease, and serum Na < 105mEq/L). Greater if rate of correction exceeds > 12mEq/24hrs, >18mEq/48hrs.

Approach overcorrection by using 1-2mcg Desmopressin SQ or hypotonic fluids such as 5% D5W or ½ NS. Some clinicians have proposed the use of hypertonic saline plus desmopressin to avoid overcorrection of hyponatremia at a dose of 1-5µg, which can be repeated every 6-8 hours based on urine output. This combined strategy may increase the risk of hyponatremia due to retention of hypotonic fluids and we do not support its use.

Approach to SIADH:

1. Concept of free water clearance (V= Cosm + CH2O ; in dilute urine CH2O= V- Cosm and in concentrated urine TC H2O (negative free water)= Cosm- V

Cosm =V x (urine Na + urine K) /plasma Na

- If the ratio of urinary sodium and urinary potassium to plasma sodium <1→ Liberal fluid restriction to 1 L/day.

- If ratio >1, fluid restriction should be stricter and is often impractical-→ **therefore, along with fluid restriction use salt tabs + urea (30g/day).**
- **Can use tolvaptan (ADH receptor antagonist) with no fluid restriction in first 24 hours with vaptan use.**

Other approaches: adding loop diuretics to hypertonic saline or use in SIADH, stopping HCTZ and other meds.

HYPERNATREMIA(plasma Na > 145meQ/L)

Always hypertonic and hyperosmolar (unlike hyponatremia)

Caused by net water loss or rarely hypertonic sodium gain.

-increased extra renal water loss (eg sweat, loss of hypotonic fluids in diarrhea, Burns, osmotic laxatives such as lactulose, enterocutaneous fistulas)
-Increased renal losses: Loop diuretics, osmotic diuresis (glucose, urea, mannitol),
-Impaired thirst response (eg damage to anterior communicating artery supplying the hypothalamus→ Adipsic Hypernatremia)
-Hypertonic sodium gain: Hypertonic sodium bicarb infusion, hypertonic NaCL, hypertonic TFs, primary hyperadlo, cushing's syndrome etc.

Diabetes insipidus (normal sodium balance but TBW depleted)
Central DI (lack of ADH release): congenital, Idiopathic, post traumatic, tumors, cysts, histocytosis, TB, sarcoidosis. Aneurysm, Meningitis, encephalitis, Guillain-Barre syndrome. + ethanol ingestion (transient)

Nephrogenic DI (unresponsive to ADH) – Hereditary: X linked recessive, Defect in V2 receptor or aquaporin channel. May be complete or partial

Gestational DI (Degradation of ADH)- Vasopressinase mediated (released by placenta)
Acquired Nephrogenic DI (ADH independent): Result from interference of medullary concentrating gradient and decreased concentrating ability such as renal disease (medullary cystic disease/amyloidosis, sickle cell disease, Sjogren's syndrome), Hypercalcemia or hypokalemia, Drugs (Lithium, Demeclocycline, ifosfamide, Foscarnet, methoxyflurane, amphotericin B, vasopressin V2 receptor antagonists

Patients with DI may not develop hyperNa if thirst mech is intact. Polyuria (> 3 L of urine a day) may be initial complaint. Hypernatremia may be apparent in conditions where access to water may be restricted such as acute encephalopathy

#Determine vol status→ hemodynamically unstable patients→ correct ECF depletion with isotonic saline / LR before water deficit is addressed. *THEN* Calculate free water deficit
THEN Choose a replacement fluid *THEN* Determine rate of repletion. *THEN* Estimate ongoing "sensible" losses *THEN* Estimate ongoing "insensible" losses *THEN* Determine underlying etiology

TBW = lean body weight x 0.5 (elderly and female) X 0.6 (adult male)
X 0.45 (obese
Free water deficit = TBW x [(plasma Na)/140-1)

Hypernatremia due to pure water loss→ prefer enteral free water (oral or NG)

Deficit of both salt and water→ 0.2% or 0.45% saline + infusion of D5W.

Rate of correction: generally recommended not to exceed 10-12 mEq decrease in Na in a 24hour period or 0.5mEQ/L/hr. However, a recent study reported no increase in mortality, seizure, alteration of consciousness and or cerebral edema in critically ill patients with hypernatremia that were corrected to > 0.5mEq/L/hr or > 12mEQ/24hrs.

Estimating ongoing sensible losses-→ calculate electrolyte free water clearance. In the presence of hypernatremia, urine with high electrolyte-free water clearance would be in appropriate. Can either result in the presence of osmotic diuresis or DI. A high U osm would be consistent with an osmotic diuresis (from glucose, urea or mannitol). Low urine osm→DI

Insensible losses- UOP + stool output + skin and resp tract. Assume 10-15ml/kg/day for women. And 15-20ml/kg/day for men (increased with fever, infection, burns, mechanical ventilation).

Central DI: rx with desmopressin.
Nephrogenic DI: Rx with HCTZ.

Common Na content in Intravenous fluids
3% saline – 513 mEq Na
0.9% saline – 154 mEq Na
Lactate Ringers – 130 mEq Na
0.45% saline – 77 mEq Na
Dextrose Water (D5W) – 0 mEq Na

Hypokalemia and Hyperkalemia

K+ is an intracellular ion- conc is approximately 150mEq/L
Extracellular fluid conc is approx. 4mEq/L.

Two systems work to maintain K homeostatsis. The first system regulates **K excretion** from the blood and the second regulates **potassium shifts** between the extracellular and intracellular compartment

Potassium Excretion:

About 90-95% of dietary potassium is excreted from the kidney (relatively slow process- takes 6 to 12 hrs to eliminate an acute load)
Remaining 5-10% excreted via the small intestine and colon in response to aldosterone. In CKD patients gut excretion of K is increased 3-4 fourfold.

Physiologic factors increasing Renal K excretion

1. Aldosterone→ increases Na/K ATPAse activity in collecting duct
2. Distal Na+ delivery→ creates electrochemical gradient
3. Urine flow→ increases concentration gradient
4. Tubular (K)→ increases conc gradient
5. Metabolic alkalosis→ decreased proximal Na+ reabsorption

Drugs and diseases that affect the above factors will therefore affect K excretion.

Potassium shifting

From extracellular to intracellular compartments
Insulin and beta 2 adrenergic agonists stimulate Na/K ATPase, primary in the skeletal muscle cells and cause decrease in extracellular K
Acid-base disorders produce K shifts in a less predictable manner. Generally metabolic acidosis- shifts K out of cells. Metabolic alkalosis-> shifts K into cells.

For metabolic acidosis,

-Mineral acidosis eg Hyperchloremic, non gap acidosis – result in hyperkalemia. Cells are relatively impermeable to chloride and so entry of protons into the cell will result in reciprocal release of K to maintain electroneutrality

-Organic acidosis: eg lactic acidosis- do not affect serum K as cells are highly permeable to the organic anions, with no net change in the electrical balance.

Bicarb administration
With normal renal function, bicarb decreases serum K, mainly due to enhanced urinary excretion of K
In dialysis patients with negligible urinary K excretion, bicarb administration does not lower plasma K acutely

Normal plasma K in general pop : 3.5-5mEq/L. Optimal K in patients on dialysis is higher.
Dialysis outcome and Practice patterns Study (DOPPS)- multinational cohort of dialysis patients- showed lowest risk of death amongst patients with predialysis serum K b/w 4 and 5.5mEq/L, a significant increase in the risks of death and arythmia outcomes at levels >/= 5.6mEq/L, and attenuation of risk associations with plasma K < 4mEq/L after accounting for potential confounding from malnutrition indicators.

Hypokalemia:
Either due to potassium deficiency (inadequate K intake or excessive K loss) or net K shifts from extracellular to intracellular compartments.

Causes of Hypokalemia

Inadequate Potassium intake
Extra renal potassium losses: Vomiting or Diarrhea
Urinary Potassium losses: Diuretics (loop diuretic,thiazides or acetazolamide) or osmotic diuresis (hyperglycemia)

Hypokalemia with Hypertension

I. Low Renin, high aldo

Primary aldosteronism

Glucocorticoid Remediable hyperaldosteronism (GRA): Autosomal dominant condition, fusion of 11β-hydroxylase and aldosterone synthase genes. Aldo secretion is stimulated by ACTH; abnormally high levels of aldo result from physiologic levels of ACTH but can be suppressed by dexamethasone. Similar clinical presentation to primary hyperaldo but patients younger + family hx of HTN.

II. **High Renin, High Aldo**

Renovascular HTN
Renin secreting tumor
Malignant HTN

III. **Low Renin, low Aldo**

Liddle syndrome: Autosomal dominant disorder, increased sodium absorption and K excretion due to Gain of function mutation of ENac channel. C/o hypokalemia, HTN and vol overload. Dx: genetic panel testing. Rx: amiloride

Congenital Adrenal hyperplasia-deficiency of 11β-hydroxylase. Pts will also have elevated deoxycorticosterone acetate. Early puberty in boys, and hirsutism and clitoromegaly in girls.

11β-hydroxy steroid dehydrogenase deficiency : Genetic or drug induced.

11β-hydroxysteroid dehydrogenase coverts cortisol to cortisone in peripheral tissues. Def of this enzyme results in increased cortisol levels→ activates the mineralocorticoid receptors that causes hypokalemia and hypertension.

Glycyrrhizic acid in chewing tobacco, certain French wines, and licorice also inhibits 11β-hydroxysteroid dehydrogenase.

Hypokalemia with normal blood pressure

I. Distal RTA (typeI)
II. Proximal RTA (type II)

III. Bartter syndrome: mutations affecting ROMK,Na/K/2 Cl- co transporter and ClC-Kb in the thick ascending loop of Henle-→ inhibit active sodium reabsorption. Patients present with hypokalemia, metabolic alkalosis, hypercalciuria, high plasma renin and aldo levels. Normal mag levels. (similar to loop diuretic ingestion)
IV. Gitelman syndrome: mutation in distal collecting tubule -Na /K co transporter (similar to thiazide ingestion)
V. Hypomagnesemia (Cis- platinum, alcholisms, diuretics)→ hypomagnesemia impairs renal K conservation.

Hypokalemia due to K shifts

I. Insulin administration
II. Catecholamine excess (Acute stress)
III. Familial periodic hypokalemic paralysis
IV. Thyrotoxic hypokalemic paralysis

Manifestations of hypokalemia: muscle weakness, paralysis. Decreased motility of smooth muscle presenting with ileus or urinary retention. Severe hypokalemia may occasionally produce rhabdomyolysis. Can also cause nephrogenic Diabetes insipidus by interfering with the concentrating mechanism in the distal nephron. Patients will have low urine osm, high serum osm and are refractory to vasopressin.
EKG changes: Low T wave, high U wave. With K < 2.5mEq/L →low T waves, high U waves, low ST-T segment.

Treatment of Hypokalemia: Oral K administration is safer than IV route. IV KCl should be reserved for severe, symptomatic hypokalemia (K < 3mEq/L) or patients who cannot ingest oral Kcl.

Draw blood sample in heparinized syringe and non heparinized syringe-if K is higher in latter (serum) than former (plasma) than diagnosis of leukocytosis /thrombocytosis associated hyperkalemia is confirmed

Hyperkalemia

CAUSES:

A. Pseudohyperkalemia: Spurious hyperkalemia that occurs without any cause or clinical manifestations and no EKG changes. Caused by invitro release of K from blood cells or platelets. Results from 1. Hemolysis 2. Severe Leukocytosis 3. Thrombocytosis 4. Prolonged tourniquet time or fist clenching

B. Decreased Renal excretion

1. Acute or chronic kidney disease
2. Aldosterone deficiency (eg type IV RTA). Also associated with diabetic nephropathy, chronic interstitial nephritis, or obstructive nephropathy
3. Adrenal insufficiency (Addison's disease)
4. Drugs that inhibit K excretion
5. Kidney disease that impair distal tubular function
    a. Sickle cell anemia
    b. SLE

C. Abnormal K distribution

c. Insulin deficiency
d. Beta blockers
e. Familial hyperkalemic periodic paralysis

D. **Abnormal K release from cells**

a. Rhabdomyloysis

b. Tumor lysis syndrome.

E.Genetic Disorders resulting in renal potassium retention

1. Pseudo hypoaldosteronism type I – Autosomal recessive (systemic PHA I- severe symptoms, presenting in childhood). Underlying genetic defect is a loss-of-function mutation of one of the ENaC subunits, with the α subunit being involved much more commonly than the β and γ subunits. Vs Autosomal dominant (AD PHA I; mild sx in early childhood that resolve as patient ages)- Most cases of AD PHA I are caused by mutations in NR3C2, the gene encoding Mineralocorticoid receptor. Presentation: hypovolemia, hyponatremia, hyperkalemia, and metabolic acidosis.

2. Pseudo hypoaldosteronism type II (Gordon syndrome)
Autosomal-dominant disorder characterized by normal renal function, hypertension, hyperkalemia, and hyperchloremic metabolic acidosis,low plasma renin activity and aldosterone. PHA II behaves similar to a gain-of-function in thiazide-sensitive NCCT and the physiologic abnormalities in these patients are corrected easily with treatment with thiazide diuretics. Mutations in WNK1 and WNK4 and two additional genes recently identified kelch-like 3 and cullin 3. Significant phenotypic heterogeneity with large variations in the age of presentation, ranging from the neonatal period to late adulthood. More severe forms of the disease can manifest with short stature, intellectual impairment, and muscle weakness.

3.Congenital Isolated Hypoaldosteronism
Rare autosomal recessive disorder characterized by aldosterone deficiency in the setting of normal cortisol and sex steroid synthesis. Defect in aldosterone synthesis is secondary to loss of enzyme activity in the last step of aldosterone synthesis (aldosterone synthase, CYP11B2)
Patients may present in early childhood with recurrent episodes of hypovolemia, associated with hyponatremia and hyperkalemia, although

most patients improve by the age of 4 years. Management consists of a high-salt diet and exogenous mineralocorticoids, and these often can be discontinued as the patients mature.

4.Salt wasting forms of Congenital Adrenal Hyperplasia secondry to 21-hydroxylase deficiency

Females present with genital ambiguity at birth, and males and females can have salt-losing adrenal crises at birth, with classic features of hyponatremia and hyperkalemia along with metabolic acidosis, as well as hypovolemia, dehydration, failure to thrive, and the potential to progress to hypovolemic shock and death.

F.Drug induced Hyperkalemia

Mechanism of Drug induced Hyperkalemia

I Decrease renal K excretion by

1. Blocking sodium channel in distal nephron
   Include K sparing diuretics: Amiloride, triamterene
   Antibiotics: Trimethoprim, Pentamidine. Trimethoprim also inhibits the collecting tubule H+/K+ ATPase
2. Blocking aldo production
   ACE inhibitors, ARBs, NSAIDs and COX-2 inhibitors, Heparin, Tacrolimus.
3. Blocking Aldo receptors
   Sprinolactone and eplernone
4. Blocking Na/K ATPase activity in distal nephron.
   Cyclosporine

II. Inhibit extra renal potassium excretionl by

1. Blocking beta -2 adrenergic mediated extra renal potassium disposal: mainly with non selective beta blockers (eg propranolol, nadolol, timolol)
2. Blocking Na/K- ATPase activity in skeletal muscles: digoxin overdose.
3. Inhibit insulin release (eg Somatostatin)

III.Potassium release from injured cells

1. Drug induced rhabdomyolysis (eg Lovastatin, cocaine)
2. Drug induced TLS (chemotherapy agents in acute leukemias and high grade lymphomas)
3. Depolarizing paralytic agents (eg succinyl choline)

IV.Drug induced AKI

*In dialysis patients, ask about prolonged fasting- often NPO 8-12 hours for procedures, Fasting decreases plasma insulin concentration→ promotes extracellular shift of K. In normal individuals, excess K is excreted into urine so that plasma K remains constant. In ESRD patients, urinary K excretion negligible. Hyperkalemia can be prevented by administration of IV dextrose infusion (to stimulate endogenous insulin secretion), however if the patient is diabetic increase insulin or add insulin to dextrose infusion to prevent hyperglycemia induced paradoxical hyperkalemia.

Clinical Manifestations of Hyperkalemia

-skeletal muscle weakness, to the point of paralysis
-severe life threatening arrythmias
-EKG: peaked T waves, flattening or absence of P waves, widened QRS complexes and sine waves.

Treatment of hyperkalemia

Hyperkalemic emergencies: Clinical manifestations (weakness, paralysis, abnormal EKG changes) or K > 6.5mEq/L or K > 5.5 mEq/L with significant renal impairment or ongoing tissue breakdown or ongoing K absorption such as in GI bleeds require immediate K lowering therapy

For patients with K < 5.5mEq/L without renal impairment (oliguria or ESRD), not requiring optimization for surgery, K can be lowered slowly- remove offending drug, dietary modification, chronic diuretic use etc

Hyperkalemic emergencies:

1. Stabilize myocardium: IV Ca gluconate - 10 mL of a 10 percent solution, infused over two to three minutes, can be repeated in 3-5 mins if EKG changes do not resolve.
2. Potassium shifting therapies
   a. IV 10 Units Regular insulin + 50mL D50 → fastest way to lower plasma potassium, starts to decrease within 15 mins. Insulin should be given alone if the serum glucose is ≥250 mg/dL
   b. Beta agonist- 20mg of albuterol by nebulization over 10 mins. Onset of action 15 mins
   c. Sodium bicarb administration: can be used in CKD patients not on dialyisis.not useful for dialysis patients, takes 3-4 hrs to work, not additive to insulin and albuterol. Should still be given if severe metabolic acidosis, serum HCO3 < 10.
3. Removing K from body
   a. Diuretics
   b. Sodium polysterene sulfate (kayexalate): resin exchanger , moves K into gut in exchange for sodium. Relatively slow acting. 1-2 hours before decrease in plasma K. Risk of colonic necrosis.
   c. Patiromer- binds potassium in exchange for Ca in the gut. More favorable than kayexalate
   d. Zirconium cyclosilicate: cation (sodium-potassium) exchanger that has a ninefold higher K binding capacity (per g) than kayexalate.
   e. Hemodialysis.

** Obstructive uropathy/Acute urinary retention- one common cause that can be quickly fixed in patients with hyperkalemia. Ask ER for bladder scan/ foley to relieve obstruction.

Chapter EIGHT:
Evidence Based Medicine (EBM)

	Disorder	No Disorder
Positive Test Result	True Positive (TP)	False Positive (FP)
Negative Test Result	False Negative (FN)	True Negative (TN)

Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)
PPV = TP/(TP+FP)
NPV = TN/(FN+TN)

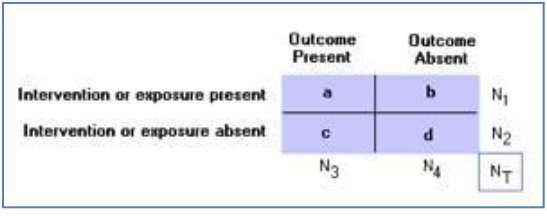
	Cases	Controls	Total
Exposed	a	b	a+b
Unexposed	c	d	c+d
Total	a+c	b+d	a+b+c+d

OR = (a/b)/(c/d)
RR = (a/a+b)/(c/c+d)

- Sensitivity-test's ability to correctly identify those with the disease. SnOut- a test with high **sensitivity** is effective in ruling **out** the disease. If a patient has a negative test result, and the test has high sensitivity, then likely the disease is ruled out in the patient.
- Specificity-test's ability to correctly identify those without the disease. SpIn- a test with high **specificity** is effective in ruling **in** the disease. If a patient has a positive test results, and the test has high specificity, then likely the patient has the disease.
- Odds Ratio (OR)- the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. OR=odds of disease in exposed / odds of disease in the non-exposed. OR of 1 means no association

- Absolute Risk- the actual event rate in the placebo or treatment group

Relative Risk



	Outcome Present	Outcome Absent	
Intervention or exposure present	a	b	N_1
Intervention or exposure absent	c	d	N_2
	N_3	N_4	N_T

The ratio of the incidence of disease among exposed to the incidence among non-exposed. A measure of the strength of an association between groups Prospective studies (RCTs and cohort studies), also called the incidence risk.

RR = risk of disease in the exposed (a/a+b) / risk of disease in the non-exposed (c/c+d). Ex: RR of 3 -> there is three times the risk. RR of 1 -> there is no association. If the RR is reported with a CI that includes 1 -> then the RR is not significant.

- Relative Risk Reduction (RRR)
  - Expressed as a percentage reduction in events in treated vs untreated groups
  - RRR= 1 – (incidence in exposed / incidence in unexposed)

- Absolute Risk Reduction (ARR)
  - incidence in exposed – incidence in unexposed
  - a measure of treatment effect
  - reverse of attributable risk

- Number Needed to Treat (NNT)
  - NNT is the number of patients who need to be treated in order to avoid one adverse event, which is the reciprocal of the absolute risk reduction

NOTABLE NEPHROLOGY TRIALS

SALT-1, SALT-2: Tolvaptan use is beneficial in euvolemic and hypervolemic hyponatremia
CREATE: Correction of anemia to normal range (13-15 g/dl) in CKD III and IV patients does not reduce risk of cardiovascular events.
Normal Hematocrit Study: In ESRD patients on hemodialysis with CHF or ischemic heart disease, administering epoetin to increase Hct to 42% is not recommended.
CHOIR: Higher Hb target associated with increased risks and no change in quality of life

TREAT: Use of ESA in those with DM, CKD (not on dialysis), and anemia did not reduce risk of death or cardiovascular event, or ESRD, but did increase stroke risk.
SHARP: LDL reduction with simvastatin and ezetimibe safely reduced major atherosclerotic events in those with advanced CKD (includes dialysis patients).
EVOLVE: Cinacalcet does not reduce risk of mortality or major cardiovascular events in those with moderate-severe secondary hyperparathyroidism in ESRD patients on dialysis.
ALLHAT: In patients with HTN, chlorthalidone, amlodipine, and lisinopril performed similarly in regards to fatal CAD and nonfatal MI
ASTRAL: Revascularization + medical treatment in renal artery stenosis (RAS) does not preserve renal function compared to medical treatment alone (in patients not clearly requiring revascularization)
STAR: Renal artery stenting + medical treatment in atherosclerotic RAS did not effect renal impairment progression compared to medical treatment alone.
SPRINT: High risk cardiovascular disease patients without DM or CVA, intensive BP control (SBP<120 mmHg) improved CV outcomes and overall survival compared to SBP 135-139 mmHg.
PATHWAY-2: In patients with resistant hypertension treated with an ACEI or ARB, a CCB and a diuretic, the addition of spironolactone is superior to placebo, doxazosin or bisoprolol in reducing SBP. No difference seen in DBP.
LUNAR: Rituximab did not improve clinical outcomes in those with class III or IV lupus nephritis, already on combination of MMF and steroids, after 1 year of treatment.
STOP-IgAN: No significant difference in renal function or clinical remission of IgA nephropathy in those who received intense supportive care (RAAS blockade, statin, smoking cessation) vs. those who also received immunosuppression (steroids or Cytoxan / azathioprine / steroids).

ELITE-Symphony Trial: In renal transplant recipients, maintenance immunosuppression with calcineurin inhibitors was superior to sirolimus and cyclosporine in renal function, allograft survival, and and lower acute rejection rates.
CREDENCE: In type II diabetics with CKD (eGFR 30-90, with albuminuria) and on RAAS blockade, canagliflozin (SGLT-2 inhibitor) decreased risk of renal failure and cardiovascular events compared to placebo at median follow up of 2.6 years.

References:

- Carvajal, Diana & C Rowe, P. Sensitivity, specificity, predictive values, and likelihood ratios. Pediatrics in review / American Academy of Pediatrics. 2010: 31, 511-3. 10.1542/pir.31-12-511.
- https://www.cebm.net/2014/03/sppin-and-snnout/
- Straus, S. E., Glasziou, P., Richardson, W. S., & Haynes, R. B. (2005). *Evidence-Based Medicine: How to Practice and Teach It.* Philadelphia: Elsevier Churchill Livingstone
- https://lifeinthefastlane.com/ccc/odds-ratio/
- https://lifeinthefastlane.com/ccc/risk-and-numbers-needed-to-treat/
- https://www.wikijournalclub.org/wiki/WikiJournalClub:List_of_landmark_papers/Nephrology
- Gilbert, SJ, et al. National Kidney Foundation's Primer on Kidney Diseases. 2018.

Chapter NINE: Glomerulonephritis

Table 2 | MEST criteria in the Oxford classification

Histological variable	Definition	Score
Mesangial hypercellularity	More than four mesangial cells in any mesangial area of a glomerulus	M0 (<50% of glomeruli showing mesangial hypercellularity) M1 (>50% of glomeruli showing mesangial hypercellularity)
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina	E0 (no endocapillary hypercellularity) E1 (any glomeruli showing endocapillary hypercellularity)
Segmental glomerulosclerosis	Adhesion or sclerosis (obliteration of capillary lumina by matrix) in part but not the whole glomerular tuft	S0 (absent) S1 (present in any glomeruli)
Tubular atrophy/ interstitial fibrosis	Estimated percentage of cortical area showing tubular atrophy or interstitial fibrosis, whichever is greater	T0 0–25% T1 26–50% T2 >50%

Abbreviations: E, endocapillary hypercellularity; M, mesangial hypercellularity; S, segmental glomerulosclerosis; T, tubular atrophy/interstitial fibrosis.

IgA nephropathy

Epidemiology: Increased incidence in Pacific Asian regions.
Presentation: Two most common presentations:
1- Asymptomatic hematuria 2- Progressive kidney disease

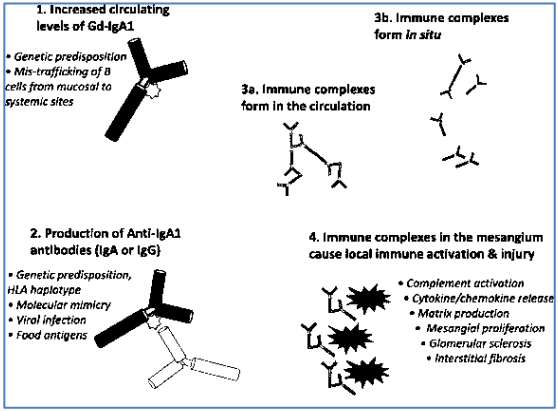
Histological manifestations?

- Polymeric IgA deposition in the mesangium, mesangial proliferative GN, complement deposits are usually C3 and properdin without C1q and C4

Serum complement levels: Normal

Oxford classification of IgA nephropathy

Pathogenesis Aberrant IgA1 O-linked glycosylation of the IgA1 hinge region with galactosylated IgA1 O-glycoforms in the circulation > leads to IgA immune complex formation and mesangial IgA deposition



Treatment:

1- Conservative therapy

Supportive therapy- anti-hypertensive with RAAS-inhibition
Life style modifications: Weight loss and smoking cessation
Dual RAS blockade may reduce proteinuria, but not being used due to risk of hyperkalemia in ONTARGET trial

2- Corticosteroids

Steroids may be considered if proteinuria > 1g/day after optimum supportive care for 3 to 6 months AND GFR is > 50ml/min.

3- Immunosuppression: Cyclophosphamide, MMF and Azathioprine are not recommended for intermediate risk patients**. Crescentic**

IgAN with rapidly progressive renal failure: GCs + cyclophosphamide

4- **Fish Oil:** We suggest using fish oil in the treatment of IgAN with persistent proteinuria>1 g/d, despite 3–6months of optimized supportive care

Prognosis:
Patients with significant proteinuria or hypertension have an intermediate prognosis.

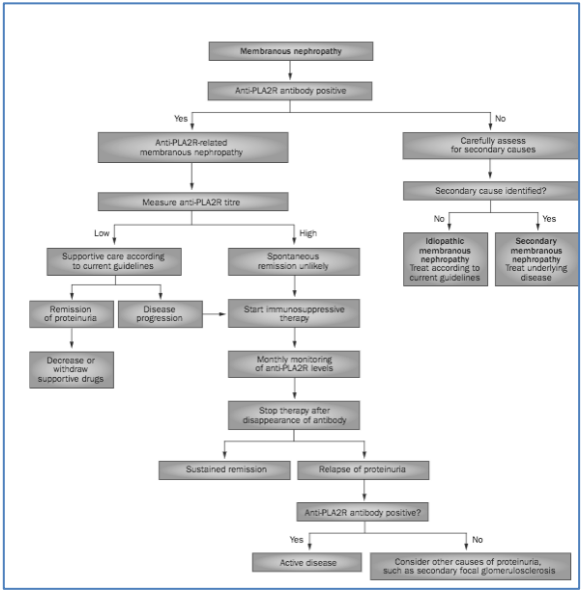
Minimal Change Disease (MCD)
Epidemiology? 10 to 15% of cases of primary nephrotic syndrome in adults. Most common cause of the nephrotic syndrome (NS) in children.
Histological manifestations?
Light Microscopy: Normal
IF: Typically, negative but may show low-level focal staining for C3 and IgM
EM: Diffuse effacement and fusion of a majority of podocyte foot processes

Complete remission: A daily urine protein excretion of <0.3 g/d, urine protein/creatinine ratio of <0.3, or trace or negative results on repeat urine albumin dipstick; partial remission was defined as ≥50% reduction of proteinuria from baseline.

Time to remission: Time from initiation of therapy to the first day on which remission is observed. **Relapse:** Increased protein excretion to >3 g/d with 3+ or 4+ results on urine albumin dipstick

Treatment and Prognosis
- Supportive care i.e. low-sodium diet and diuretics
- Initial therapy for presumed or biopsy-proven MCD:
- PO prednisone daily (1mg/kg/d) or every other day (2mg/kg/day)

- Response determines prognosis-steroid responsive vs. steroid resistant MCD
- Immediate steroid responsiveness is a marker of good long-term prognosis
- 20%- refractory to steroids
- 10% - completely free of relapses after initial treatment
- 30% - infrequent relapses requiring re-treatment with corticosteroids
- 30% - $\geq$ 2 episodes in 6 months treated with intermittent steroid therapy
- 30% - frequently relapsing/steroid dependent and are candidates for 2nd line therapy due to side effects from chronic steroid use
- Second line therapy options:
- Cyclophosphamide (2-2.5mg/kg/d) x 8-12 weeks.
    - Results in prolonged remission in 70% of patients
- Mycophenolate Mofetil (1-1.5g BID)
    - Results in 50% reduction in relapse rate
- Tacrolimus (0.05-0.3mg/kg/d in divided doses)
    - Associated with higher remission rate of 80-90%, but relapses shortly after cessation of therapy
- Rituximab (375 mg/m^2 weekly x 4 weeks)
    - Used for steroid-dependent or frequently relapsing MCD in steroid sensitive patients, along with Tacrolimus
- Rare cases of presumed MCD in childhood, who have a poor outcome and progressive GFR loss, may actually represent unidentified FSGS



Membranous Nephropathy (MN)

Primary MN

Epidemiology: Primary membranous nephropathy can affect up to 40% in adults older than 60 years old. Rarely happens in children around 1-7% of biopsies.

Histological findings:

Light microscopy: Sub epithelial immune complex of IgG and complement, possible presence of PLA2R if anti PLA2R positive MN

Electron microscopy: Sub epithelial electron dense deposits

Treatment:
Low salt diet, protein 08mg/kg/day, blood pressure control, diuretics, statins
Anticoagulation if (proteinuria> 10 grams or albumin <2.5g/L

When to add immunosuppression? Progressive loss of GFR or proteinuria refractory to 6 months of supportive care. In order to select the best treatment option: divide patients into 3 categories: a) Low risk (less than 4 grams proteinuria, stable GFR). b) Moderate risk (4-8 grams/d with stable GFR); c) high risk (>8 grams/day <50% decrease from baseline)
Start I/S for B and C.

Focal Segmental Glomerulo-Sclerosis (FSGS)
Epidemiology: 35% of the nephrotic syndrome in adults
Histological findings: Different types based on the histological findings; perihilar- cellular- Collapsing and tip. Peri hilar is frequent in secondary forms of FSGS and cellular is usually primary.
Light microscopy: Hyalinosis, endocapillary foam cells and adhesions to bowman capsule
Electron microscopy: Complete effacement of the foot process, increased ECM matrix
IF: Positive for IgM, C3 and maybe C1
How many types?
FSGS is categorized into two subtypes: 1- Primary FSGS: could be associated with suPAR (soluble urokinase plasminogen activator receptor) – More common in African Americans. FULL effacement of the foot process 2- Secondary FSGS: Genetic (e.g. APOL1, mutations in nephrin); Infection (viral infections; HCV); Medications (e.g. bisphosphonates); Adaptive

(HTN, Obesity, Reflux → less nephrons to filter the blood). SEGMENTAL effacement of foot process

Treatment:
Secondary FSGS: Treat the underlying cause
Primary FSGS: Treat with immunosuppressive therapy: prednisone is first line. If patient is steroid resistant; secondary treatment oral cyclosporine, tacrolimus, MMF or cyclophosphamide

Treatment: (detailed): Only primary FSGS should be treated with immunosuppressive therapy; Prednisone daily (1mg/kg/d) or every other day (1.5-2mg/kg/d) for a minimum of 4 weeks and maximum of 16 weeks, with a slow taper over 6 months after achieving complete remission.
Options for steroid-resistant patients: Oral cyclosporine 3-5 mg/kg/day for 4-6 months (many clinicians extend to one year with slow taper due to high relapse rate). Tacrolimus in patients who are intolerant of cyclosporine; Oral MMF 1-1.5g bid plus dexamethasone for 4-6 months for patients who do not tolerate CNIs; Oral cyclophosphamide 2mg/kg/day for 2-4 months; Patients with secondary FSGS- Treat underlying cause

Prognosis: Without therapy or response to therapy, majority will progress to renal failure; Only 5-25% of patients undergo spontaneous remission of proteinuria. 50% of patients develop ESKD in 10 years from presentation. African Americans experience a more rapid progression to renal failure Outcomes are best for tip variant and worse for collapsing variant of primary FSGS

Transplantation:
- Approximately 40% of patients with primary FSGS develop recurrent FSGS in the allograft
- Those with prior allograft loss due to recurrent FSGS = highest risk of recurrence

- Plasma exchange has been used successfully to induce remission of proteinuria associated with recurrence
    - Results more favorable in children > adults.

Membranoproliferative Glomerulonephritis (MPGN)

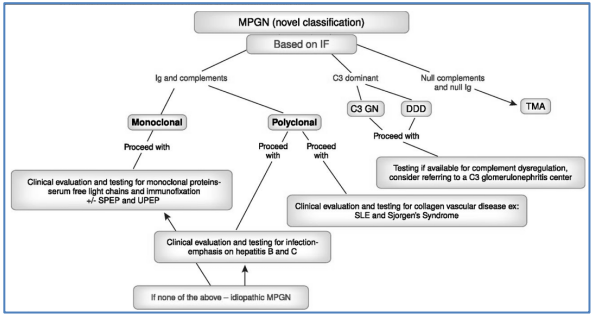
Epidemiology: Idiopathic MPGN is one of the least common types of GN.

Presentation: Nephritic GN but may display nephrotic range proteinuria

***Histological manifestations*?**

- Hypercellularity and intrinsic glomerular cell proliferation**,** double-contouring of the GBM, deposition of IgG, IgM and C3, separation of GBM from membrane, mesangial, subendothelial and even subepithelial

Types of MPGN



- Type 1: Ig and complements
- Type 2: C3 dominant
- Type 3: Null complement

Serum complement levels: Low

Treatment:

Idiopathic MPGN:

Nephrotic syndrome plus progressive decline in renal function > Cyclophosphamide (Rituxan alternatively) or MMF + GCs
In the setting of RPGN: Cyclophosphamide or MMF + high dose pulse steroids.
Secondary MPGN treat underlying cause. Ritux if HCV once HCV clear. **Prognosis:** 50% mortality or need for RRT within 5 years after diagnosis

	Light Microscopy	**Electron Microscopy**
Class I (Minimal Mesangial LN)	Normal glomeruli	
Class II (Mesangial Proliferative LN)	Pure mesangial hypercellularity – More than 3 mesangial cells in areas away from the vascular pole.	
Class III (Focal LN)*	Focal segmental or global, endocapillary or extracapillary GN, affecting less than 50% of the total sampled glomeruli.	Sub-endothelial deposits
Class IV (Diffuse LN)*	Diffuse segmental or global, endocapillary or extracapillary GN, affecting 50% or more of the total sampled glomeruli.	Sub-endothelial deposits
Class V (Membranous LN)	Defined by sub-epithelial immune deposits. Membranous changes may be present alone or on a background of mesangial hypercellularity and mesangial immune deposits. Patients with additional features of class III and IV are classified as V+III or V+IV respectively.	sub-epithelial deposits
Class VI (Advanced Sclerosing LN)	Global glomerular sclerosis, affecting $\geq$ 90% glomeruli.	

Lupus Nephritis (LN)
Epidemiology: Peak incidence from 15-45 years, more common in females but in people with lupus, lupus nephritis affects both genders equally.
Presentation: Proteinuria (100%), microhematuria (80%), reduced GFR (40-80%), RPGN (10-20%), HTN (15-50%).
Histological manifestations:

IF: IgG is the dominant immunoglobulin, and C4 and C1q are usually present along with C3. "Full-house Staining" – Presence of IgG, IgA and IgM, along with C3 and C1q → highly suggestive of LN. Strong C1q staining is also suggestive of LN. May show aggregates of C3 in tubular basement membrane (found in 60-65% of biopsy specimens).

EM: Some electron dense deposits have organized microtubular or fibrillar sub-structure, known as "fingerprinting Tubuloreticular inclusions may be found in endoplasmic reticulum of renal endothelial cells, and are thought to reflect increased interferon expression.

Treatment: Unless contraindicated, all should be treated with hydroxychloroquine

- Treatment is divided into initial phase and maintenance phase-
  - *Initial therapy*-guided by ISN/RPS histological classification
    - ISN class I and II → no therapy indicated
    - ISN Class III (A and A/C), Class IV (A and A/C) and Class V → combined corticosteroid and immunosuppressive therapy
    - Corticosteroids are started at high dose (1mg/kg/day orally or 1g IV daily for 3 days) and then tapered to 10 mg/day by 3-6 months.
    - Steroids + PO cyclophosphamide daily or IV monthly pulses (0.5-1g/m2) for 6 months can be used.

- Mycophenolate Mofetil (MMF) + steroids for 6 months can be used for initial therapy and are at least as effective as cyclosphosphamide + steroid regimens.
- Optimum dose remains unclear, but 2-3 g/d of MMF orally can be used for initial therapy.
- Azathioprine can be used if MMF or cyclophosphamide is contraindicated
  - CNIs- tested as an alternative to cyclophosphamide and have favorable short-term response

Maintenance Therapy

- PO prednisone- continue at 5-15mg/day
- Azathioprine or MMF are effective maintenance drugs and improve survival
- For most patients, MMF > AZA but AZA can be used in appropriate clinical settings, e.g. a patient who wants to get pregnant.
- CNIs can be used for patients who cannot tolerate MMF and AZA.

Treatment for Membranous Lupus Nephropathy:

- For patients with sub-nephrotic proteinuria, reno-protective and anti-proteinuric therapies should be used. Short course of steroids or a CNI can be considered.
- Immunosuppressive regimens should be considered for all patients with nephrotic range proteinuria.
  - MMF, AZA, or CNI is preferred
- Cyclophosphamide = reserved for refractory cases.
- Membranous nephropathy can exist in association with class III and IV LN. In these patients, treatment is directed at the proliferative component.
  - Remission only occurs in 30-40% of LN patients by 12 months.
- Defined as reduction in proteinuria to less than 0.5g/24h, absence of glomerular hematuria/RBC casts and stabilization/normalization of GFR.

Transplantation

- Most centers defer transplantation until lupus is quiescent for 6 months
- If ↑ anti-DNA antibody levels, transplant immunosuppressive medications can be started few weeks before living donor transplantation
- Patients with Anti-phospholipid antibody are at high risk for allograft thrombosis.
- Recurrent LN occurs in 2-11% of transplanted kidneys

Infection-Related GN (IRGN)

Presentation: Hematuria, proteinuria, HTN, edema maybe present. Hypocomplementemia (30-80% of patients); commonly 7-10 days after oropharyngeal infection and 2-4 weeks after skin infection

Histological findings:

Biopsy findings influenced by organism, site and duration of infection.

Light Microscopy: Wide range of proliferative glomerular lesions- most common is diffuse endocapillary proliferation with ↑ infiltrating neutrophils. A membranoproliferative pattern can be seen when infection is long-standing. Subacute or remote cases may show focal endocapillary proliferation or mesangial proliferative appearance. Necrotizing and crescentic GN: a pattern associated with endocarditis

IF: Dominant or co-dominant staining for C3, with lesser degree of Ig staining. In classic PSGN, IgG is seen in a similar distribution to C3. In staphylococcus infections, IgA is commonly the dominant immunoglobulin. Endocarditis associated IRGN may have pauci-immune appearance

EM: Classic finding is hump-shaped subepithelial electron-dense deposits. Mesangial deposits and subendothelial deposits are also present

Treatment:

- Mostly supportive and treat underlying symptom/infection
- In select cases with aggressive crescentic GN and rapidly progressive disease-immunosuppression with IV methylprednisolone may be of benefit

AL- Amyloid and Light Chain Deposition Disease (LCDD)

AL- Amyloid

Presentation: Typically involves other organs, proteinuria, reduced GFR.

- Histological findings: Light Microscopy: Mesangial nodules that enlarge and cause progressive effacement of glomerular capillaries
- IF: Light chain deposits in mesangium, subepithelial space of capillary loops and may penetrate GBM in advanced stages. + congo red stain that produces apple-green birefringence under polarized light and with thioflavin T and S.
- EM: Randomly oriented, non-branching fibrils: 7-10 nm in diameter.

Treatment: For AL-amyloidosis without features of MM, high-dose chemotherapy with autologous peripheral stem-cell transplantation (HDT/SCT) are an option

- More conservative approaches = patients age > 80 years, LVEF < 40%, SBP < 90 mmHg, oxygen saturation < 95% on room air, or overall significant functional impairment
- Patients who undergo HDT/SCT have a median survival of 4.6 years compared to patients ineligible for HDT/SCT whose median survival is 4 months
- Thalidomide, Lenalidomide and Bortezomib based regimens can be used to reduce monoclonal plasma cell population and light chain production

HIV Associated Nephropathy (HIVAN)

Epidemiology: Patients of African descent more susceptible due to high frequency of APOL1

Presentation: Nephrotic range proteinuria, Decreased GFR, bland urine sediment.

Histological findings. Light Microscopy:

- Collapse of glomerular capillaries involving entire glomerulus, visceral glomerular epitheliosis, podocyte hypertrophy and proliferation surrounding shrunken glomerulus, and mesangial prominence and hypercellularity
- Tubular injury is marked by tubular dilation, tubular atrophy, and proteinaceous casts
- Modest interstitial inflammation may be present with lymphocytes, plasma cells, and monocytes
- Histology of HIV-ICD includes MPGN types I and II, IgA nephropathy, membranous nephropathy, lupus-like GN, TMA and post-infectious GN.
- IF: Generally non-specific in HIVAN.
- EM: diffuse foot process effacement and possible endothelial tubuloreticular inclusions (TRIs) without immune-complex deposits.

Treatment: Starting HIV treatment.

Diabetic Nephropathy

Epidemiology: Leading cause of ESRD

Presentation: Proteinuria.

Histological findings:

Light Microscopy:

- Progressive diffuse mesangial expansion, seen mainly on PAS stain.
- Areas of extreme mesangial expansion called Kimmelstiel-Wilson nodules (50% of patients)
- Arteriolar hyalinosis

- GBM and Tubular BM (TBM) thickening may be seen
- Changes in type II diabetes are more heterogeneous than type 1 DM.

- IF: ↑ in linear staining of GBM, TBM and Bowman capsule, mainly for IgG (IgG4) and albumin.
- EM: Thickening of GBM and TBM, and ↑ in mesangial matrix from 20% (normal) of glomerular volume to 40% when proteinuria begins to 80% in stage 3 CKD

Treatment:

- Goals- slowing the rate of kidney disease progression as well as primary and secondary prevention of CV disease.
- In type 1 diabetes patients who receive pancreas transplant, normoglycemia for ~ 10 years: see reversal and disappearance of abnormalities on LM, including Kimmelstiel-Wilson nodular lesions
- Target hemoglobin A1C < 7% → reduces risk of kidney disease progression

Chapter TEN: Transplantation

Indications for Kidney Transplant:
Dialysis dependent ESKD, or creatinine clearance / GFR < 20 ml/ minute
Contraindications to kidney transplantation:
Absolute Contraindications:

1. Active infection or malignancy
2. Active alcohol or drug use, or chemical dependency
3. High potential for medical non-compliance
4. AIDS with CD4 counts < 200/mm3 or detectable viral load, despite anti-retroviral therapy (ART), or noncompliance with ART or inability to tolerate ART as prescribed
5. Poorly controlled psychosis

Relative Contraindications:

1. Significant uncorrected cardiac disease (e.g. congestive heart failure with significantly reduced ejection fraction; uncorrectable advanced coronary artery disease, active angina, significant valvular heart disease).
2. Significant pulmonary disease including severe pulmonary hypertension.
3. Advanced liver disease (e.g. cirrhosis by biopsy or other criteria where patient is not a simultaneous liver transplant candidate), active hepatitis B, short gut syndrome or other severe malabsorptive state.
4. Severe vascular disease: coronary, cerebral or peripheral.
5. Renal disease with significant potential for recurrence causing early kidney graft loss: e.g., active or recurrent atypical Hemolytic Uremic Syndrome (HUS) or type 2 (dense deposit) MPGN.
6. Multiple prior abdominal surgeries or radiation exposure with extensive adhesions.

7. Obesity: BMI >35 with significant abdominal obesity (Different centers have different cut-offs)

Immunosuppression:

Induction for high-risk patient population (Current or historic PRA > 30%, re-transplant patients, African Americans < 50 years of age, DSA + but crossmatch – patients)

Thymoglobulin 1.5mg/kg/day – T-lymphocyte depleting agent - First dose given intra-operatively followed by daily dosing for a total of 3 doses (Immediate graft function) or 5 doses (for delayed graft function) – Dose can be reduced to 0.75mg/kg/day if WBC count is less than 3K or platelet count is less than 50K.

Methylprednisolone 250 mg IV is also given on the day of surgery

Induction for low-risk patient population (Anyone who is not high-risk OR Kidney transplant in a patient with a functioning non-renal transplant)

Basiliximab (Simulect) – Interleukin-2 (IL-2) Inhibitor - 20 mg IV on days 0 and 4

Methylprednisolone 250 mg IV given on the day of surgery

Maintenance Immunosuppression: (Please see Figure 1)

Three-drug regimen is the standard of care in most institutions.

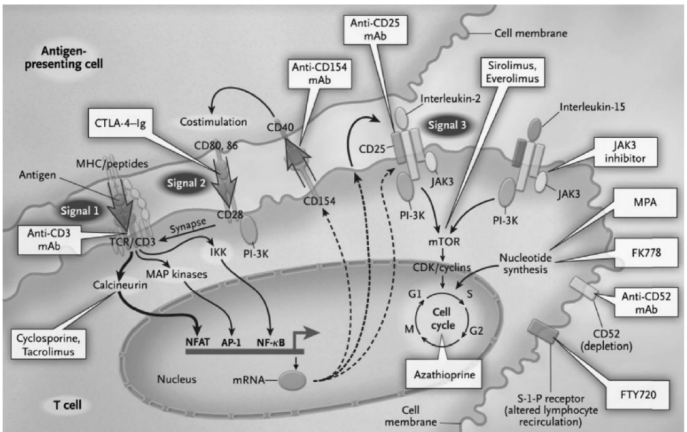


Figure 1. Mechanisms of immunosuppression. Abbreviations: AP-1, activator protein 1; CTLA, cytotoxic T-lymphocyte–associated antigen; FTY, finglolimod; IKK, I κ B kinase; JAK3, Janus kinase 3; MAP, mitogen-activated protein; MHC, major histocompatibility complex; MPA, mycophenolic acid; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor κB; PI-3K, phosphoinositide 3-kinase; S-1-P, sphingosine-1-phosphate; TCR, T-cell receptor. Adapted from Halloran (*N Engl J Med.* 2004;351(26):2715-2729) with permission of the Massachusetts Medical Society; original content © 2004 Massachusetts Medical Society.

1/Tacrolimus (FK-506, Calcineurin-Inhibitor): Works on signal 1 to inhibit T-cell proliferation. Both tacrolimus and cyclosporine exert their effects by binding their respective cytoplasmic receptors,
cyclophilin and tacrolimus-binding protein (also known as FK506 binding protein [FKBP]), respectively, thus inhibiting calcineurin and the expression of several cytokines that are integral for lymphocyte proliferation.
Timing of initiation of Tacrolimus is variable across institutions. But most centers, start tacrolimus by post-op day 1 at a dose of 0.05 mg/kg (6 am, 6 pm dose schedule). Dose is titrated according to 12 hour trough level. First trough level should be drawn 48 hours after the first dose.
Target trough level (drawn 30 minutes before 6am dose) depends on duration since transplant. Goal FK level is 8-10 ng/ml up to 6 months, 6-8 ng/ml until 1 year and then 4-6 ng/ml thereafter. Dose can be adjusted based on side-effects and frequency and severity of infections. If tacrolimus cannot be given orally, half of required dosage can be given sublingually, and IV dose can be given in a 4:1 ratio.
Hyperkalemia is a side-effect of tacrolimus, caused by a decrease in sodium delivery to collecting duct, and may respond to thiazide diuretics. It is metabolized by cytochrome P-450 and there are several drug interactions, as listed in Table 1.

Cyclosporine (CyA) is an alternative calcineurin-inhibitor that can be used as a maintenance agent with target trough level of 75-125 ng/ml after first year of transplant.

2/Mycophenolate Mofetil (MMF/Cellcept):
MMF is a prodrug for which the active metabolite is mycophenolic acid (MPA), an inhibitor of the enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH catalyzes the generation of guanosine nucleotides from inosine in de novo purine synthesis. MPA specifically inhibits T-cell proliferation because other cell lines are less affected due to a salvage pathway for the production of guanosine nucleotides. MPA also downregulates the

Table 1. Common Drug Interactions

Agent	Comment
Common Drugs That Increase CNI Level	
Erythromycin, clarithromycin	Potent inducers of cytochrome P450 *Alternatives:* Azithromycin is an acceptable alternative in some cases, less impact on drug metabolism
Azole antifungals	Potent inhibition of cytochrome P450
Diltiazem, verapamil	Moderate inhibition of cytochrome P450 *Alternatives:* Nondihydropyridine calcium channel blockers or β-blockers
Protease inhibitors (eg, ritonavir, darunavir, indinavir)	Very potent inhibitors of metabolism *Alternatives:* nucleoside reverse-transcriptase inhibitors, non-nucleoside reverse-transcriptase inhibitors, or integrase inhibitors
Common Drugs That Decrease CNI Level	
Rifampin	Inducer of cytochrome P450
Rifabutin	Inducer of cytochrome P450
Carbamazepine	Inducer of cytochrome P450
Phenobarbital	Inducer of cytochrome P450

Note: This is by no means an exhaustive list. It is advised to check for drug interactions when initiating new medications in transplant recipients.
Abbreviation: CNI, calcineurin inhibitor.

expression of adhesion molecules and thus limits lymphocytes from binding to vascular endothelial cells, inhibiting lymphocytes from entering rejection sites.
MMF is usually started on post-op day 0 or 1 if using basiliximab induction. However, if using thymoglobulin for induction, usually need to wait for thymoglobulin dosing to finish before starting MMF. Target dose is 1000 mg oral BID for majority of patients. Dose can be adjusted based on GI tolerability and frequency and severity of infections. Dose may need to be reduced in the setting of neutropenia. Myfortic (720 mg oral BID) is an enteric-coated mycophenolic acid (MPA) alternative that can be used if MMF is causing severe GI adverse effects, although the benefit of switching is not well-established.
3/Prednisone: Corticosteroids inhibit nuclear factor κB (NFκB), a transcription factor necessary for the expression of several cytokines that are integral for T-cell activation. Glucocorticoids also induce lymphopenia as a result of lymphocyte migration from the vascular compartment to the lymphoid tissue.
Steroids are usually tapered over the first few weeks post-transplant, down to a maintenance dose of 5 mg oral daily. Steroid-sparing protocols stop steroids within the first 3 months after transplant or do not use steroids at all. Risk of acute rejection is higher if steroids are used for less than 14 days or are withdrawn later in the post-transplant period, as shown in a large meta-analysis of 48 studies by Haller et al.

- Less commonly used immunosuppressive agents are mTOR inhibitors (Sirolimus, Everolimus), Belatacept and Azathioprine. Details are not discussed in this chapter.

Anti-Infection Prophylaxis
PCP prophylaxis: TMP-SMX (bactrim) SS daily or DS 3x/week should be used for 1-year. TMP-SMX protects against PCP, toxoplasmosis, nocardia, listeria, common respiratory, urinary and GI pathogens. Second-line agents include Dapsone (50-100 mg daily/contraindicated in G6PD deficiency) and Atovaquone (1500 mg daily). In sulfa-allergic patients, aerosolized

Pentamidine nebs (300mg) can be used once every 4 weeks but risk of breakthrough infections is high with Pentamidine compared to bactrim.
CMV prophylaxis: Valganciclovir (Valcyte) is used for CMV prophylaxis. Dose of Valcyte should be adjusted for GFR and can be reduced to 3x or 2x/week. Dose, duration and decision to use Valcyte depends on donor and recipient CMV-IgG antibody status.
If D+/R-, Valcyte 900 mg daily for 200 days
If D+/R+ or D-/R+, Valcyte 450 mg daily for 100 days
If D-/R-, no need for Valcyte unless thymoglobulin induction was used, or donor was transfused prior to harvest.
Fungal prophylaxis: Nystatin (5ml swish and swallow 4x daily) or clotrimazole (10mg troches 3x daily) are used for 1 month. Clotrimazole can interfere with FK/CyA metabolism and dose of CNIs needs to be adjusted once clotrimazole is stopped.
Monitoring Kidney Function Post-Transplant and Evaluation of Acute Kidney Injury
Regular monitoring of kidney function is required throughout the life of the transplanted kidney. Early after transplantation, kidney function is monitored twice weekly for a month, with a gradual decrease in the frequency of monitoring over the first year. Standard practice is to monitor laboratory values indicative of transplant function no less than every 3 months indefinitely. Should a recipient develop an acute illness, especially a viral illness or urinary tract infection, it is wise to check the Scr concentration after the illness because a generalized immune
response can trigger rejection. A general rule in monitoring transplant recipients is that a 20% to 25% increase in Scr concentration above baseline warrants attention. Evaluation includes at a minimum kidney ultrasound to rule out obstruction, as might be seen with inadequate bladder emptying, stone, or ureteral stricture. Doppler studies should be included with the ultrasound to assess vascular inflow if blood pressure is elevated or bruit is appreciated over the kidney. Assessment for BK viremia can also shed light on the cause of an elevated Scr level.

Serum viral load > 10,000 copies is associated with BK nephropathy. Major causes of AKI in kidney transplant recipients are summarized in Table 2.

Table 2. Differential Diagnosis of Acute Kidney Injury in Kidney Transplant Recipients

	Comments	Evaluation
Decreased Kidney Perfusion		
Volume depletion	Poor intake or diarrhea	Physical examination, assess electrolytes
Renal artery stenosis	Typically associated with hypertension	Ultrasound with Doppler study
Calcineurin inhibitor toxicity	Causes vasoconstriction	Tacrolimus or cyclosporine level
Obstructive Causes		
Ureteral stricture	May be seen with BK infection	Ultrasound with evaluation of the ureter
Bladder dysfunction	Neurogenic bladder	Ultrasound, postvoid residual
Bladder outlet obstruction	Prostatic enlargement	Ultrasound and postvoid residual
Intrinsic Kidney Injury		
Acute cellular rejection	Can be triggered by recent infection or immunosuppression reduction	Renal allograft biopsy
Acute antibody-mediated rejection	Especially if immunosuppression has been reduced	Donor-specific antibodies, renal allograft biopsy
Drug toxicity	Calcineurin inhibitors, antibiotics	Therapeutic drug level monitoring, kidney allograft biopsy
Infection	Transplant pyelonephritis, BK virus infection	Urine culture, BK viral load in plasma
Posttransplantation lymphoma	Rare occurrence	EBV plasma viral load, kidney allograft biopsy
Recurrent disease	IgA, MN, FSGS, MPGN, immune complex disease	Kidney allograft biopsy

Abbreviations: EBV, Epstein-Barr virus; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis.

Proteinuria is another indication for kidney allograft biopsy. Non–nephrotic-range proteinuria may be seen with early transplant glomerulopathy associated with chronic antibody-mediated rejection (CAMR). Nephrotic range proteinuria can be associated with transplant glomerulopathy as well but may be an indicator of diabetes or recurrent or de novo diseases such as focal segmental glomerulosclerosis (FSGS), membranous glomerulopathy, or other immune complex deposition diseases. The gold standard in assessment of an increased serum creatinine concentration is the kidney allograft biopsy. The biopsy may identify

acute or chronic rejection, recurrent or de novo kidney disease, viral or other infections, or progressive scarring with interstitial fibrosis and tubular atrophy. Acute and chronic rejection is graded based on severity, typically using Banff criteria.
Rejection: A reference guide to BANFF classification of antibody and cell-medicated rejection can be found here: https://banfffoundation.org/wp-content/uploads/2019/01/A_2018_Reference_Guide_to_the_Banff_Classification.14-1.pdf

Diagnosis and treatment of Acute Antibody Mediated Rejection (AMR):
Acute AMR usually presents within 6 months post-transplant (although can present later as well) with increase in creatinine, fever of unclear source and tenderness over the transplant. The
most common mechanism underlying AMR is an anamnestic antibody response that results from prior antigenic exposure such as pregnancy, blood transfusions, or prior transplants. Diagnosis requires 1/morphologic changes like microvascular inflammation characterized by neutrophils and mononuclear cells in glomeruli and peritubular capillaries, acute tubular injury, thrombotic microangiopathy, or intimal or transmural arteritis, 2/presence of donor specific HLA antibodies and 3/ biopsy evidence of complement activation as shown by peritubular capillary staining for C4d.
Treatment options include:
Solumedrol: 250-500 mg IV x 3 days, followed by prednisone 80 mg tapered to original dose over 1-2 weeks.
Plasma exchange (TPE): TPE daily for 3 days, followed by TPE every other day for a total of up to 5 sessions. 1-1.5 x plasma volume is exchanged with albumin. FFPs should be used as replacement fluid if a kidney biopsy is planned within 24-hours of TPE.
IVIG: Unclear mechanism of action and benefit but may cause enhanced antibody clearance,

inhibition of complement, and negative regulatory signals through Fc receptors. Dose ranges from 500mg-2g/kg and ideally should be given after TPE. If using > 1g/kg, IVIG should be given in 2 divided doses.
Rituximab: Anti-CD20 chimeric monoclonal antibody that targets B-cells and may reverse cellular and antibody mediated rejection. 375mg/m^2 IV infusion is given and can be repeated in 7-14 days if DSA is still elevated.
Eculizumab: inactivates C5a stopping the activation of the MAC complex of complement. Off-label use for rejection, sometimes tried when other treatments fail. Patients must get meningococcal vaccine before using eculizumab.
Thymoglobulin: There may or may not be evidence of concurrent acute T-cell mediated rejection (ACR) in a patient with AMR. If there is evidence of ACR, thymoglobulin needs to be used. However, some transplant nephrologists propose that even in the absence of obvious ACR, thymoglobulin should be used to suppress helper T-cells as there is cross-talk between T and B-cells. Usually, 4-6 mg/kg of thymoglobulin is used in divided doses of 1.5-2mg/kg per dose. Risk of malignancy increases with a cumulative thymoglobulin dose of more than 20 mg/kg in a patient's lifetime. There should be at least 24-hours between thymoglobulin dose and TPE to minimize removal of drug.

Diagnosis and Treatment of Acute T-Cell Mediated Rejection (ACR):
Cellular rejection is most likely to occur in the early weeks to months post-transplantation, though it can manifest later, especially if immunosuppression is reduced due to either provider recommendation or patient's non-adherence to treatment. Cellular rejection commonly presents as an asymptomatic increase in serum creatinine level. Symptoms of acute rejection including fever, graft tenderness, oliguria, and hypertension are uncommon. Cellular rejection can take the form of tubulointerstitial or vascular rejection. In tubulointerstitial rejection, T lymphocytes, monocytes, and plasma cells infiltrate the interstitium and invade renal tubules, causing tubulitis. The degree of interstitial infiltration and *tubulitis* define the degree of type 1 cellular rejection according to the Banff classification. Cell-

mediated vascular rejection manifests as lymphocytes, monocytes, and macrophages invading the sub-endothelium and intima of arteries and corresponds to type 2 rejection. Type 3 rejection manifests with transmural arterial fibrinoid necrosis.
Treatment of ACR depends on the severity and degree of background chronicity. Banff 1A and borderline rejections are treated with steroids alone (Solumedrol 250-500 mg IV x 3 doses, followed by oral prednisone taper). Banff 1B and higher rejections are treated with thymoglobulin (1.5mg/kg daily for 5-7 doses) in addition to steroids. Mycophenolate dose should be reduced to 50% during treatment with thymoglobulin. CD3 levels may be monitored to assess the response to thymoglobulin.

General rules for acute rejection:

1. Add or restore maintenance Prednisone in patients not on steroids.
2. If on cyclosporine, change to Tacrolimus. If on Azathioprine, change to MMF/Myfortic.
3. Re-biopsy borderline and IA rejections only if serum creatinine does not return to baseline values. For others, re-biopsy in one month.
4. Anti-infective prophylaxis to be started after treatment of rejection:
a. Treated with steroids alone: Bactrim x 6 weeks / Anti-fungal prophylaxis x 1 month / CMV prophylaxis x 1 month
b. Treated with Thymoglobulin: Bactrim x 3 months / Anti-fungal prophylaxis x 1 month / CMV prophylaxis x 6 weeks (R+ patients) and 3 months for D+/R- pts