Almost everything you didn’t want to but need know about administering iodinated contrast media in patients with kidney disease

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Disclosure

Neither I nor my immediate family members have a financial relationship with any commercial interest or organization that may have a direct or indirect interest in the content of this presentation.
Why are we (you) here? (Objectives)

- Chronic Kidney Disease
- Contrast-induced AKI
- Screening for CKD
- Measuring renal function
- Guidelines for minimizing the risk of CI-AKI - who’s doing what and when?

Warning!! This presentation contains almost NO radiographic images
Chronic Kidney disease
• In 2002, NKF made a big effort to increase awareness of CKD publishing clinical guidelines
  – Definitions, evaluation, risk factors, and risk of loss of kidney function

• Chronic Kidney Disease (CKD)
  – Patients with kidney failure have annual mortality rate of 15%
  – Average life expectancy for 60 year-old
    – w/o CKD - 21 years
    – w/ CKD - 4.6 years
GFR and mortality rates

Chronic Kidney Disease - Staging

• Based on Glomerular Filtration rate
  – Stage 1  GFR ≥ 90 ml/min/1.73m²  damage w/ normal GFR
  – Stage 2  GFR 60-89 ml/min/1.73m²  mild decrease in GFR*
  – Stage 3  GFR 30-59 ml/min/1.73m²  moderate decrease in GFR
    – Estimated 50% loss of renal function
  – Stage 4  GFR 15-29 ml/min/1.73m²  severe decrease in GFR
  – Stage 5  GFR < 15 ml/min/1.73m²  kidney failure

*May be normal for age
Chronic Kidney Disease

• Decrease in GFR is independently associated with an increased mortality

• Why does CKD matters to radiologists?
  – Risk factor for
    – Contrast induced acute kidney injury (CI-AKI)
    – Nephrogenic systemic Fibrosis (NSF)
  – 4 - 6.5% of outpatients who present for CECT have elevated creatinine (≥ 1.5 mg/dl in most labs)
  – But - We now live in a GFR world … relationship of Creatinine to GFR and CKD must be understood
CKD - definition & prevalence

• CKD defined as GFR < 60 ml/min/1.73m² for more than 3 months
• Or kidney damage documented by biopsy or proteinuria

• Prevalence
  – GFR ≥ 90  3.3%
  – GFR 60-89  3.0%
  – GFR 30-59  4.3%
  – GFR 15-29  0.2%
  – GFR < 15  0.2%

  Total prevalence: 4.5%
Minimizing CI-AKI (& NSF) requires identifying patients at increased risk

- Most radiologists use serum Creatinine
  - Wide variability in “cutoff”
  - 1.5 mg/dl – 35%
  - 1.7 mg/dl – 27%
  - 2.0 mg/dl – 31%
  
  Eicker BM, AJR 2006;186:1651

- Serum creatinine depends on body mass, wt, age, and sex

- Serum creatinine does not rise until GFR is reduced by 50%
Contrast-Induced Acute Kidney Injury (formerly Nephropathy)

Over 1000 medline articles last 10 years
Contrast-Induced Acute Kidney Injury

• Definition
  – Reduction in renal function following contrast administration *AFTER* exclusion of other etiologies
  – Generally defined by changes in serum creatinine
    – Increase by 0.5 mg/dl
    – Increase by 25% over baseline

• Usually transient, creatinine peaks at 24-72 hours
  – Resolved by 2-3 weeks
  – *Perhaps restrict to patients with baseline creatinine 1.0 mg/dl? (Toprak O Renal Failure 2007;29:387-8)*
    – 0.6 - 0.9 mg/dl increase is “CIN” without renal dysfunction
Contrast-Induced Acute Kidney Injury

• Pathophysiology
  – “not clear” - several theories, combination of events
  – Most commonly recognized theory is reduction in renal perfusion caused by direct cytoxic effects by iodinated contrast on the renal tubules

• Noteworthy
  – High-osmolar agents reduce RBC deformability - trapping RBCs in renal capillaries
  – Contrast aggravates hypoxic injury to outer medullary portion
    – Persson PB et al, Kid International 2005;68:14-22
Contrast-induced AKI

• Patients at highest risk for CI-AKI?
  (Toprak Am J Med Sciences 2007;334:283-290)
  – Chronic kidney disease
  – Dehydration
  – Diabetes
  – Age > 70
  – Nephrotoxic drugs
  – CHF
  – Large contrast volume

• Incidence of CI-AKI - reported 1-30% ...

• Most studies of CI-AKI are studies of ...
  – Intra-arterial injections (angiography, cardiac catheterization)
  – Contrast agent studies assessing high v. low, low v. iso-osmolar

• Few studies looking directly at CIN with intravenous contrast for CT scans
Sampling of a few CI-AKI studies with IV contrast

- **Katzberg & Barrett, Radiology 2007;243:622**
  - Risk of ‘CIN’ with IA admin 2.2x that of IV admin

- **Mitchell et al 2006**
  - 1224 ED CT PE patients
  - 4% ‘CIN’ - None renal failure (creatinine +3 mg/dl)

- **Barrett BJ, Invest Radiol 2006;41:815-821**
  - 166 pts with CKD
  - 4% of patients developed ‘CIN’

- **Josephson SA et al 2005**
  - 1075 patients CTA/perfusion
  - 4.8% ‘CIN’ by sCR + 0.5 mg/dl
  - 0.37% renal failure
Combination of Diabetes and CKD highest risk for CI-AKI

• Lautin AJR 1991
  – 38% DM & azotemic patients
  – 16% DM, non-azotemic patients
  – 2% non-DM, non-azotemic patients

• Parfrey NEJM 1989
  – Creatinine increase > 50% - 8.8% DM and CKD v 1.6% controls
  – Creatinine increase > 25% - 7% with CKD v 1.5% controls
  – Study conclusions:
    – “Little risk for DM without CKD”
    – Risk of ‘CIN’ for DM and CKD is 9%
Screening for patients with CKD & other CI-AKI risk factors
How should we screen for CKD?

- **Choyke et al. Techniques in Urol 1998;4:65**
  - Serum creatinine 1.7 mg/dl cutoff
  - Screening form - Age > 60, recent CM, Heart Disease, Gout, DM, HTN, Kidney disease / surgery, proteinuria, OTC pain relievers
  - 98% of patients with negative questionnaires had sCr below cutoff
  - Could eliminate 28% pf patients from measuring serum creatinine ($12k)

- **Tippins et al. Radiology 2000;216:481**
  - Renal insufficiency, DM, age, male, nephrotoxic drugs (Lasix, chemo)
  - Risk factors positive in 97% of patients with creatinine ≥ 2 mg/dl
Age and CKD, CI-AKI

- Serum creatinine is a poor screening test for renal failure in elderly (> 65 yrs) patients
- Creatinine > 1.7 mg/dl only 12.6% sensitive for CrCL (CG) ≤ 50 ml/min
  - Swedko PJ Arch Int Med 2003;163:356
- Age > 60 yrs - independent risk factor for CIN in angiographic procedures
Risk factors for CI-AKI

- **CI-AKI risk factors**
  - Dehydration
  - CHF
  - Diabetes
  - Kidney disease
  - Large contrast volume
  - Age > 70 yrs

- **CKD risk factors**
  - Age > 60 yrs
  - HTN
  - DM
  - CVD
  - Family history

- **AKI / CKD risk factors**
  - Nephrotoxic drugs
  - Renal surgery / infection
Measuring renal function
Methods of measuring renal function

**Exogenous**
- Inulin clearance
- $^{125}$I-lothalamate

- Accurate
- Precise*
- Inconvenient
- $\$Expensive

**Endogenous**
- Creatinine - serum
- Creatinine - urinary clearance
- Cystatin C

- sCr - inexpensive, widely available
- 24 hr CrCl - cumbersome, moderately expensive, inefficient, unreliable
Creatinine

• Filtered by glomeruli

• Also secreted by proximal convoluted tubules
  – Therefore measured Creatinine clearance will be greater than GFR

• Interference
  – Cimetidine & trimethoprim inhibit secretion, elevating serum creatinine and lowering CrCl w/o changing GFR

• Creatinine - Jaffe method (alkaline picrate) measures serum creatinine

• POCT testing is usually a whole-blood assay
  – Creatinine results will increase by 0.25 mg/dL per every 1 mmol/L of acetaminophen
Factors affecting serum creatinine levels

- Aging  
  \[ \uparrow \text{age} \quad \downarrow \text{sCr} \]  
- Gender  
  F  \[ \downarrow \text{sCr} \]  
- Race  
  AA  \[ \uparrow \text{sCr} \]  
- Body habitus  
  \[ \uparrow \text{muscle} \quad \uparrow \text{sCr} \]  
- Chronic Illness  
  \[ \downarrow \text{health} \quad \downarrow \text{sCr} \]  
- Diet  
  vegetarian  \[ \downarrow \text{sCr} \]
Creatinine-based equations to estimate renal function

<table>
<thead>
<tr>
<th></th>
<th>Cockcroft-Gault</th>
<th>MDRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population/Year</td>
<td>Canadian VA/1976</td>
<td>Multicenter/USA/1999</td>
</tr>
<tr>
<td>Source of pt population</td>
<td>Inpatients</td>
<td>Outpatients with CKD</td>
</tr>
<tr>
<td>Reference method</td>
<td>Creatinine clearance</td>
<td>$^{125}$I-iothalamate clearance</td>
</tr>
<tr>
<td>Mean CrCl/GFR</td>
<td>73 ml/min</td>
<td>40 ml/min/1.73 m$^2$</td>
</tr>
<tr>
<td>Variables in equation</td>
<td>Age, gender, <strong>weight</strong></td>
<td>Age, gender, <strong>race</strong></td>
</tr>
<tr>
<td>Mean age</td>
<td>? (range 18-92)</td>
<td>51 (s.d. 13)</td>
</tr>
<tr>
<td>Percent females</td>
<td>4%</td>
<td>40%</td>
</tr>
<tr>
<td>African American race</td>
<td>unknown</td>
<td>12%</td>
</tr>
<tr>
<td>Adjusted for BSA</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
MDRD v. Cockcroft-Gault

• C-G ‘less inaccurate’ for normal renal function

✓ MDRD more accurate in outpatients with CKD

✓ We are not looking for accuracy in patients with normal renal function, just need sensitivity for identifying CKD
  • Ergo use MDRD to screen for CKD in outpatients…

• Neither meant for inpatients with acute renal dysfunction
Outpatient CT - creatinine versus eGFR

- Correlated sCr with eGFR based on MDRD (4) and (6)
  - MDRD (4)
    - 6.2% with sCr > 1.4 mg/dl v.
    - 15.3% eGFR < 60 ml/min/1.73m²
  - MDRD (6)
    - 5.8% with sCr > 1.4 mg/dl v.
    - 17.3% eGFR < 60 ml/min/1.73m²

[Herts et al, Radiology, July 2008]
Patients with normal serum creatinine and reduced renal function

• 15.2% of outpts with sCr < 1.5 mg/dl had creatinine clearance (Cockcroft-Gault) < 50 ml/min

• 9.9% of patients with sCr < 1.5 mg/dl had eGFR < 60 ml/min/1.73m²
  – Herts et al, Radiology 2008
Cystatin C as a marker of GFR

✓ Constant rate of production
✓ Lack of effect of gender or muscle mass on generation
✓ Free filtration at the glomeruli because of its small size and basic pH
✓ (Almost) complete reabsorption and catabolism by the proximal tubule cells → not found in urine
✓ No renal tubular secretion
Administering IV contrast - guidelines
(Who’s doing what and when?)
<table>
<thead>
<tr>
<th>GFR &gt; 60 mL/min/1.73m²</th>
<th>Normal or near-normal renal function. Extremely low risk. No specific prophylaxis or follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR 30 to 60 mL/min/1.73m²</td>
<td>Moderate renal dysfunction and low-to-moderate risk for CIN.</td>
</tr>
<tr>
<td>GFR &lt; 30 mL/min/1.73m²</td>
<td>Severe renal dysfunction and high risk for CIN</td>
</tr>
<tr>
<td>GFR &lt; 15 mL/min/1.73m²</td>
<td>Renal failure. These patients are usually on dialysis</td>
</tr>
</tbody>
</table>
Canadian Association of Radiologists

• Inpatients: 0.9% NaCl at 1 ml/kg/hr x 12 hours prior and 12 hours following the procedure

• Same day / outpatients: 0.9% NaCl or NaHCO3 1-2 ml/kg/hr x 3-6 hours before and after

• Oral hydration: 250-500 ml of “Saline” (i.e. salty chicken soup) up to 2 hours before the morning of the procedure and the day before. Continue fluids for 24 hours after contrast.

• Acetylcysteine (AC) has been advocated to reduce the incidence of CIN; however, not all studies have shown a benefit. It is difficult to formulate evidence-based recommendations at this time. Its use may be considered in high-risk patients but is not considered mandatory
European Society of Uroradiology (ESUR)

• CI-AKI
  – Risks: eGFR < 60, dehydration, CHF, gout, Age > 70, Nephrotoxic meds
    – Recent eGFR < 7 days
  – Recommendations for eGFR < 60 & pts with increased risk of nephrotoxicity
    – Stop nephrotoxic drugs x 24 hrs before
    – IV hydration 1 ml/kg 6 hours before and after

Special thanks to Henrik Thomsen, MD
Additional publications affecting CC policy

  – 421 patients with eGFR < 60 ml/min/1.73m²
  – 6.5% developed sCr increase ≥ 25%, but
  ✓ < 1% of patients with eGFR > 45 ml/min/1.73m² developed sCR increase > 0.5 mg/dl
  – None required dialysis
  – Hospitalization and death (30-days) were unrelated to CI-AKI

  ✓ Outpatient risk extremely low, especially with eGFR > 45 ml/min/1.73m²
Cleveland Clinic guidelines (as of Jan 2009)

• Who gets screened?
  – Known chronic kidney disease
  – Diabetes Mellitus
  – Patient age greater than 60
  – Dehydration
  – Congested Heart Failure (CHF)
  – Multiple Myeloma
  – History of kidney surgery / Kidney neoplasm
  – Recent nephrotoxic chemotherapy or other nephrotoxic drugs

• Within 2 months or more recent per history
<table>
<thead>
<tr>
<th>eGFR (mg/ml/1.73 m²)</th>
<th>Conditions and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>Considered at no increased risk of CI-AKI</td>
</tr>
</tbody>
</table>
| 45-59                | w/ risk factors (diabetes, dehydration, drugs)  
O_Oral hydration suggested, consider IV hydration individual basis  
w/o risk factors  
Oral hydration suggested (but not proven to be helpful) |
| 30-44                | w/ risk factors (diabetes*, dehydration, drugs)  
**IV hydration necessary**  
w/o risk factors  
Oral hydration recommended |
| 15-29                | Consider alternative studies  
IV hydration necessary |
| < 15                 | Only if on dialysis or emergent indication |
Preventing CIN - what do we know?
IV hydration

- **Inpatients** - 1 mg/kg/hr for 12 hours both before and after contrast (coordinated with primary service)

- **Outpatients**
  - 150 ml/hr over 2-3 hours depending on patient
  - 0.9% normal saline solution
  - Bicarbonate solution (3 amps in 500 ml D5W)
  - Push p.o. fluids after (?)
High, Low and Iso-Osmolar contrast

- Studies conclusive that low osmolar non-ionic agents reduce the risk of CIN (large prospective studies, meta-analyses)

- Iso-osmolar (Iodixanol) v. low osmolar?
  - “Little experimental evidence” (Persson)
  - Major study quoted is in diabetic cardiac catheterization patients
    - Iodixanol v. Iopamidol
      - CIN rate “similarly low” (Barrett BJ Invest Radiol 2006;41:815)
      - Incidence of CI-AKI was 4% of renal impaired patients undergoing MDCT
Low versus Iso-Osmolar contrast
Meta-Analyses

• 16 studies w/ 2727 patients - McCullough et al J AM Coll Cardiol 2006;48:692
  – Benefit with iodixanol in CKD & CKD / DM patients - all IA

• 25 studies - Heinrich et al, Radiology 2009:250:68-86
  – 8 studies IV contrast, 17 studies IA contrast
  – Pooled - no significant difference
  – Subgroup analysis -
    – low risk with iodixanol compared with iohexol
    – No difference between iodixanol and other low osmolar agents (iopamidol, iopromide, ioversol, iomeprol, iobitridol)
N-Acetylcysteine (Mucomyst)(NAC)

- Scavenges oxygen free radicals (antioxidant) and vasodilatory

- Studies? Majority state NAC reduces risk
  - NAC + hydration prevents CIN in CKD pts (83 CECT pts; 2% v 21%) (Tepel M, NEJM 2000;343:180)
  - NAC 0.4% v 18.5% (meta-analysys) (Alonso A, Am J Kid Dis 2004;43:1)
  - NAC relative risk 0.62 (41 studies, meta-analysis)(Kelly AM, Ann Int Med 2008;148:284)

- 600 mg bid day before and day of the procedure is the dosing generally studied
Other renoprotective agents?

- Theophylline - relative risk 0.49 - but not statistically significant
- Saline - relative risk 0.62
- Bicarbonate - relative risk 0.12
- Ascorbic acid - relative risk 0.46
- Others without effect
  - Furosemide, mannitol, fenoldopam
Meta-analysis of drug prevention of CIN

• Kelly AM et al Ann Int Med 2008;148:283
  – 41 studies meeting criteria - 6379 patients receiving radiographic procedures involving contrast agents
    – 34 trials of patients with impaired renal function
    – 2 trials of patients with only normal renal function
  – Only 1 trial of CT, remainder cardiac catheterization!
IV hydration

• Normal saline v. half-normal saline v. bicarbonate solution
  – study of 1620 patients - CIN 1.4% overall
  – Lowest NSS (0.7%); DM patients saline 0% vs 5.5%; more than 300 ml
  – No difference for patients with significant CKD (creat > 1.6 mg/dl)
  – Another study NaHCO$_3$ better than NSS

Are we performing well-controlled studies?

• IV contrast studies are few

• Medline search - contrast, contrast medium, contrast media or radiocontrast & nephropathy, nephrotoxicity, or renal / kidney failure

• 40 of 3081 publications (1.3%) had patients IV contrast injected

• 2 of 40 (5%) had non-contrast control groups
  – Rao & Newhouse Radiology 2006;239:392
Variability in creatinine measurements?

• Newhouse et al, AJR 2008;191:376

  – Adults w/ serum creatinine of 5 consecutive days w/o contrast admin
  – 50% showed a creatinine change of ± 25%
  – 32,161 pts - 25% increase in creatinine occurred in 27% of patients with sCr 0.6-1.2 mg/dl

  – Limitations - not noted, but these are likely inpatients with a pre-selection bias for renal dysfunction (who else gets 5 consecutive creatinines); no abstraction of the electronic data for accuracy

• Take home point: Possible if not likely that some of the creatinine changes following contrast are unrelated to IV and IA contrast administration

  – REMEMBER THE DEFINITION OF CI-AKI!
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials

- Smith GCS, Pell JP BMJ 2003;327:1458

- Results: We were unable to identify any randomized controlled trials of parachute intervention

- “Everyone might benefit if the radical protagonists of evidence-based medicine participated in a double blind randomized, placebo controlled cross-over trial”
Oral hydration??

• Few studies
  – IV hydration shown to be better than unrestricted water as oral hydration
  – One Asian study looking at water and salt tablets over 3 days, conclusion: uncertain benefit
  – One study no difference between oral hydration and 1/2 NSS x 6 hours

• General thoughts -
  – hydration before is likely better than after
  – Need salt / fluid loading rather than water alone
    – The question is how?
Contrast media and Dialysis

• Morcos S. European Radiology 2002
  – HD not helpful in preventing CI-AKI (CIN) when done immediately after
  – "the poor efficacy of hemodialysis in preventing contrast nephrotoxicity is related to the very rapid onset of renal injury after administration of contrast medium"
    – from: Br J Radiol 1998;71:357
  – Theoretical risks of elevated plasma [CM] include adverse effects on the CNS (lower seizure threshold and respiratory depression) due to either contrast media or uremia.

• "Immediate post procedure is unnecessary”
  – AJR 1994;163:969
  – Based on a study of 10 patients!
Metformin - purported risk is development of lactic acidosis after AKI

• Evidence?
  – Only a few series, intra-arterial & intravenous contrast
  – No evidence to support retesting after single I dose in patients with normal renal function
    – Goergen et al 2010

• Guidelines - variable
  – Manufacturer - d/c at the time of or prior to the procedure, withhold x 48 hours after and reinstituted only after function is normal
  – ESUR guidelines - eGFR 30-60 ml/min/1.73m² stop x 48 hrs before to 48 hrs after contrast
  – ACR - d/c x 48 hrs after contrast, resume usually w/o checking renal function (risk)
Preventing - or “minimizing the risk” of CIN & NSF

• General recommendations
  – Minimize dehydration - d/c Lasix other diuretics for 24 hours before study (if clinically feasible)
    – rarely done
  – IV hydration for those at greatest risk
  – N-acetylcystine inexpensive and may be beneficial
  – Oral hydration before with salt load in pt with mild risk factors
  – Determine for yourself the relative risk-benefit of CECT v. MR w/ Gd
  – Don’t do high dose or multiple Iodine or Gd studies
Summary / conclusions
Thoughts on research …

- Most studies are IA injections and without NC control groups
- Retrospective studies are pre-selected for patients with “issues”
  - Who else gets creatinine levels 2-4 days or more in a row?
- Need better controlled studies (NC control groups)
- Need studies of pts w/ normal and mildly reduced renal function
- Need better definition of outcome than an increase in creatinine
  - Clinically significant CI-AKI?
- True “risk” of CI-AKI after CECT is likely over-stated
Summary …

• GFR is now the preferred method for assessing patients for CKD, a major risk factor for CI-AKI

• … GFR / eGFR should be, but is not yet proven to be a better determinant of CI-AKI risk

• Screen patients using eGFR
  – 4-variable MDRD for outpatients
  – 6-variable MDRD for inpatients, chronic liver disease

• Keep an eye out for Cystatin-C as it may be a better indicator of renal function
Guidelines

- IV hydration only method consistently proven to lower the risk of CI-AKI
- Plan for patients with eGFR < 60 ml/min/1.73m²
- Worry about patients with eGFR < 45 ml/min/1.73m²
- N-acetylcysteine ‘can’t hurt’ and may even help but need not be mandatory
- And as always, consider each patient individually in the context of their health and the clinical indication
Selected References

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Toprak O. Renal Failure 2007;29:387-8
“Policies” versus “Guidelines”

THE RULES
They may be stupid, arbitrary and irritating, but god help you if you break them.