Renal Dosing of Medications: A Case-Based Review

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Disclosures

- Janna Beavers and Mollie Grant have no conflicts of interest to disclose

Objectives

- Explain how to appropriately calculate creatinine clearance
- Assess medication regimens for patients with cardiorenal syndrome
- Evaluate antibiotic utilization in hemodialysis patients
- Develop a plan for medication dose adjustments in ICU patients with acute kidney injury

Assessing Renal Function using Creatinine Clearance

Patient Case

- CT is a 80 y/o F who presents with sepsis. Her initial blood and urine cultures are both positive for GNR, and she has a history of *Pseudomonas* UTI. Her provider asks you to estimate her renal function so tobramycin can be initiated.
  - Ht: 64”
  - Wt: 54 kg
  - SCr: 0.4 mg/dL

Patient Case

- What equation would be most appropriate to describe CT’s renal function for dosing tobramycin?

A. Modification of Diet in Renal Disease (MDRD) equation
B. Cockcroft-Gault (CG) equation
C. Schwartz equation
D. Call the pharmacist

MDRD vs. CG

- Per 2002 KDOQI guidelines, MDRD is preferred for staging chronic kidney disease
- MDRD Study Group (1999): found stronger correlation between actual glomerular filtration rate and MDRD, as compared with CG
  - Large sample size (n=1070), validated across many different ages, races, SCr levels

Am J Kidney Dis 2002; 39:S1-S266 (suppl 1)
Ann Intern Med 1999;130:461-70

What About Drug Dosing?

- *"Because exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges."*
- **The "creatinine clearance" used above and in the vast majority of drug trials is CG, not MDRD**

Lovenox® (enoxaparin) [package insert]. Sanofi-Aventis, 2013.

CG Equation

$$\frac{(140\text{-age})(\text{Wt in kg})\ (0.85 \text{ if female})}{\text{SCr} \times 72}$$

Estimating Renal Function

1. What equation?
   - Cockcroft-Gault preferred for drug dosing

Estimating Renal Function

1. What equation?
   - Cockcroft-Gault preferred for drug dosing
2. What weight?

What Weight to Use?

- Total Body Weight (TBW)
  - Generally used, though may overestimate CrCl in obesity
- Ideal Body Weight (IBW)
  - Since creatinine is made by muscle, may be good estimate of lean body weight
  - May be used in obesity, though may underestimate CrCl in obesity
- Adjusted Body Weight (ABW)
  - Equations vary, though generally [0.4(TBW-IBW)+IBW]

The Preferred Weight to use in CG for Obese Patients is…

- Lean Body Weight as determined by bioelectrical impedance analysis (BIA)!!!
  - "all patients were required to fast for at least four hours before BIA measurement"
  - "A portable impedance Quantum II analyzer using the standard tetrapolar method was utilized"
  - "The resistance measurements from the impedance device were used along with height, weight, and age in a regression equation derived by Gray and colleagues…"
- **If you don't have a portable impedance device on your unit, then either IBW or ABW is a reasonable estimate**

Am J Health-Syst Pharm 2009;66:642-48

What About No Weight?

- Wilhelm, et al (2011) found that removing body weight was a closer estimate than TBW or IBW

$$\frac{(140\text{-age})(\cancel{\text{Wt in kg}})\ (0.85 \text{ if female})}{\text{SCr x } \cancel{72}}$$

- Since this is a single meta-analysis, this practice has not been widely adopted
- Potential to overestimate CrCl in patients with low body weight not addressed

Pharmacother 2011;31:658-65

Estimating Renal Function

1. What equation?
   - Cockcroft-Gault preferred for drug dosing
2. What weight?
   - Total body weight (TBW) unless obese, which would necessitate ideal body weight (IBW) or adjusted body weight (ABW)

Estimating Renal Function

1. What equation?
   - Cockcroft-Gault preferred for drug dosing
2. What weight?
   - Total body weight (TBW) unless obese, which would necessitate ideal body weight (IBW) or adjusted body weight (ABW)
3. What serum creatinine?

Rounding of SCr

- Since creatinine is made from muscle, patients who are malnourished, debilitated, or elderly may have falsely low SCr that may lead to overestimation of CrCl
- In elderly and other patient population groups (ie, quadraplegia), it is common for SCr to be rounded up to 0.8 mg/dL or 1 mg/dL
- There is little data to support this practice

Back to the Case…

- CT is a 80 y/o F who presents with sepsis. Her initial blood and urine cultures are both positive for GNR, and she has a history of *Pseudomonas* UTI. Her provider asks you to estimate her renal function so tobramycin can be initiated.
  - Ht: 64”
  - Wt: 54 kg
  - SCr: 0.4 mg/dL

Patient Case

$$\frac{(140-80)(54)\ (0.85)}{0.4 \times 72} = 96 \text{ mL/min}$$

$$\frac{(140-80)(54)\ (0.85)}{1 \times 72} = 38 \text{ mL/min}$$

- **Which CrCl seems reasonable to you?**

Estimating Renal Function - Summary

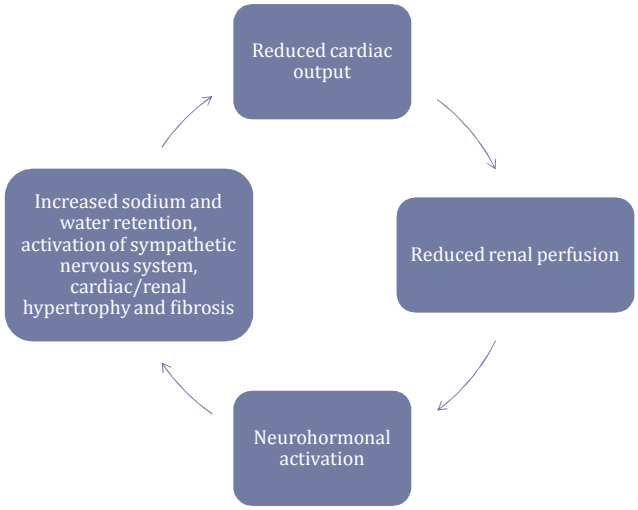
1. What equation?
   - Cockcroft-Gault preferred for drug dosing
2. What weight?
   - Total body weight (TBW) unless obese, which would necessitate ideal body weight (IBW) or adjusted body weight (ABW)
3. What serum creatinine?
   - Consider rounding low SCr to 1 mg/dL in the elderly and other special cases

Cardiorenal Syndrome

Patient Case

- R.W. is a 68 y/o male admitted shortness of breath due to acute decompensated heart failure
  - PMH: heart failure (EF 35-40%), atrial fibrillation, coronary artery disease (remote MI), chronic kidney disease (baseline SCr 1.8 mg/dL)
  - Pertinent baseline labs: SCr 2.4 mg/dL, K 4.8 mEq/L, Na 135 mEq/L, BNP 1600 pg/mL
  - Pertinent vitals: BP 142/88 mmHg, HR 76 bpm, weight 86 kg (dry weight 80 kg)
  - Home Medications:
    - Furosemide 80 mg PO daily
    - Lisinopril 10 mg daily
    - Carvedilol 12.5 mg twice daily
    - Aspirin 81 mg daily
    - Apixaban 2.5 mg twice daily

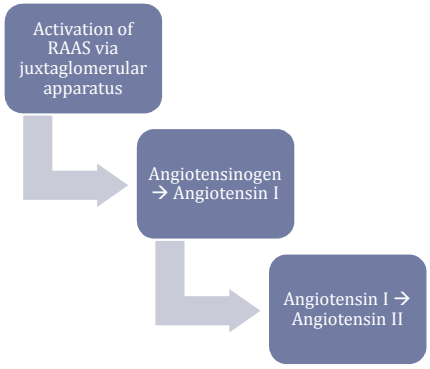
Cardiorenal Syndrome



Crit Care Med 2014;42:2109-2117
Cardiorenal Med 2015;5:254-266

Neurohormonal Activation

Renin Angiotensin Aldosterone System (RAAS)



Management

- Combat long-term effects using RAAS inhibitors
- Therapeutic Options:
  - ACE inhibitors (ACEi)
    - Blocks conversion of angiotensin I → angiotensin II
  - Angiotensin receptor blockers (ARBs)
    - Blocks receptors to prevent effects of angiotensin II

Crit Care Med 2014;42:2109-2117
Cardiorenal Med 2015;5:254-266

Use of ACEi & ARBs in Cardiorenal Patients

Benefits

- Slows progression of kidney disease
- Reduced mortality in heart failure with reduced ejection fraction
- Benefits in multiple comorbidities

Limitations

- May contribute to acute decline in renal function
- Risk of hyperkalemia
- Hypotension may reduce renal perfusion

Am J Kidney Dis 2002;39:S1-S266
J Card Fail 2010;16:e1-194
Circulation 2013;128:e240-327

ACEi & ARB Utilization in Chronic Kidney Disease with Cardiovascular Disease

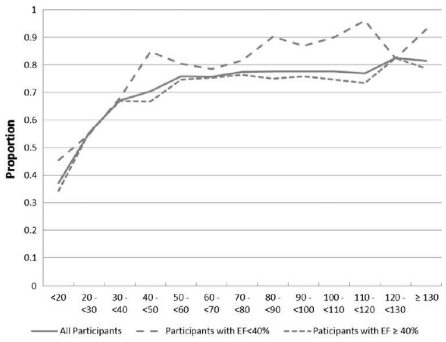
Clinical Outcomes:

Study	Design	Results
Molnar et al (2014)	Retrospective cohort study evaluated all-cause mortality in patients with non-dialysis-dependent CKD	Reduced all-cause mortality in patients on ACEi or ARB at baseline (HR 0.81, 95% CI 0.78-0.84)
Qin et al (2016)	Meta-analysis evaluated use of ACEi or ARB in non-dialysis-dependent CKD patients	Reduced all-cause mortality in patients on ACEi or ARB (HR 0.83, 95% CI 0.78-0.87)

JACC 2014; 63:650-658
Pharmacoepidemiol Drug Saf 2016 DOI: 10.1002/pds.3941

ACEi & ARB Utilization in Chronic Kidney Disease

- Wetmore et al
  - RAAS inhibition after myocardial infarction
  - Lower rates of ACEi or ARB with reduced renal function
    - Renal function guided therapy rather than ejection fraction in heart failure



Renin-angiotensin system inhibitor use proportion by eGFR.

ACE inhibitor use:

	eGFR*					
	Dialysis (n = 81)	<30 (n = 146)	30-59 (n = 818)	60-89 (n = 1958)	≥90 (n = 1220)	P
All	49 (60.5%)	73 (50.0%)	594 (72.6%)	1505 (76.9%)	956 (78.4%)	<.001
EF < 40%	11 (57.9%)	22 (52.4%)	130 (79.8%)	293 (83.0%)	184 (89.3%)	<.001
EF ≥ 40%	38 (61.3%)	51 (49.0%)	462 (76.6%)	1212 (75.6%)	770 (76.1%)	<.001
No AKI	–	51 (54.8%)	486 (75.3%)	1386 (77.9%)	850 (78.4%)	<.001
AKI	–	22 (41.5%)	108 (62.4%)	119 (66.9%)	106 (77.9%)	<.001

*In mL/min per 1.73 m^2.

Am Heart J 2015;170:735-743

Loop Diuretics

- Loop diuretics help manage fluid status in patients with volume overload (i.e., heart failure)
  - Inhibit sodium-potassium-chloride cotransporter in the thick ascending loop of Henle
  - Efficacy depends on secretion of active metabolites in the proximal tubule

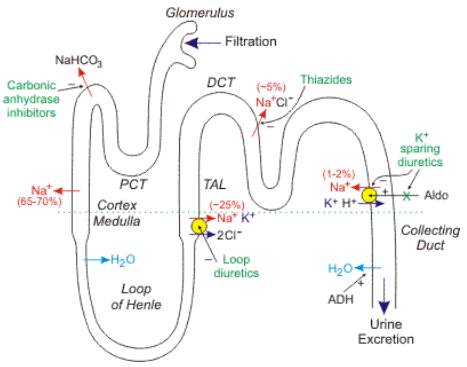


Image from cvpharmacology.com

Loop Diuretics

Loop Diuretic	Equivalent Dose	Bioavailability	Onset (peak effect)	Duration of effect
Bumetanide	1 mg	~80%	PO: 0.5-1 hr (1-2 hrs) IV: 2-3 min (15-30 min)	PO: 4-6 hours IV: 2-3 hours
Furosemide	40 mg (IV-20 mg)	~50%	PO: 30-60 min (1-2 hours) IV: ~5 minutes	PO: 6-8 hours IV: 2 hours
Torsemide	20 mg	~100%	PO: within 1 hr (1-2 hours) IV: 10 min (within 60 min)	PO/IV: 6-8 hours

Dosing considerations in acute heart failure:
- Initial diuretic doses should always be IV
- Inpatient dose ≥ home dose
- Expect and monitor for acute kidney injury
- Frequent reassess response to diuretics

Diuretic Resistance

- Long-term use of loop diuretics can lead to diuretic resistance and nephrotoxicity
  - Upregulate cotransporters in the loop of Henle
  - Hypertrophy of renal tubules
  - Post-diuretic sodium retention
  - Reduced volume may lead to further neurohormonal activation
- Therapeutic considerations
  - Adjust dose/frequency of loop diuretics
  - Sequential nephron blockade with thiazide or thiazide-like diuretics

Curr Treat Options Cardio Med 2016;18:1-15

Back to our patient case …

- R.W. is a 68 y/o male admitted shortness of breath due to acute decompensated heart failure
  - PMH: heart failure (EF 35-40%), atrial fibrillation, coronary artery disease (remote MI), chronic kidney disease (baseline SCr 1.8 mg/dL)
  - Pertinent baseline labs: SCr 2.4 mg/dL, K 4.8 mEq/L, Na 135 mEq/L, BNP 1600 pg/mL
  - Pertinent vitals: BP 142/88 mmHg, HR 76 bpm, weight 86 kg (dry weight 80 kg)
  - Home Medications:
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    - Carvedilol 12.5 mg twice daily
    - Aspirin 81 mg daily
    - Apixaban 2.5 mg twice daily

Patient Case

- R.W. takes lisinopril 10 mg daily at home. What is the best option for the ACE inhibitor on hospital admission based on his renal function? *(Remember: SCr 2.4 mg/dL, baseline 1.8 mg/dL)*
  - Continue lisinopril 10 mg daily
  - Reduce dose of lisinopril to 5 mg daily
  - Hold lisinopril until acute kidney injury resolves
  - Discontinue lisinopril indefinitely given chronic kidney disease

Patient Case

- What do you recommend for R.W.'s diuretic regimen?
  (Remember: home regimen furosemide 80 mg PO daily)
  - Bumetanide 1 mg IV daily
  - Furosemide 80 mg IV twice daily
  - Furosemide 40 mg IV daily
  - Bumetanide 3 mg PO daily

Patient Case

- After 24 hours of treatment with furosemide 40 mg IV twice daily, R.W.'s weight is unchanged with minimal urine output. What is an appropriate next step to optimize his diuresis at this time?
  - Increase dose of IV furosemide
  - Add metolazone 2.5 mg daily.
  - Increase frequency of IV furosemide
  - Add dopamine 5 mcg/kg/min
  - Ultrafiltration

Summary

- Cardiorenal syndrome most frequently occurs as a result of reduced cardiac output and continues to progress over time.
- ACE inhibitors and ARBs should be considered in chronic kidney disease due to beneficial long-term renal and cardiac effects.
- Strategies to overcome diuretic resistance include dose/frequency adjustments or the use of thiazide diuretics.

Antibiotic Considerations in Hemodialysis

Patient Case

- MJ is a 60yoF admitted for fever 102.4°F and overall fatigue
- PMH: ESRD on HD M/W/F with right IJ permcath, upper arm AVF placed one month PTA, CHF, HTN, DM, depression
- Baseline vitals: Temp 97.6°F, RR 16, HR 78, wt 168kg
- Baseline labs: Scr 10.13, WBC 12.4
- CXR negative
- Blood and urine cultures- pending

What empiric antimicrobial therapy would you start in MJ?

Intermittent Hemodialysis (IHD)

- Gold standard
- Acute scenarios may necessitate initiation in an inpatient setting
  - Think…AEIOU
- Generally use high-flux membranes
  - Higher blood and dialysate flow rates
  - Better at removing solute (e.g. drug molecules)

Antibiotics in Hemodialysis

Factor affecting Dialyzability		Change in Dialyzability
Molecular Weight	↑	↓
Water Solubility	↑	↑
Lipid Solubility	↑	↓
Ionization	↑	↓
Volume of Distribution	↑	↓
Protein Binding	↑	↓
Dialysate flow rate	↑	↑
Blood Flow Rate	↑	↑
Duration of HD session	↑	↑

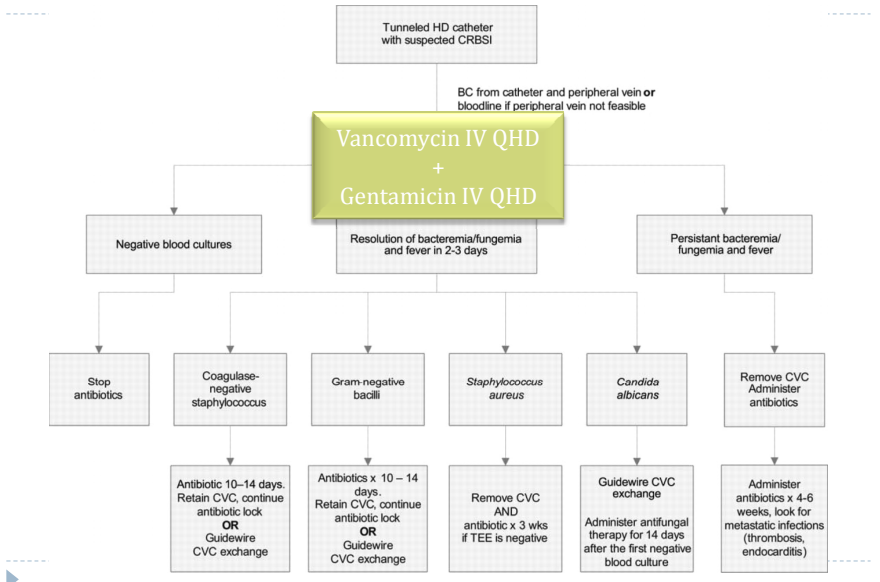
Johnson CA. Dialysis of Drugs 2009.

Antibiotics dosed only on HD days

- Cefazolin 2-3g IV qHD
- Daptomycin 6 mg/kg IV qHD
- Vancomycin (approximately 30-50% removed)
- Ceftazidime 2 g IV qHD
- Aminoglycosides (approximately 40-60% removed)

Clin Infect Dis 2007;44:190
Nephrol Dial Transplant 2010;25:1279
Antimicrob Agents Chemother 2011;55:1677

CA-BSI Guidelines



Clin Infect Dis 2009;49:1-45

Vancomycin in HD

- Typically administer during last portion (hr) of HD
  - Still controversy between "during HD" vs "following HD"
- Literature review
  - 20-40% removed during high flux HD with intradialytic administration of vancomycin
  - 2010 study evaluated 20 mg/kg load with 1g IV QHD (n=34)
    - 79% patients had troughs 10-25 mcg/mL
    - 15% patients had troughs >25 mcg/mL

Nyman HA et al. ACCP abstract 2006;
Am J Kidney Dis 2010;55:1163

Patient Case

- MJ blood cultures report: MSSA
- What changes would you make to her empiric regimen?
  A. Continue vancomycin and gentamicin QHD
  B. Continue vancomycin and DC gentamicin
  C. DC vanc/gent and start cefazolin IV QHD
  D. DC vanc/gent and start Ceftriaxone IV daily

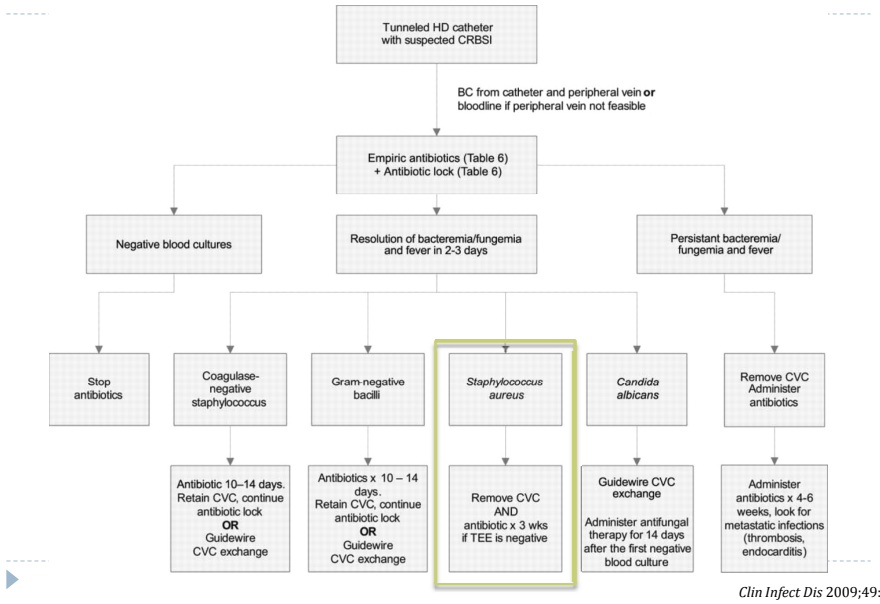
MSSA Bacteremia

- Beta-lactams are the preferred agent
- Cefazolin vs vancomycin in MSSA bacteremia
  - Prospective study in dialysis patients (n=140)
    - Cefazolin 2g, 2g, 3g IV qHD
    - Vancomycin 15mg/kg IV x1 then 500mg qHD

Endpoint	Vancomycin	Cefazolin	p value
Treatment failure	24 (31.2%)	6 (13.05%)	0.02
Death	8 (10.4%)	2 (4.4%)	0.32
Recurrent infection	16 (20.8)	4 (8.7)	0.08

Mandell, et al. Principles and Practice of Infectious Diseases, 7th ed. 2009
Clin Infec Dis 2007;44:190-196
Circulation 2005:111:3167-3184
Clin Infect Dis 2004;39:1267-1284
Clin Infect Dis 2013:56:e1-25

CA-BSI Guidelines



Clin Infect Dis 2009;49:1-45

Antibiotics in Dialysis Patients

- Molecular properties of antibiotics affect how much will be removed by hemodialysis session
- High flux hemodialysis can remove up to 60% of aminoglycoside and vancomycin serum concentrations
- MSSA CA-BSI should be treated with cefazolin IV during hemodialysis

Pharmacokinetic Implications in Critical Illness

Pharmacokinetic changes

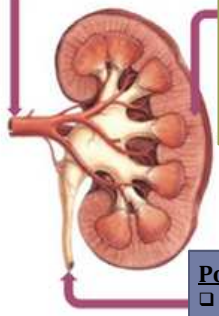
Pharmacokinetic Parameter	Changes in Critical Illness
Absorption	Perfusion abnormalities Intestinal atrophy GI motility dysfunction
Distribution	pH changes Fluid shifts Plasma protein binding
Metabolism	Hepatic blood flow Protein binding
Excretion	Augmented renal clearance Acute kidney injury (AKI)

Crit Care Clin 2006;22:255-271
CHEST 2012;141(5):1327-1336

Causes of acute kidney injury

Pre renal disease
- Blood or fluid loss
- Liver failure
- Severe burns
- Severe dehydration
- NSAIDs, ACE inhibitors

Intrinsic renal disease
- Blood clots in the renal vasculature
- Glomerulonephritis
- Drugs (antibiotics, chemotherapy)
- Toxins (alcohol, cocaine)



Post renal disease
- Urinary tract obstruction (stones, tumor, prostate enlargement)

Crit Care Res Pract 2013:479730
Image adapted from: http://www.davita.in/acute_kidney_injury.php

Altered drug excretion

- Up to 78% of critically ill patients develop AKI
- AKI in critically ill patients can lead to reduced renal drug clearance and increased risk of adverse drug events
- Most data for renal dose adjustments are based on patients with CKD
- Lack of steady state serum creatinine makes dosing in AKI difficult

Kidney Int 2011;80:1122-37
Crit Care Res Pract 2013:479730
Pharmacotherapy 2009;29(5):562-577

Patient case

Initial Presentation

- HPI: 53 y/o M admitted with increased scrotal pain and swelling at home, CT abdomen/pelvis on admission showed gas tracks through the soft tissue centered on the scrotum and perineum consistent with Fournier's gangrene
- PMH: DM, HTN, HLD, peripheral neuropathy, chronic pain
- Home medications:
  - Glyburide 5 mg PO daily
  - Amlodipine 10 mg PO daily
  - Gabapentin 600 mg PO TID
  - Rosuvastatin 20 mg PO nightly
  - Oxycodone/acetaminophen 5/325 mg PO q6h prn

Baseline labs and vitals

- Labs

130	107	85
3.8	20	6.1

	10.4	
12		244
	30	

- Vital signs
  - Afebrile
  - BP 110/60
  - HR 80
- Estimated GFR
  - 14 ml/min

Clinical Course

- HPI, continued:
  - Patient was intubated due to worsening MS and inability to protect his airway, general surgery consult placed and the decision was made to take the patient emergently to the OR for I&D

Clinical Course

- Post-op, the following admission orders were placed:

- Famotidine 20 mg IV bid
- Enoxaparin 40 mg SC daily
- Vancomycin pharmacy to dose
- Piperacillin/tazobactam 3.375g IV q8h
- Clindamycin 900 mg IV q8h
- Glyburide 5 mg PO daily (continuation of home medication)
- Gabapentin 600 mg PO TID (continuation of home medication)
- Fentanyl titratable IV infusion
- Norepinephrine titratable IV infusion

- **Which medications need to be adjusted?**

What do we need to adjust?

Original Ordered Dose	Recommended Dose Modification	Rationale
Famotidine 20 mg IV bid	Famotidine 20 mg IV daily	Up to 70% renal elimination Half life prolonged in renal impairment Decreased receptor binding specificity May lead to increased CNS side effects
Enoxaparin 40 mg SC daily	Enoxaparin 30 mg SC daily (or SC heparin)	Dose reduce to 30 mg SC daily since CrCl <30 ml/min per manufacturer instructions May increase bleed risk if not reduced Anti-Xa levels
Vancomycin pharmacy to dose	Vancomycin dosed per levels	Renal function likely to change Received 2500 mg IV x1 loading dose Assess Cr next day prior to redosing
Piperacillin/tazobactam 3.375g IV q8h	Piperacillin/tazobatam 2.25g IV q8h	Dose recommendation given estimated CrCl <20 ml/min
Clindamycin 900 mg IV q8h	Clindamycin 900 mg IV q8h	Limited renal excretion No need for dose adjustment

Pepcid® (famotidine) [package insert] Merck & Co 2011
Lovenox® (enoxaparin) [package insert] Sanofi-Aventis 2013
Zosyn® (piperacillin-tazobactam) [package insert] Pfizer, Inc 2012
Cleocin phosphate® (clindamycin injection) [package insert] Pfizer 2005

What do we need to adjust? (cont.)

Original Ordered Dose	Recommended Dose Modification	Rationale
Glyburide 5 mg PO daily	Hold for now, change to SC insulin while acutely ill	50% renal excretion May contributed to hypoglycemia due to decreased renal clearance
Gabapentin 600 mg PO TID	Gabapentin 300 mg PO BID	Half life is prolonged in renal dysfunction Can lead to oversedation Titrate based on mental status
Fentanyl IV titratable infusion	No change	No need for dose adjustment Accumulation of drug more dependent on hepatic blood flow and hepatic metabolism
Norepinephrine IV titratable infusion	No change	Titrate to effect Use of vasopressors can increase renal perfusion, which can increase renal drug clearance

Diaβeta® (glyburide) [package insert] Pfizer 2010
Neurontin® (gabapentin) [package insert] Pfizer 2015

The next day…

- Cr 2.4 mg/dL (from 6.07 mg/dL), CrCl ~36 ml/min, UOP improving

Original Ordered Dose	Recommended Dose Modification	New Dose Recommendation
Famotidine 20 mg IV bid	Famotidine 20 mg IV daily	Continue daily dosing until CrCl >50 ml/min
Enoxaparin 40 mg SC daily	Enoxaparin 30 mg SC daily	Increase to enoxaparin 40 mg SC daily since CrCl > 30 ml/min May need to increase dose even further if obese
Vancomycin pharmacy to dose	Vancomycin dosed per levels	Continue to dose by levels, but if Cr continues to improve, can start a scheduled regimen If no evidence of MRSA infection, could discontinue to avoid unnecessary risk of nephrotoxicity
Piperacillin/tazobactam pharmacy to dose	Piperacillin/tazobatam 2.25g IV q8h	Increase to piperacillin/tazobactam 3.375g IV q8h
Glyburide 5 mg PO daily	Hold for now	Continue to hold since patient is not eating Continue subcutaneous insulin
Gabapentin 600 mg PO TID	Gabapentin 300 mg PO BID	Continue same dose, but may be able to increase Titrate based on mental status
Clindamycin 900 mg IV q8h	Clindamycin 900 mg IV q8h	No need for dose adjustment May be able to discontinue if no evidence of group A streptococcal infection

Pepcid® (amotidine) [package insert] Merck & Co 2011, Lovenox® (enoxaparin) [package insert] Sanofi-Aventis 2013, Zosyn® (piperacillin-tazobactam) [package insert] Pfizer, Inc 2012, Cleocin phosphate® (clindamycin phosphate) [package insert] Pfizer 2005, Diaβeta® (glyburide) [package insert] Pfizer 2010, Neurontin® (gabapentin) [package insert] Pfizer 2015

Two days later…

- Renal function continues to improve, Cr now 1.5 mg/dL (CrCl ~58 ml/min)

Current Dose	New Recommended Dose	Rationale
Famotidine 20 mg IV daily	Increase to famotidine 20 mg IV BID	CrCl >50 ml/min
Enoxaparin 40 mg SC daily	Continue current dose	CrCl > 30 ml/min May need to increase dose even further if obese
Vancomycin dosed per levels	Discontinued	No evidence of MRSA infection Prolonged exposure to broad spectrum antibiotics like vancomycin increases risk of nephrotoxicity and resistant organisms
Piperacillin/tazobatam 3.375g IV q8h	Continue current dose	CrCl >20 ml/min
Gabapentin 300 mg PO BID	Increase back to home dose of gabapentin 600 mg TID	Continue same dose, but may be able to increase Titrate based on mental status
Clindamycin 900 mg IV q8	Discontinued	Cultures grew only anaerobes, already on piperacillin/tazobactam Prolonged use increases risk of *Clostridium difficile* infection

Pepcid® (famotidine) [package insert] Merck & Co 2011, Lovenox® (enoxaparin) [package insert] Sanofi-Aventis 2013, Zosyn® (piperacillin-tazobactam) [package insert] Pfizer, Inc 2012, Cleocin phosphate® (clindamycin phosphate) [package insert] Pfizer 2005, Neurontin® (gabapentin) [package insert] Pfizer 2015

Summary

- Nephrotoxicity vs increased drug effects
  - Ex. Vancomycin—can be nephrotoxic if not dose reduced for AKI
  - Ex. Glyburide—may cause hypoglycemia if not dose reduced (or withheld) during AKI
- Need for constant reevaluation of medication doses given changing renal function
- True GFR hard to predict given changing creatinine values
- Discontinue any potentially nephrotoxic drugs that are no longer indicated

Patient case

Initial Presentation

- HPI
  - 56 y/o F initially presents to the ED with altered mental status. Reported feeling badly for about 3 days. History was hard to obtain because of how altered she was. In the ED, she was noted to have dyspnea, tachypnea, tachycardia, and bilateral infiltrates on CXR.
- PMH
  - HTN, arthritis, otherwise unknown

Initial Labs and Vital Signs

127	95	13
3.5	24	0.63

	10.8	
2.2		26
	32	

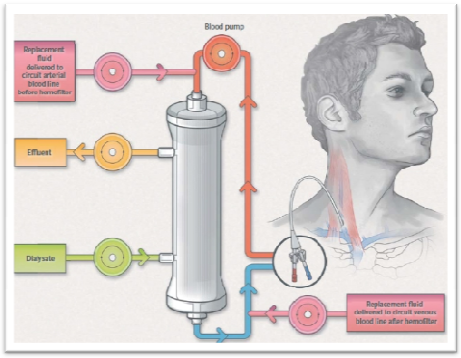
- Labs (cont.)
  - Ammonia WNL
  - Lactate WNL
  - AST 197
  - ALT 62
- Vitals
  - BP 93/54
  - HR 124
  - O2 sat 96% on 4L NC
  - Temp 101.7°F

Clinical Course

- Intubated on day 2 of hospitalization due to worsening encephalopathy
- CXR showed acute respiratory distress syndrome (ARDS)
- Concern for possible pneumonia vs. intra-abdominal process
- Cr 0.63 mg/dL → 2.7 mg/dL → anuric
- Started on continuous renal replacement therapy (CRRT)

CRRT

- Many ICU patients who develop AKI will need CRRT
- ~50% of patients with an estimated CrCl <40 ml/min receive drug doses that are 2.5x higher than the recommended maximum dose
- Some patients may also be underdosed
  - Variability in published dosing recommendations
  - Use of CRRT can be more efficient than earlier reported observations



Pharmacotherapy 2009;29(5):562-577
N Engl J Med 2012;367:2505-2514

Factors affecting elimination of antibiotics in patients on CRRT

Factors	Effects
Volume of distribution	Increase in volume of distribution results in a need for larger loading doses and reduces efficacy of removal by CRRT
Protein binding	Only the unbound fraction of a drug is removed by CRRT
Dose of CRRT delivered	Effluent volume is the most important CRRT variable in determining drug elimination
Blood flow rate	Usually does not effect drug elimination

Crit Care Med 2009;37:2268-2283

Audience response question

- What is the estimated creatinine clearance for a patient on CRRT?

30-50 ml/min

Audience response question

- Which of the following ordered medications need to be dose adjusted for renal dysfunction?

★ Vancomycin 1250 mg IV q12h
★ Cefepime 2g IV q12h
Metronidazole 500 mg IV q8h
★ Fluconazole 200 mg IV daily

Dose adjustments in CRRT

Ordered drug dose	Rationale for dose adjustment
Vancomycin 1250 mg IV q12h	• Dose based off of CrCl 30-50 ml/min • Usually adjust to daily dosing • Important to not if machine clots, as doses may need to be held
Cefepime 2g IV q12h	• Cleared by the kidneys, will accumulate in renal dysfunction • Keep current dose (assuming CrCl 30-50 ml/min) • Beta lactams commonly underdosed in CRRT
Metronidazole 500 mg IV q8h	• No need to dose adjust
Fluconazole 200 mg IV daily	• 80% of dose is eliminated unchanged via kidneys • Can accumulate in pts with renal insufficiency, dose should be reduced • If on CVVHD or CVVHDF, clearance may be equal or greater to that of patients with normal renal function • Concern for azole resistant *Candida* species • Empiric dose needs to be increased from 200 mg IV daily to 800 mg IV daily if the dialysate flow rate is ≥ 2L/hr

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Summary

- Medications should be adjusted in the setting of AKI to avoid adverse drug effects
- Use of serum creatinine is limited due to
  - Changes in creatinine production
  - Lack of steady state conditions in critical illness
  - Alterations in renal tubular secretion
- Renal function associated with critical illness is often fluctuating, so drug dosing should be reassessed daily

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Renal Dosing of Medications: A Case-Based Review

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