Answering the Most Common Renal Questions

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Disclosures

- None

Learning Objectives

- Improve assessment of the risks and benefits of iodinated and gadolinium-based contrast administration in patients with renal dysfunction?
- Improve management of emergent and non-emergent hyperkalemia
- Understand how to correct hyponatremia safely and the risks of overcorrection
- Understand how to interpret elevated troponins in patients with advanced CKD

Contrast-Induced Acute Kidney Injury (CI-AKI)

Which of the following patients is at the highest risk of CI-AKI

A. 70 yr old male with HTN, CKD, and creatinine of 1.4mg/dL

B. 65 yr old male with Class II NYHA CHF and creatinine of 1.4mg/dL

C. 40 yr old female with ESLD (MELD 20) and creatinine of 1.2mg/dL

D. 40 yr old male with DM2, CKD, and creatinine of 2.0mg/dL

Contrast induced AKI

- Definition
  - Rise in creatinine > 0.5mg/dL or >25% from baseline 24-72hr post-contrast
  - AKI cannot be attributed to another etiology
- Third leading cause of AKI in hospitalized patients
- Published incidence quite variable
  - <1% to > 30%
  - Studies fraught with confounders
- Is there a high risk population for CI-AKI?

Nsah K et al. Am J Kidney Dis, 2002
Wilhelm-Leen E et al. J Am Soc Nephrol, 2017

Traditional risk factors for CI-AKI

- Age > 75 years
- CKD
- Diabetes
- CHF (NYHA III or IV)
- Anemia
- Hypotension
- Volume of contrast

Mehran R et al. JACC, 2004

Risk of CI-AKI in cirrhosis

- Retrospective study of 451 hospitalized cirrhotic patients
  - 249 received CECT vs 203 matched controls
  - Baseline creatinine, 0.8-0.9mg/dL
  - MELD scores, 9-11
- 8.8% risk of AKI in hospitalized cirrhotic patients receiving CECT
- 3% risk of AKI in hospitalized cirrhotic patients not receiving CECT
- Risk factors for CI-AKI in cirrhosis (OR)
  - Female (5.2)
  - Ascites (2.8)
  - Azotemia (1.02)
- AKI persisted at 3 months in 59% of CECT group vs 17% in non-CECT group

Filomia R et al. Medicine, 2016

Is the AKI really caused by contrast or the result of underlying comorbidities?

CLINICAL EPIDEMIOLOGY www.jasn.org

Estimating the Risk of Radiocontrast-Associated Nephropathy

Emilee Wilhelm-Leen, Maria E. Montez-Rath, and Glenn Chertow
Department of Medicine, Division of Nephrology, Stanford University School of Medicine, Palo Alto, California

J Am Soc Nephrol 28: 653–659, 2017.

- Utilized the Nationwide Inpatient Sample for 2009
- 5,922,537 hospitalizations
- Compared AKI rates among patients receiving contrast with patients of similar comorbidity and illness severity not exposed to contrast

Contrast nephropathy

Table 2. Risk of AKI, entire sample and diagnosis-defined strata

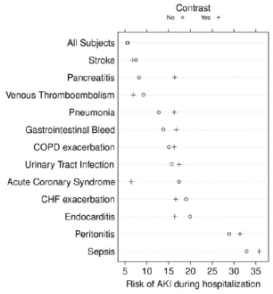
Population	No Contrast (n=28,272,751)	Contrast (n=1,667,694)	*P* Value
Entire sample (n=29,940,445)	5.6 (5.4 to 5.8)	5.5 (5.2 to 5.8)	0.51
Cardiac			
CHF exacerbation (n=804,846)	19.0 (18.3 to 19.8)	16.6 (15.7 to 17.6)	<0.001
ACS (n=1,251,812)	17.4 (16.6 to 18.1)	6.4 (6.0 to 6.8)	<0.001
Infectious			
Sepsis (n=773,258)	32.9 (32.2 to 33.6)	35.8 (33.8 to 37.8)	0.003
Pneumonia (n=1,946,602)	12.7 (12.3 to 13.2)	16.3 (15.3 to 17.5)	<0.001
UTI (n=2,221,705)	15.7 (15.3 to 16.2)	17.4 (16.5 to 18.4)	0.001
Peritonitis (n=12,466)	28.9 (26.6 to 31.2)	31.4 (11.6 to 61.5)	0.85
Endocarditis (n=21,376)	19.9 (18.7 to 21.1)	16.4 (12.2 to 21.8)	0.20
Vascular			
CVA (n=504,144)	7.5 (7.2 to 7.8)	6.7 (6.1 to 7.5)	0.03
VTE (n=66,330)	9.2 (8.7 to 9.8)	6.9 (5.7 to 8.2)	0.001
GIB (n=457,195)	13.8 (13.4 to 14.3)	16.8 (15.4 to 18.3)	<0.001
Other			
COPD exacerbation (n=175,134)	15.1 (14.4 to 15.9)	16.3 (13.8 to 19.2)	0.38
Pancreatitis (n=373,154)	8.2 (7.8 to 8.5)	16.4 (13.6 to 19.5)	<0.001

Data displayed as % AKI (95% confidence interval). CHF, congestive heart failure; UTI, urinary tract infection; CVA, cerebrovascular accident; VTE, venous thromboembolism; GIB, gastrointestinal bleeding; COPD, chronic obstructive pulmonary disease.

Wilhelm-Leen E et al. J Am Soc Nephrol, 2017

AKI varies by diagnosis

- Higher risk associated with:
  - Sepsis, PNA, UTI, Peritonitis
  - GI bleed
  - COPD
  - Pancreatitis
- Lower risk associated with:
  - ACS, CHF exac., CVA, VTE
  - Endocarditis
- More comorbidities = higher risk



Wilhelm-Leen E et al. J Am Soc Nephrol, 2017

A Brief Word About CI-AKI Prophylaxis

- Preventative measures with good data to support:
  - Avoid NSAIDs
  - Limit dose
  - Fluid administration if:
    - Hypovolemic
    - Guided by LVEDP
      - POSEIDON Trial. Brar SS et al. Lancet, 2014
- Data on fluid administration is otherwise mixed
  - AMACING Trial - Nijssen EC et al. Lancet, 2017
    - Single center, randomized, controlled, non-inferiority trial
    - 603 patients
    - GFR 30-59ml/min/1.73m^2
    - No difference in rate of AKI (2.7% overall)
    - 5.5% vs 0% risk of heart failure, hyponatremia, or arrythmia in saline group

A Brief Word About CI-AKI Prophylaxis

- Preventative measures for which data is mixed:
  - Indiscriminant fluid administration
    - AMACING Trial - Nijssen EC et al. Lancet, 2017
  - Isotonic bicarbonate over normal saline
  - Acetylcysteine
  - Holding ACEi/ARBs
  - Statins
  - Forced diuresis
  - Remote ischemic preconditioning
  - Prophylactic dialysis

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Take Home Points for CI-AKI

- Risk may not be as high as suspected
- Be aware of high risk patients
- Other etiologies must be ruled out
- Weigh the risks and benefits
- CI-AKI typically resolves
  - Associated with increased LOS and costs
  - Cirrhotics at risk of permanent damage

Gadolinium Toxicity

Case and Question:

An 80 kg, 30-year-old man has MSSA bacteremia with back pain and LE weakness concerning for epidural abscess. His course is complicated by anuric AKI with a serum creatinine of 1.6 mg/dL up from 0.8mg/dL the day before. Based on MDRD, his eGFR is approximately 50 mL/min. What is his true GFR and would you order an MRI with gadolinium?

A. True GFR is ~50ml/min. Yes, order the MRI with gadolinium
B. True GFR is ~50ml/min. No, do not order the MRI with gadolinium
C. True GFR is <10ml/min. No, do not order the MRI with gadolinium
D. True GFR is <10ml/min. Yes, order the MRI with gadolinium

Nephrol Dial Transplant (2006) 21: 1104–1108
doi:10.1093/ndt/gfk062
Advance Access publication 23 January 2006

Interesting Case

Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis?

Thomas Grobner

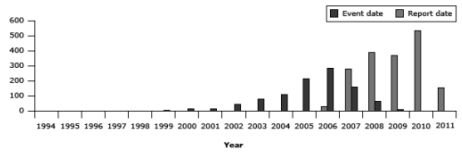
Department of Nephrology, General Hospital of Wiener Neustadt, A-2700 Wiener Neustadt, Austria

Nephrogenic systemic fibrosis (NSF)

- Thickening/hardening of skin overlying the extremities and trunk
- Expansion/fibrosis of dermis with CD34-positive fibrocytes
- Chronic deposition in
- Develops 2-4 weeks after exposure
- Limited to those with ESRD, advanced CKD, and AKI

- Gadolinium can deposits in brain and bone in normal renal function
  - Dose-dependent
  - Clinical significance unclear

Incidence has dramatically declined



The number of cases reported to the US Food and Drug Administration's adverse events reporting system declined in 2011.
Courtesy of Dr. Ira Krefting, FDA presented at: 5th Annual Scientific Symposium on Nephrogenic Systemic Fibrosis and Allied Fibrotic Disorders. May 20, 2011 at the Yale University School of Medicine, New Haven, CT.

UpToDate®

Gadolinium pharmacology

- Excreted unchanged, almost exclusively by kidneys
- Half-life varies by GFR
  - 1.3 hrs if normal GFR
  - 10 hrs for GFR 20 to 40 mL/min
  - 34 hrs for ESRD
  - 2-2.5 hrs with HD

Penfield JG and Reilly RF. Semin in Dial, 2011

Not All Gads Are Equal

TABLE 2. Gadolinium-based chelating agents (GBCA)

GBCA	Brand names	Structure	Charge	Relaxivity	Elimination
Gadodiamide	Omniscan[a,b]	Linear	Non ionic	–	Renal
Gadoversetamide	OptiMARK[a,b]	Linear	Non ionic	–	Renal
Gadopentetate dimeglumine	Magnevist[a,b]	Linear	Ionic	–	Renal
Gadofosveset	Ablavar[c]/Vasovist[b]	Linear	Ionic	–	Renal
Gadobenate	MultiHance[a,b]	Linear	Ionic	Increased	2–4% liver
Gadoxetic acid	Eovist[a]/Primovist[b]	Linear	Ionic	Increased	50% liver
Gadoteridol	ProHance[a,b]	Cyclic	Nonionic	–	Renal
Gadobutrol	Gadovist[b]/Gadavist[a,c]	Cyclic	Nonionic	Increased	Renal
Gadoterate meglumine	Dotarem[b]	Cyclic	Ionic	–	Renal

[a]Brand names marketed in the United States.
[b]Brand names marketed in Europe.
[c]Approved by the FDA for use in the United States on March 14, 2011 (42).

Penfield JG and Reilly RF. Semin in Dial, 2011

Risk varies with degree of renal failure

- Case reports of NSF in patients with GFR of 30-45ml/min/1.73m^2
  - All exposed to high risk agents
- Also reported in AKI
  - Patients with HRS at increased risk
- 2.5-5% risk with GFR < 30ml/min/1.73m^2
- Variable risk among dialysis patients
  - 4.6 per 100 PD patients exposed
  - 0.61 per 100 HD patients exposed PD

Penfield JG and Reilly RF. Semin in Dial, 2011

Utilizing a Restrictive Policy

- Screen all patients
  - Avoid if GFR < 30ml/min/1.73m^2
- Dose reduction
- HD post exposure in pts w/ ESRD

Remember

Creatinine must be stable to accurately interpret

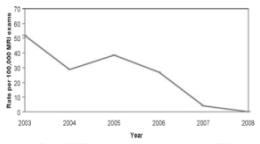


FIG. 1. Rate of NSF cases per year. A restricted use GBCA policy was adopted in January 2007.

Perez-Rodriguez J et al. Radiol, 2009

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Hyperkalemia Management

Case and Question

60 year old female with diabetic CKD on Lisinopril and Spironolactone is admitted with abdominal pain and nausea 4 days after total hip replacement for which she is taking opioids for pain control. Her creatinine is 2.5mg/dL and her potassium is 6.2 without ECG changes. Blood glucose is 140mg/dL.

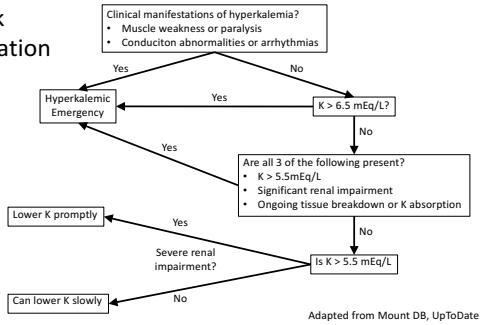
On exam: BP 100/60mmHg, HR 90bpm, she appears mildly hypovolemic

She has made 250mL of urine over 4 hours in the ED.

Which is the best initial approach to manage this patient's hyperkalemia?

A. Intravenous calcium
B. Sodium polystyrene sulfonate with sorbitol (Kayexalate)
C. Normal saline with loop diuretic added once euvolemic
D. Hemodialysis

Risk Stratification



Adapted from Mount DB, UpToDate

Emergent and Non-emergent management

Emergent

- Protect
  - IV Calcium
- Shift
  - IV Insulin and glucose
  - Beta-2-adrenergic agonist
  - Sodium bicarb (if acidemic)
- Eliminate
  - Diuretics +/- saline
  - GI cation exchanger (patiromer, ZS-9)
  - Dialysis

Non-Emergent

- Decrease input
  - Low K diet
- Increase output
  - Diuretics if HTN or hypervolemic
  - Hold RAAS inhibitors, NSAIDs, etc.
  - Cation exchanger (patiromer, ZS-9)
    - *Avoid sodium polystyrene sulfonate*

Risks of sodium polystyrene sulfonate (SPS)

- Intestinal necrosis in animal and human studies (2% risk)
  - Primarily when dosed with sorbitol
- Avoid in patients who are/have:
  - Postoperative
  - Receiving opiates
  - Ileus, small or large bowel obstruction
  - Underlying bowel disease (C.diff, IBD, etc.)
- SPS should be a last resort when:
  - Hyperkalemia is life-threatening AND
  - Dialysis not readily available AND
  - Patiromer or other therapies to remove K not available

Risk > Efficacy

Gerstman BB et al. Am J Kidney Dis, 1992

Effectiveness of Patiromer (and ZS-9)

- AMETHYST-DN Trial (Phase II, open label)
  - 306 Diabetic CKD 3 and 4 outpatients with hyperkalemia
  - Δ K was -0.45mEq/L (low dose), -0.92mEq/L (high dose) at 4 weeks
  - Constipation (6.3%), hypomagnesemia (8.6%), no serious AE's (52 week f/u)
- OPAL-HK Trial (Phase III, randomized, placebo controlled)
  - 243 CKD 3 and 4 outpatients
  - 4 weeks of patiromer, then randomized to continuation or placebo
  - Mean Δ K was -1.0 at 4weeks (- 0.6 to -1.2 for 4.2g bid and 8.4g bid, respectively)
  - Δ K was +0.7 mEq/L 4 wks after discontinuation, no change when continued
- Limitations:
  - Not studied in emergent hyperkalemia or ESRD
  - Must dose 3 hrs before or 3 hrs after other oral medications

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D. Hemodialysis

Hyponatremia Management

"Damned if we do and damned if we don't"

Case

49 year old female with history of HTN, chronic anxiety, alcohol abuse, and previous hospitalization for hyponatremia presents with 2 days of increasing malaise, weakness, and "feeling drunk". On admission she is difficult to arouse. Medications include clorazepate, HCTZ, atenolol, nortriptyline, and amitriptyline.

On exam she was uncomfortable and inattentive

HR 84bpm, BP 150/70mmHg, RR 20/min

Cranial nerves intact, speech was slurred, reflexes normal except for bilateral upgoing toes on Babinski reflex

Labs reveal:

98	59	5
1.6	21	0.8

124

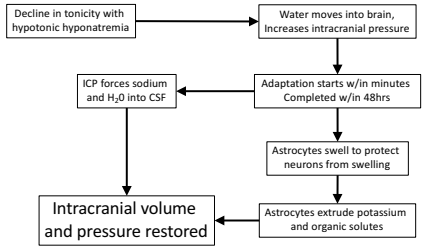
Urine Osm = 248 mOsm/kg H_2O
Urine Na = 38 mEq/L, Urine K = 41mEq/L

Question

Which is the safest approach to correcting this patient's hyponatremia?

A. Fluid restriction alone
B. Normal saline
C. Hypertonic saline
D. ddAVP and normal saline
E. ddAVP and hypertonic saline

Tonicity and Cerebral Edema



Patients at risk for cerebral edema

- Post-operative women of child-bearing age
- Ederly women on thiazides
- Children
- Psychiatric polydipsic patients
- Hypoemic patients

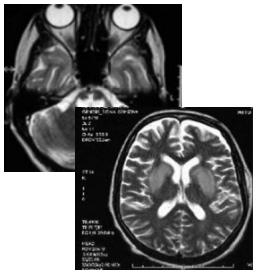
Lauriat SM and Berl T. J Am Soc Nephrol, 1997

Osmotic Demyelination Syndrome (ODS)

- Loss of osmolyes is relatively quick
- Reaccumulation of osmolytes is relatively slow
- Brain volume shrinks with rapid correction of hyponatremia
- Exact mechanisms of demyelination not clear

Signs and Symptoms

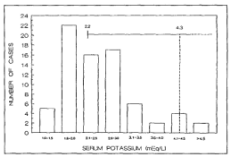
- Movement disorders
  - Increased muscle tone, tremors, myoclonic jerks, abnormal reflexes
  - Dysarthria, dysphagia, paresis
  - 'Locked-in'
- Behavioral disturbances
  - Lethargy, confusion, disorientation, catatonia
  - Seizures, obtundation, coma
- Confirm diagnosis with MRI
  - Findings may be delayed up to 4 weeks



Sterns RH et al. J Am Soc Nephrol, 1994

Risk Factors for ODS

- Degree of hyponatremia
  - Typically, $[Na]_s$ < 105mEq/L
  - Very rare when $[Na]_s$ > 120mEq/L
- Duration of hyponatremia
- Alcoholism
- Malnutrition
- Liver disease
- Hypokalemia
- Rate of correction



Lohr JW. Am J Med, 1994

Causes of Overly Rapid Correction

- Saline administration in a volume depleted patient
- Discontinuation of thiazide diuretic
- Discontinuation of drugs causing SIADH
  - Resolution of condition causing SIADH
- Glucocorticoid administration in a patient with adrenal insufficiency
- Treatment with a vasopressin receptor antagonist (vaptan)
  - Be sure to lift fluid restriction

Equations often fail to predict rate of correction
No substitute for frequent monitoring

Prevention of ODS

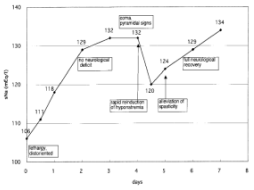
- Goal correction less than 6-8 mEq/L in any 24hr period if $[Na]_s$ < 120
- Anticipate patients who may 'autocorrect'
- Three strategies
  - **Proactive**: for patients with a reversible impairment of water excretion
    - Give ddAVP (1-2mcg IV) before correcting
    - Co-administer 3% saline at 15-30mL/hr and adjust as needed
  - **Reactive**: if unexpected water diuresis emerges or initial trajectory too fast
    - Replace free water losses with 5% dextrose in water (D5W)
    - If free water losses are excessive, may require ddAVP (1-2mcg IV)
  - **Rescue**: when rate of correction has exceeded 0.5mEq/L per hour
    - Give ddAVP (2mcg IV) to stop the rise in $[Na]_s$
    - Decrease the $[Na]_s$ with 5% D5W
      - 6mL/kg lean body mass) over 2 hours
      - Should lower $[Na]_s$ by ~2mEq/l (repeat as needed to get to goal $[Na]_s$)

Rafat C et al. Clin J Am Soc Nephrol, 2014
Perianayagam A et al. Clin J Am Soc Nephrol, 2008
MacMillan TE et al. Am J Med, 2015

Treatment of ODS

- Relowering effective in animal studies
- Rats corrected by 30mEq/L in 24hrs
  - Control rats left overcorrected
    - 1 of 13 alive at 10 days
  - Group relowered to <20mEq/L change
    - 7 of 15 survived
    - Neuro sxs attenuated or resolved in all
    - Only 2 had demyelinating lesions
    - Those treated earlier had better outcomes
- Case reports of benefit in humans

Soupart A et al. J Neuropathol Exp Neurol, 1996
Soupart A et al. Clin Nephrol, 1999



Oya S et al. Neurology, 2001

Take home points regarding Na correction

- ODS can be catastrophic and irreversible
- So can severe untreated hyponatremia
- Weigh the risk of slow/under correction vs overcorrection
- Anticipate patients who may overcorrection
- Re-lower patients who have overcorrected
- If in doubt or planning to give 3% saline or ddAVP, call a nephrologist

Troponins in Patients with CKD

Case and Question

65 year old gentleman with history of HTN, Type 2 DM, TIA, and ESRD presents to the emergency department (ED) from his outpatient dialysis unit with chest tightness that started in the last hour of his treatment.

On exam: BP 130/80mmHg, HR 65 bpm, Pox 98% on RA

He is at his estimated dry weight.

Labs show normal BMP, his TnI is 0.40ng/mL (lab ref <0.05ng/mL)

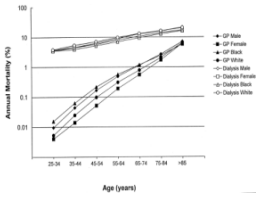
Which of the following would be the LEAST reassuring regarding this patient's risk of a myocardial infarction?

A. An ECG without ST segment or T wave changes
B. A TnI of 0.38ng/mL when the patient was seen in the ED 2 weeks prior for gout
C. A TnI of 0.02ng/mL four hours after initial TnI in the ED
D. A normal chest radiograph

Cardiac disease in hemodialysis patients

- HEMO Study subanalysis
  - 1846 HD patients
  - 0.9 to 6.6 yrs of follow up
  - 80% of dialysis pts have CVD
    - 39% ischemic heart disease
    - 40% CHF
- 1685 cardiac related hospitalizations
  - 43% for angina or MI
- 39% of all deaths cardiac related
  - 61.5% from MI

Cheung AK et al. Kidney Int, 2004



Parfrey PS and Foley RN. J Am Soc Nephrol, 1999

Interpreting elevated troponins (Tn) in CKD

- Elevated Tn w/o MI common in CKD
  - ~40% have Tn levels > 99th % without acute myocardial ischemia
- False positives more common with TnT than TnI

Values (median and interquartile range) of high-sensitivity (HS) troponin T (TnT) and troponin I (TnI) in patients admitted to the emergency department without a final diagnosis of myocardial ischemia

Variable	GFR >60 ml/min	GFR <60 ml/min	p
n	29	19	
Age (yrs)	61 (52–73)	78 (56–82)	<0.01
Gender (F/M)	9/10	14/15	0.95
CKD-EPI GFR (ml/min)	70 (61–91)	39 (26–45)	<0.01
HS-TnT			
Value (ng/L)	3.0 (3.0–12.5)	30.6 (9.1–66.2)	0.04
>99th URL (14 ng/L)	6/29 (21%)	12/19 (63%)	<0.01
HS-TnI			
Value (ng/L)	6.0 (3.1–26.1)	21.1 (6.2–128.5)	0.12
>99th URL (>32 ng/L)	6/29 (21%)	7/19 (37%)	0.22

Serial or historical measurements necessary

Lippi G and Cervellin G. Am J Cardiol, 2013

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