Acute Kidney Injury & CRRT

(Cardiorenal Syndrome)

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Outline

- Epidemiology of AKI in the CTICU
- Risk factors for AKI & what actually happens to the kidney after cardiac surgery
- Strategies and common medications involved in the AKI patient in the CTICU: can we ameliorate AKI?
- Summary and personal recommendations

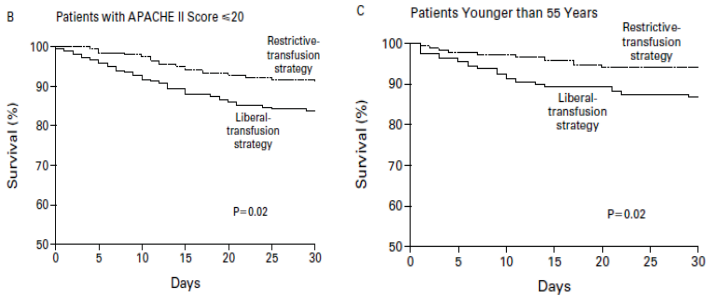
The Wizard of Oz

(American Film Industry ranking #6 all-time)

Paradigm Shifts: Unlearning the Learned

- For many years (decades?), we were taught that if PRBCs were needed, transfuse 2 units
- Conversation w/ gen'l surgeon while moonlighting:
  - Me: "The patient needs PRBCs; I'd like to give a unit."
  - Surgeon: "You should give 2 units."
  - Me: "Why is that?"
  - Surgeon: "Because giving 1 unit is like spitting in the wind."
  - Me: "Errr....OK...."

Paradigm Shifts: Unlearning the Learned



Hebert et al NEJM 340:409, 1999

Epidemiology of AKI in CTICU

- Published estimates of incidence vary by
  - Definition of AKI (e.g., 30% increase in Cr, 50% increase in Cr, doubling of Cr…)
  - Type of surgery (elective CABG << emergent CABG + valve surgery)
- Extreme ranges are 1%[1] to 50%[2]
- A more helpful number is 7-8%[3,4] when a rise in Cr of ≥ 1 mg/dL is used
- "Roughly 10% have a Cr increase of 1" – more if your pop'l has lots of CKD

[1]Rosner et al CJASN 1:19, 2006
[2]Dasta et al Am J Med 104:343, 1998
[3]Conlon et al NDT 14:1158, 1999
[4]Mangano et al Annals 128: 194, 1998

How Often is Dialysis Required?

- Evidence here clusters a bit more closely: 1-2%[1,2] of all patients (not AKI patients)
- This would suggest that roughly 1/6 of AKI patients are "AKI-D"
- Adding valve surgery to CABG roughly triples the risk of AKI and AKI-D

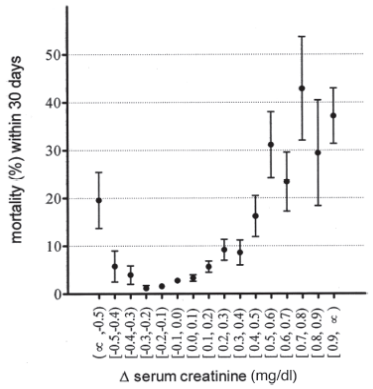
1 Conlon et al NDT 14:1158, 1999
2 Chertow et al Am J Med 104:343, 1998

How Does AKI Impact Mortality?

- Again, heavily dependent of AKI def'n and period studied (e.g., hospital D/C, 30-d survival, etc).
- 15-30% overall mortality with AKI is a good estimate[1]
- Dialysis-requiring AKI (AKI-D) is ominous − 40-60%[1,2]
- AKI-D increases mortality rate by ~ 8-fold (multivariable-adjusted)[3]
- In-hospital mortality 1% (no AKI) vs 19% (AKI) vs 63% (AKI-D)[4]

[1]Rosner et al CJASN 1:19, 2006
[2]Stafford-Smith et al Curr Opin Crit Care 15:498, 2005
[3]Chertow et al Am J Med 104:343, 1998
[4]Mangano et al Annals 128: 194, 1998

Slight Rises in Cr Impact Mortality



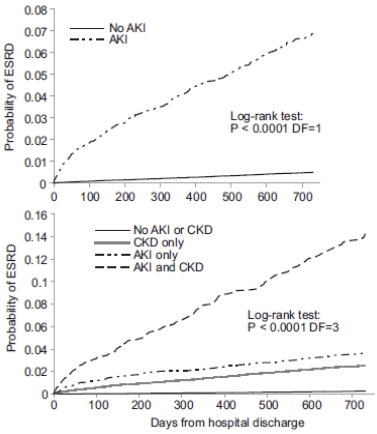
Lassnig et al JASN 15:1597, 2004

Long-Term Impact of AKI on ESRD

- There's great interest in past few years about CKD and ESRD following AKI
- Not specific data in post-CPB patients − but good epidemiologic data on AKI as a whole

Long-Term Renal Impact of AKI

- The 2000 5% Medicare Beneficiary Sample was used to examine individuals ≥ 67 (*n* = 233,803)
- 2-yr F/U
- 5.3 per 1000 developed ESRD



Ishani et al JASN 20:223, 2009

Long-Term Renal Impact of AKI

AKI and CKD		Hazard Ratio
both AKI and CKD	79.45	41.19 (34.58 to 49.08)
AKI only	24.52	13.00 (10.57 to 15.99)
CKD only	19.88	8.43 (7.39 to 9.61)
no AKI or CKD	2.08	1.00

Ishani et al JASN 20:223, 2009

The Kidney After Cardiac Procedures: AKI Risk Factors

Table 1. Risk factors associated with ARF[a]

Patient-Related	Procedure-Related
Female gender	Length of CPB
Chronic obstructive pulmonary disease	Cross-clamp time
Diabetes	Off-pump *versus* on-pump
Peripheral vascular disease	Nonpulsatile flow
Renal insufficiency	Hemolysis
Congestive heart failure	Hemodilution
LV ejection fraction <35%	
Need for emergent surgery	
Cardiogenic shock (IABP)	
Left main coronary disease	

[a]LV, left ventricular; IABP, intra-aortic balloon pump; CPB, cardiopulmonary bypass.

[1]Rosner et al CJASN 1:19, 2006

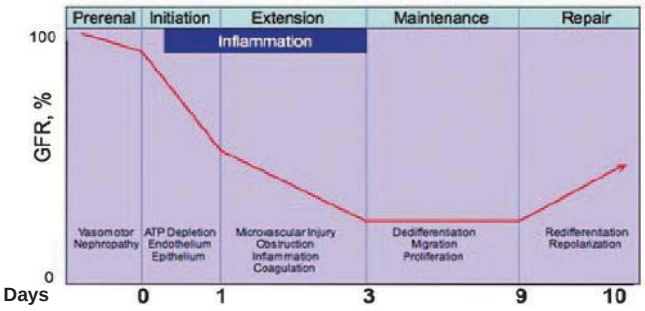
The Kidney After Cardiac Procedures: Pathophysiology

Preoperative	Intraoperative	Postoperative
Lack of renal reserve	Decreased renal perfusion	Systemic inflammation
Renovascular disease	hypotension	Reduced LV function
Prerenal azotemia	lack of pulsatile flow	Vasoactive agents
recent diuresis	vasoactive agents	Hemodynamic instability
NPO status	anesthetic effects	Nephrotoxins
impaired LV function	Embolic events	Volume depletion
ACEI/ARB	CPB-induced inflammation	Sepsis
Nephrotoxins	Nephrotoxins	
intravenous contrast	free hemoglobin	
other medications		
Endotoxemia		
Inflammation		

[a]ARF, acute renal failure; NPO, nothing by mouth.

[1]Rosner et al CJASN 1:19, 2006

The Kidney After Cardiac Procedures: Pathophysiology



[1]Rosner et al CJASN 1:19, 2006

Risk Stratification: The Cleveland Clinic AKI Scoring System[1]

Risk Factor	Points
Female gender	1
Congestive heart failure	2
LV ejection fraction <35%	1
Preoperative use of IABP	2
COPD	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only (reference to CABG)	1
CABG + valve (reference to CABG)	2
Other cardiac surgeries	2
Preoperative creatinine 1.2 to <2.1 mg/dl (reference to 1.2)	2
Preoperative creatinine >1.2[b]	5

[a]COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft. From Thakar *et al.* (30).
[b]Minimum score = 0; maximum score = 17.

[1]Thakar et al JASN 16:162, 2005

Timing of Events in AKI

- When to call the nephrologist
  - No consensus; nephrologists argue
  - If calling when dialysis needed, too late (in an ideal scenario)

Timing of Events in AKI: Concepts

- When dialysis is commenced?
  - No consensus; nephrologists argue
  - From 2000-2010, trend was to start early (BUN > 40 mg%)
  - BUN alone is frequently the least important metric
  - K > 5.0, pH < 7.2, rising vent support (>60% FIO_2), 6+ hours of anuria warrant a consult in most instances
  - Increased vent support: though many insults to gas-exchange are not due to volume overload, a dialyzer allows you to address what you can
  - What is overall direction of the patient? ("If they are going to be worse tomorrow then they are today, start today")

Dialysis: Conceptual Issues

- Modalities:
  - "conventional" intermittent hemodialysis (IHD)
  - slow low efficiency extended dialysis (SLED)
  - continuous (CRRT)
- Conceptualization of dialysis is important for non-nephrologists
  - Clearance (BUN and other toxins)
  - Electrolyte & acid-base control
  - Ultrafiltration

Off- vs. On-Pump CPB

- CABG, but not valve replacement, can be done off-pump (OP)
- Potential benefits of OP-CABG
  - Less inflammation, oxidative stress, and C' activation induced by the pump
- Potential debits of OP-CABG:
  - Greater hemodynamic instability

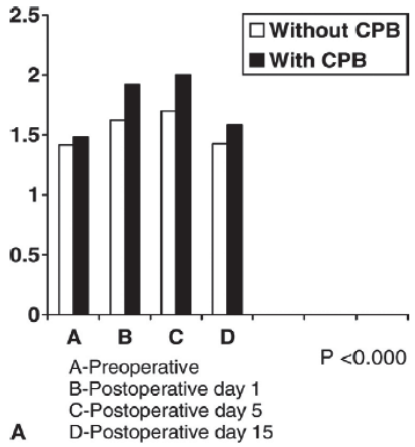
Off- vs. On-Pump CPB

- Largest study was an RCT of 2200+ patients
- Vast majority of patients w/o CKD
- AKI not an endpoint, but dialysis requirement was
- No difference in requirement for HD
- Most metanalayses reflect this; more studies with CKD patients are required

Shroyer et al NEJM 361, 1827, 2009

Off- vs. On-Pump CPB

- Best study in CKD randomized 116 patients to on- vs. off-pump CABG.
- Mean Cr 1.45, mean eGFR ≈ 52 mL/min
- 3 in on-pump, 0 in off-pump required HD



Sajja et al, J Thorac CV Surg 133:378, 2007

Medications Involved in AKI

- NAC (N-acetylcysteine)
- Dopamine
- Fenoldopam
- ANP (atrial naturetic peptide)
- Lasix

Preoperative NAC

- The evidence for N-acetylcysteine is extremely variable
- >24 studies and ≥ 3 metaanalyses have been performed
- A consensus around proof of efficacy simply has not emerged
- Even metaanalyses differ in their findings!

Perioperative NAC

- Most promising evidence is for high-dose NAC (1200, vs 600, mg), particularly in IV form
- One study[1] showed benefit of ↓ AKI with 1200 mg **IV** before emergent angioplasty for MI
- Another[2] showed decreased circulating oxidative stress markers with high-dose oral (no AKI benefit)
- Oral NAC is considered "harmless" but even oral NAC is associated with anaphylaxis, rates are much higher in IV

[1]Marenzi et al NEJM 354:2273, 2006
[2]Thiele JACC 55:2201, 2010

Role for Dopamine

- At low doses, dopamine (1-3 ug/kg/min) increase renal blood flow in experimental models and increases naturesis/diuresis (β_1 at 5-10, α_1 at 10-20)
- This does not appear to be the case in humans; it seems to have a pressor effect at <5.
- Studies repeatedly show that is not effective in reducing AKI[1-3]

[1]Denton et al KI 50: 4, 1996
[2]Tang et al Eur J CT Surg 15:717, 1999
[3]Woo et al Eur J CT Surg 22:106, 2002

Dopamine is Arrhythmogenic

- Dopamine is not benign
- A retrospective registry study[1] of 1700+ CABG patients found an OR of 1.74 for Afib or Aflutter
- An older study showed Dop. was most signif. Afib predictor[2]

Effect	*p* Value	Odds Ratio Estimate (95% Confidence Interval)
COPD/asthma, present vs. absent	<.01	2.86 (1.85–4.42)
Renal-dose dopamine, present vs. absent	<.01	1.74 (1.18–2.56)
Age[a]	<.01	
Gender[a]	.013	
Age × gender interaction[b]	.024	
Male age (10-yr increments)		1.57 (1.34–1.84)
Female age (10-yr increments)		2.58 (1.72–3.87)

[1]Argalious et al CCM 33:1327, 2005
[2]Chiolero Thor CV Surg 39:81, 1991

Fenoldopam

- Long-studied with both animal and human evidence suggesting higher eGFR but no major change in AKI incidence w/ the drug
- Best RCT[1] so far tested fenoldepam in 193 patients with ≥1 risk factor
  - Cr >1.5 mg/dL
  - Age >70 y
  - DM
  - Previous CABG
- 0.1 μ/kg/min vs. placebo as incision was made

[1]Cogliati et al J CT Vasc Anaesth 21: 847, 2007

Fenoldopam

- Fenoldopam group had less AKI (p = 0.02), defined as Cr ≥ 2.0, and less need for HD (p = 0.004)

	T1	T2	T3	p Value
Fenoldopam group				
Creatinine clearance (mL/min)	39.7 ± 7.3	68.1 ± 14.3	65.4 ± 18.4	<0.01
Urine output (mL/h)	–	158 ± 56	150 ± 38	NS
Serum creatinine (mg/dL)	1.8 ± 0.4	1.6 ± 0.2	1.5 ± 0.3	<0.01
Fluid intake (mL/h)	–	120 ± 10	115 ± 40	NS
Placebo group				
Creatinine clearance (mL/min)	45.7 ± 12.3	38.6 ± 9.2	33.7 ± 11.2	<0.05
Urine output (mL/h)	–	110 ± 47	88 ± 52	NS
Serum creatinine (mg/dL)	1.9 ± 0.3	2.5 ± 0.6	2.8 ± 0.4	<0.03
Fluid intake (mL/h)	–	120 ± 25	126 ± 34	NS

NOTE. Data are given as mean ± standard deviation.
Abbreviations: T1, before surgery; T2, 24 hours after surgery; T3, 48 hours after surgery; NS, not significant.

A "definitive" RCT of 1000 patients is currently underway (NCT00621790)

Cogliati et al J CT Vasc Anaesth 21: 847, 2007

ANP: The Most Promising Intervention to Date

- Peptide made by atria; there is a human recombinant form (hANP)
- Previous small hints of promise; approved in Japan for AKI prevention
- Three fairly recent RCTs[1-3] and a metaanalysis[4] have recently all suggested benefit
- The best one in CABG patients[3] involved randomizing 504 patients to hANP at 0.02 µg/kg/min

[1]Mentzer et al JACC 49:716, 2007
[2]Sezai et al JACC 54:1058, 2009
[3]Sezai et al JACC 55:1844, 2010
[4]Nigwekar et al J CT Vasc Anaesth 23:151, 2009

ANP in CABG for AKI Prevention

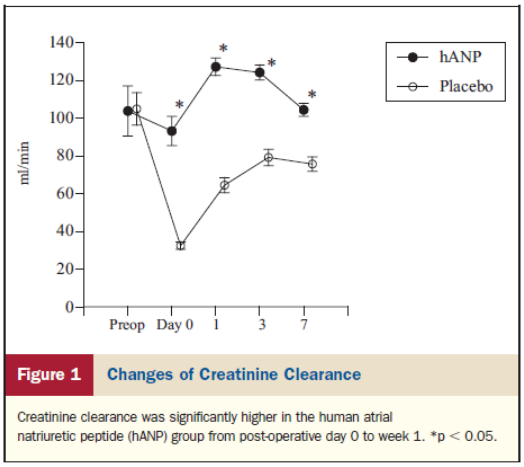


Figure 1 Changes of Creatinine Clearance

Creatinine clearance was significantly higher in the human atrial natriuretic peptide (hANP) group from post-operative day 0 to week 1. *p < 0.05.

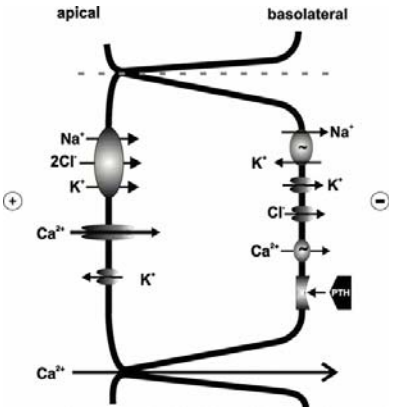
Sezai et al JACC 54:1058, 2009

Lasix Mechanism

- Lasix works on the Na/K/2Cl pump in the think ascending limb

→

- This pump is very metabolically active; theoretically, poisoning it could ↓metabolic demands



Lasix Decreases Time on Ventilator

- RCT of 1000 patients radomized to “liberal” vs. “conservative” fluid management in the MICU
- The conservative group (naturally) got much more diuretics
- At 7 days, conservative group was ~ -100 cc fluid balance; the liberal (“traditional”) group was +7 L
- No difference in mortality

NHLBI ARDSNet NEJM 354:2564, 2006

Lasix Decreases Time on Ventilator

Outcome	Conservative Strategy	Liberal Strategy	P Value
Death at 60 days (%)	25.5	28.4	0.30
Ventilator-free days from day 1 to day 28†	14.6±0.5	12.1±0.5	<0.001
ICU-free days†			
Days 1 to 7	0.9±0.1	0.6±0.1	<0.001
Days 1 to 28	13.4±0.4	11.2±0.4	<0.001

NHLBI ARDSNet NEJM 354:2564, 2006

Volume Overload May Be Associated with Mortality

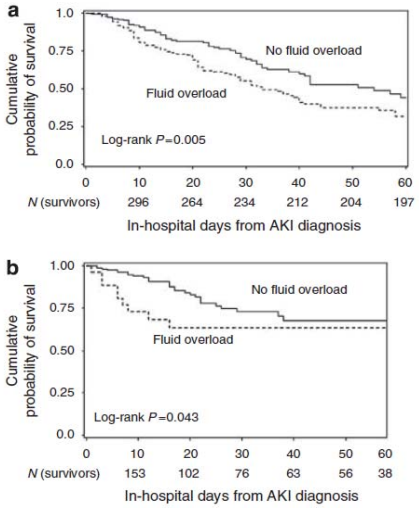
- Fluid overload may result in endothelial injury, volume overload, and other deleterious events in critical illness[1]
- An observational study of >600 patients at 5 AMCs assessed risk of fluid overload in AKI and AKI-D[2]

[1]Prowle et al Nat Rev Nephrol 6:107, 2010
[2]Bouchard et al KI 76:422, 2009

Volume O/L May Be Assoc. w/ Mortality

a, dialyzed
OR = 2.1

b, non-dialyzed
OR = 3.1



Bouchard et al KI 76:422, 2009

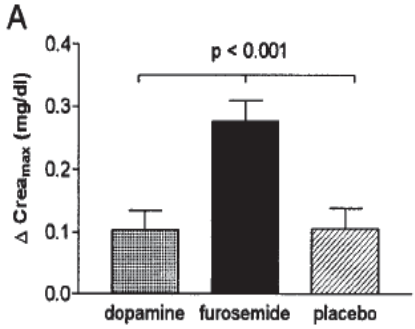
Lasix in AKI: The Nuances

- Non-oliguric AKI has a better prognosis than oliguric/anuric AKI
- This does **not** mean that “converting” a patient to a better state improves AKI or other outcomes.
- 3 older trials all showed no difference in outcomes with lasix[1,2,3]

[1]Kleinknecht et al Nephron 17: 51, 1976
[2]Brown et al Clin Nephrol 15:90, 1981
[3]Shilliday NDT 12:2592, 1997

Lasix May Be Harmful

- 126 cardiac surgery patients with normal renal function randomized to lasix, dopamine, or placebo



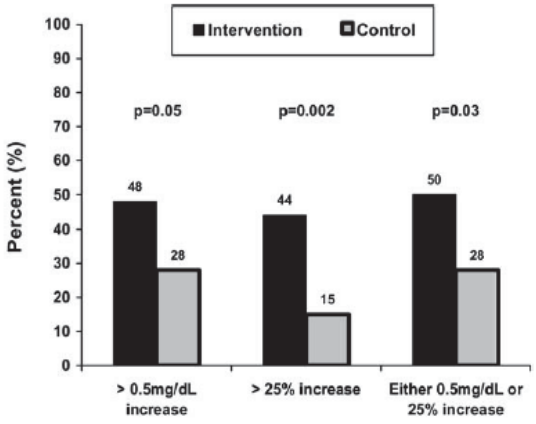
Lassnig et al JASN 11:97, 2000

Lasix and Forced Euvolemic Diuresis

- Perhaps it is throughput of the kidney, not diuresis *per se*, that is helpful
- This was tested in an RCT of 138 patients getting contrast w/ cardiac cath[1]
- All patients had CKD (Cr ≥ 1.7), and were assigned saline alone vs (saline + mannitol + lasix)
- Diuresis group matched mL-for-mL
- Outcome: 25% increase in Cr within 48 hrs

[1]Majumdar AJKD 54:602, 2009

Lasix and Forced Euvolemic Diuresis



[1]Majumdar AJKD 54:602, 2009

Lasix and Forced Euvolemic Diuresis

- Trial terminated for futility after < 50% enrollment
- AKI occurred in 50% in intervention arm vs. 23% in controls (*P* = 0.03, adj. OR 3.7)
- Within hours, Cr increase 0.8 in intervention arm vs. 0.2 in controls

[1]Majumdar AJKD 54:602, 2009

Lasix: Summary

- The kidney is smarter than any doctor
- While lasix will decrease vent/ICU days, it will not help in AKI prevention; if anything, it is likely to be harmful in at-risk kidneys
- Lasix should be used to protect the cardio-pulmonary status; there is no evidence for <u>any</u> renoprotective effects

What Information Can the ICU Nurse Provide for the Nephrologist?

- Hemodynamic trends
- Filter performance
- Citrate anticoagulation

Hemodynamics

- Nephrologists, as consultants, generally work with primary physicians on UF goals
- Nephrologists sometimes have a differing perspective
  - "Is that infiltrate on CXR really pulmonary edema? We'll do what we can, but…"
  - "We can pull fluid off, but are you prepared to support the patient with pressors? Are you prepared to treat the consequences of a tachyarrhythmia?"
- When asked to aggressively UF, nurse input is critical

Hemodynamics

- Discussion with the nurse about the (hemodynamic) course of the patient is essential
  - What is the trend in BP, HR? -- timecourse of interest is minutes to hours
  - What is trend in other pressors or cardioactive meds (CCU)?
  - What is overall trend in patient's course (better/worse/same)?
  - What events are known to be planned for the day (OR or procedure, extubation, etc)?

Hemodynamics

- As UF rate is increased (say, 100cc/hr to 150cc/hr), BP/HR must be carefully watched
- At the first sign of a true trend in BP or HR, nephrologist should be notified
- While not rigorously studied, a UF "holiday" of perhaps 4 hrs is probably appropriate – i.e., no UF to allow for vascular refill, followed by a re-challenge with UF
- If the vent support is high, or if the primary team accedes to increase in pressors, UF holiday is probably not optimal course

Filter Performance: Clotting and Clogging

- Clotting causes filter failure due to obstruction of the membrane pores from the molecular products of the clotting cascade
- Clogging is an entity – at least theoretical and perhaps of clinical significance – in which inflammatory mediators degrade filter performance
  - Some claim this process to be beneficial since these mediators are components of SIRS

Filter Performance

TMP *(< 450)*	TransMembrane Pressure = [Filter Pressure + Return Pressure] / 2 – Effluent Pressure	**CLOGGING:** Measures pressures in the middle of the filter – the force necessary to pull fluid across the membrane – isolates the problem to membrane clogging versus hollow capillary fibers clogging.
ΔP *Delta P* *(<100 change from baseline ΔP)*	"Filter Pressure Drop" ΔP = Filter Pressure – Return Pressure *(Baseline ΔP is pressure with initial BFR)*	**CLOTTING:** increase in filter pressure alone insufficient to rule-out if the problem is the actual filter or return line pressure. 1. ↑ filter pressure + ↑ ΔP = Filter pressure increasing while return pressure remains normal. Therefore, cause is due to clotting of the filter and not a return line problem. 2. Unchanged filter pressure + ↑ ΔP = Filter is patent, but there may be a return line problem.

Note that the delta P should be recorded at the beginning of the filter life and at other "natural" intervals, like beginning of a shift.

If the delta P increases beyond 100 (a delta-delta P!) this suggests clotting is occurring

A rise in TMP (which should be <450) suggests clogging

Citrate: Special Challenges

- Citrate is used to chelate $Ca^{2+,}$ a component of the clotting cascade, in the circuit
- Citrate is introduced prefilter, depleting Ca locally
- A separate Ca^{2+} infusion (thru another central line) is used to reverse this
- Blood flow rate affects citrate rate, and citrate rate affects Ca^{2+} rate – true cascade

Citrate: CRRT Prescription Cascade

b. Infuse at ____ mL/hr (initiate at 1.5 times BFR, not to exceed 300 ml/hr unless ordered by Nephrologist)
{Example: BFR is 180 ml/min. The ACD-A infusion would be started at 1.5 x 180 = 270 ml/hour}
c. Titrate citrate ACD-A infusion rate per parameters (see hyperlink) using post-filter (blue port) ionized calcium.

d. Stop BOTH Citrate and Calcium infusions any time the blood pump is not running including when the filter clots and when CRRT is discontinued.
Attach PDF of "Citrate Infusion Adjustment" table as hyperlink on MAR
calcium chloride 8g/NS 1,000 mL IV infusion, Titrate
a. Infuse via central line only
b. Start calcium chloride infusion at _____ ml/hr. Initial rate should be 40% of citrate infusion rate.
***Example: if BFR=100ml/min, citrate infusion rate=150 ml/hr and calcium chloride infusion rate= 60 ml/hr
***Example: if BFR=150ml/min, citrate infusion rate=225 ml/hr and calcium chloride infusion rate= 90 ml/hr
c. Titrate calcium chloride infusion rate per parameters (see hyperlink) using systemic ionized calcium.

Citrate: Calcium and Citrate Adjustments

Systemic Ionized Calcium (mmol/L)	Calcium Infusion Adjustment
<0.85	↑ Rate 15 mL/hr, Give 1 gram calcium gluconate(4.5 mEq calcium)IV AND call renal fellow
0.85 – 0.94	↑ Rate 10 mL/hr & Give 1 gram calcium gluconate IV
0.95 – 1.09	↑ Rate 5 mL/hr
1.10 – 1.20 (Optimum Range)	No Change
1.21 – 1.35	↓ 5 mL/hr
>1.35	↓ 10 mL/hr and call renal fellow

CRRT Citrate Anticoagulation Protocol

Titrate citrate ACD-A infusion rate per parameters below using post-filter (blue port) ionized calcium:

Post Filter (blue port) Ionized Calcium (mmol/L)	Citrate Infusion Adjustment
< 0.25	Decrease rate by 5 mL/hr
0.25 - 0.45 (Optimum Range)	No Change
0.46 – 0.5	Increase rate by 5 mL/hr
> 0.5	Increase rate by 10 mL/hr

Citrate: Special Challenges

- A patient in steady state should require only a few dose changes – perhaps 3 – of Ca^{2+} before equilibration
- If the systemic ionized Ca^{2+} is, say, 0.93 mmol/L, this doesn't look too bad at first glance
- Nurse gives an amp and increases rate by 10 mL/hr

Citrate: Special Challenges

- 1st reading: 0.93→ amp given and rate increased
- 2nd reading: 0.92→ amp given and rate increased
- 3rd reading 0.94 → amp given and rate increased

- This is a warning sign! The Ca^{2+} is going somewhere!
- The nephrologist should be made aware that by the end of the first shift, steady-state has not been achieved
- The nephrologist should ask – but the nurse should tell

"Citrate Lock"

- Anion-gap metabolic acidosis
- Persistently low systemic (patient) ionized $Ca^{2+,}$ refractory to calcium boluses
- A rising total serum calcium.

- Typically seen in patients with liver failure (citrate not metabolized to bicarbonate, so citrate is binding ionized Ca^{2+} -- while total Ca^{2+} increases as it is dumped in
- Citrate must be held or ceased

Other Citrate Complications

- Alkalemia can increase by the citrate infusion

- ABG or VBG will show steady rise in pH – 7.45, 7.50, even 7.60 over 6-12 hours

- Nephrologist should be ordering extra VBGs on citrate patients – ICU teams won't be thinking of this

- Nephrologist should ask for gases – but nurse should tell!

Other Citrate Complications

- Long-term, changing protocols to use less citrate while maintaining anticoagulation is the answer

- Short-term, holding citrate for several hours then resuming citrate at 70% of previous rate is appropriate

Lowering the Risk of Postoperative AKI: Personal Recommendations

- **For non-emergent procedures, hold diuretics and ACE-I/ARBs for 2-3 days prior and thereafter (admittedly, not possible in decompensated CHF)**
- **Hydration with IVF (Na bicarb preferred) for several hours before in CKD patients (eGFR < 60 mL/min); no fluid if CKD not present (to reduce dangers of volume O/L)**
- **Use diuretics to protect cardiopulmonary status only; do not give solely for oliguria, rising Cr, etc.**
- **Fluid challenge certainly reasonable in oliguria if pulm status will tolerate**
- **Follow the literature on ANP, but dopamine and fenoldopam have no demonstrated utility**

Thanks for your attention!

Questions?

AFI top-ranking movie list (by critical acclaim)

#6 Wizard of Oz (Judy Garland)

#5 Lawrence of Arabia (Peter O'Toole)

#4 Gone with the Wind (Clark Gable)

#3 The Godfather (Marlon Brando)

#2 Casablanca (Humphrey Bogart)

#1 Citizen Kane (Orson Welles)