



## Senior Medicine Rotation: Evidence-Based Medicine Project

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## Case SIGNOUT:

81 y/o M with h/o HTN, chronic renal insufficiency, gout, spinal stenosis, >100 pack-year smoking history, bronchoalveolar carcinoma s/p RUL/RLL segmentectomy in 2004, now p/w SOB worse with exertion, orthopnea, PND, BNP of 1197, negative troponins x3/no ST changes on EKG, CXR with congestion, TTE showing LVEF 15-20% and global LV hypokinesis with regional variations, consistent with new-onset CHF, DCM with possible ischemic etiology. Now euvolemic after diuresis on regimen of furosemide 40 mg PO daily. Carvedilol started and titrated to effect. Pursuing RHC/LHC to assess for underlying CAD and potential role of revascularization. Cr currently 1.7 (baseline). Plan to start ACE inhibitor post-cath.

Clinical Question: In addition to gentle peri-procedural hydration with NS, should I give acetylcysteine to my patient with stable chronic renal insufficiency prior to coronary angiography in order to reduce the risk of contrast-induced nephropathy?

Clinical Context: A commonly quoted prospective study from the 1980s noted contrast-induced nephropathy (CIN) ranked as the third leading cause of hospital-acquired renal insufficiency (HARI); a follow-up study from the same author in 2002 similarly found CIN to be an important cause of HARI, with nearly 50% of cases attributable to cardiac catheterization.<sup>1-2</sup> Contrast-induced nephropathy is commonly defined as >25% or >0.5 mg/dL increase in serum Cr within 2-5 days of IV contrast administration in the absence of another etiology.<sup>3</sup> Relevant to this case, baseline renal insufficiency, increased age, and heart failure are risk factors for CIN following coronary angiography; one study placed the risk of CIN following coronary angiography at 14.5% (in-hospital mortality of 7.1% vs. 1.1% for no CIN) and of CIN requiring HD at approximately 0.8% (35.7% in-hospital mortality).<sup>4</sup>

Pre-procedural IV hydration is widely accepted for patients undergoing coronary angiography, particularly in the presence of pre-existing renal insufficiency or other risk factors.<sup>5-7</sup> N-acetylcysteine has the potential to improve renal function through vasodilatation, enhancement of renal medullary blood flow, and antioxidant properties; contrast causes vasodilation followed by prolonged vasoconstriction, as well as shunting of blood away from the renal medulla.<sup>8</sup> However, results of clinical trials have been quite inconsistent, with some studies showing clear benefit and others showing no benefit, perhaps due to differences in the populations studied and underlying risks, differing acetylcysteine formulations, or other factors.<sup>3</sup> In a 2006 "Clinical Practice" feature in NEJM, pre-procedural IV hydration but not acetylcysteine were recommended for routine prophylaxis against CIN in patient with chronic renal insufficiency.<sup>6</sup>

Table 2. Causes of Renal Insufficiency and Mortality by Cause

Cause	Episodes	Mortality
Decreased renal perfusion	147	20 (13.6)
Medications	61	9 (15)
Radiographic contrast media	43	6 (14)
Postoperative	35	1 (2.8)
Sepsis	25	19 (76)
Post-liver transplantation	14	4 (28.6)
Post-heart transplantation	8	3 (37.5)
Obstruction	7	2 (28.6)
Hepatorenal	7	5 (71.4)
Rhabdomyolysis	4	1 (25)
Artifactual	3	1 (33.3)
Glomerulonephritis	3	1 (33.3)
Nephrectomy	3	0 (0)
Atheroemboli	2	0 (0)
Hypercalcemia	2	1 (50)
Interstitial nephritis of unknown cause	2	0 (0)
Acetaminophen overdose	1	0 (0)
Unknown	13	1

Nash et al., Am J Kidney Dis, 2002

**Search Strategy Database: Medline**

("Acetylcysteine"[Mesh] AND "Coronary Angiography"[Mesh]) AND "Contrast Media"[Mesh] AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp]) AND English[lang] AND jsubsetaim[txt] AND "2000/08/29"[PDat] : "2010/08/26"[PDat]) Results: 14

Article Chosen<sup>9</sup>: Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA*. Feb 5 2003;289(5):553-558.

Group	Criteria or definition	n
Population screened	Patients with stable moderate renal insufficiency undergoing elective coronary angiography with or without PCI, single center	219
Inclusion criteria	Scheduled for elective coronary angiography ± PCI Serum Cr >1.2 mg/dL <b>OR</b> CrCl <60 mL/min by Cockcroft-Gault, confirmed by 24-hr urine Cr collection Known chronic renal disease with stable creatinine OK (not excluded)	200
Exclusion criteria	Patients on hemodialysis, with acute renal failure, <u>change in hypertensive or diuretic regimens</u> or received nephrotoxic agents or iodinated contrast <u>within 30 days</u> Patients with overt CHF, severe valvular disease, or <u>LVEF &lt;35%</u> Patients with acute chronic obstructive lung disease, acute asthma exacerbation, or allergy to acetylcysteine	12 (7 declined entry)
Treatment group	Acetylcysteine 600 mg PO BID on the day prior and the day of the procedure	102
No treatment group	Placebo tablets (matched to the above) BID on the day prior and the day of the procedure	98

\* All patients received 1 mL/kg/hr NS for 12h before and 6h after procedure and PO hydration permitted except for the 4 hours pre-procedure. Metformin was withheld pre-procedure, with glucose levels optimized using insulin and oral sulfonylureas. All patients received low-osmolality contrast.

Primary endpoints: (1) Occurrence of acute contrast-induced reduction of renal function (>25% or >0.5 mg/dL increase in Cr level that occurred within 48 hours after contrast exposure for which alternative explanations for renal impairment had been excluded)  
(2) Change in serum Cr 24h, 48h and 7 days post-procedure and change in CrCl 48h and 7 days post-procedure

Secondary endpoints: (1) Incidence of acute pulmonary edema  
(2) Major adverse cardiac events (cardiac death, non-fatal MI)  
(3) Need for hemodialysis  
(4) Length of hospitalization

Statistical consideration: Chi-square used to compare incidence of CIN and repeated measure ANOVA to compare Cr and CrCl between and within groups. Sharpened Bonferroni method used to adjust for individual  $\alpha$  level when multiple tests performed.

- Are the Results of the Trial Valid?
  - Randomized? Yes, allocation via random number generation by computer.
  - All patients accounted for at end? Yes; in acetylcysteine group, 3 dropouts and 1 to urgent CABG; in control group, 2 dropouts and 2 to urgent CABG.
  - Intention to treat? Designed as modified intention-to-treat to include all patients who received at least one dose of acetylcysteine or placebo, BUT, all patients randomized received at least one dose anyway.
  - Blinding? Yes, double blinded; participants, healthcare workers, those assessing outcome were all blinded.
  - Groups similar at start of trial? Yes; similar with respect to age, sex, BMI, cause of renal impairment, serum BUN/Cr, CrCl; h/o of DM, HTN, MI, CABG, PCI; LVEF, medications, angiographic diagnosis, contrast volume, etc.

- Equal treatment of groups? Yes; all received IV hydration and low osmolality contrast, metformin held
- Did randomization work? Yes.
- Are the Results of the Trial important?
  - Size of treatment effect? Possibly, as relatively low NNT needed to avoid one episode of acute contrast-induced reduction in renal function or one extra day in the hospital. However, study lacked power to compare incidence of HD or in-hospital mortality.
  - Precision of the estimate of the effect? Suboptimal given relatively small trial size, though significant (i.e. confidence interval for RR of CIN extends from 0.10 to 0.98).

Endpoint	Result	Significance	ARR	NNT
1° Acute contrast-induced reduction in renal function	4/102 (4%) Acetylcysteine. 12/98 (12%) Control	RR 0.32 (0.10-0.98) p=0.03	8.3%	12.0
1° Admission SCr	1.35 (A) vs. 1.36 (C) mg/dL	p=0.02	(-0.09)	N/A
Δ Serum Cr 24hr post-cath	-0.13 (A) vs. -0.04 (C) mg/dL	p=0.006	(-0.15)	
Δ Serum Cr 48hr post-cath	-0.13 (A) vs. +0.02 (C) mg/dL	p=0.23	(-0.06)	
Δ Serum Cr 7d post-cath	-0.04 (A) vs. +0.02 (C) mg/dL			
Admission CrCl	44.8 (A) vs. 42.1 (C)			
Δ CrCl 48hr post-cath*	+14.1 (A) vs. +2.0 (C) mL/min	p<0.001	(12.1)	
Δ CrCl 7d post-cath	+10.4 (A) vs. +6.3 (C) mL/min	p=0.045	(4.1)	
2° Need for hemodialysis	None in any groups	p=1.0	0%	N/A
2° Length of hospitalization	3.4d (±0.9) Acetylcysteine 3.9d (±2.0) Control	p=0.02	(0.5d)	(Save 1 hosp day per 2 pts treated)
Morbidity	Result	Significance	ARI	NNH
Major adverse cardiac events**	0/102 (0%) Acetylcysteine 1/98 (1%) Control (NSTEMI)	p= 0.49	-1.0%	-98.0

\*CrCl also significantly better among subgroups with DM, lower LVEF, higher contrast volume.

\*\* One patient in the acetylcysteine group developed UA and CHF, but this was not considered a major adverse cardiac event

Other adverse events: One patient self dc'ed the placebo pills due to nausea. No other adverse events.

General Limitations: Poor power to assess clinical outcomes beyond CIN (HD, mortality, etc). Adverse events poorly defined, aside from major adverse cardiac events. Drug/assistant provided by Zambon.

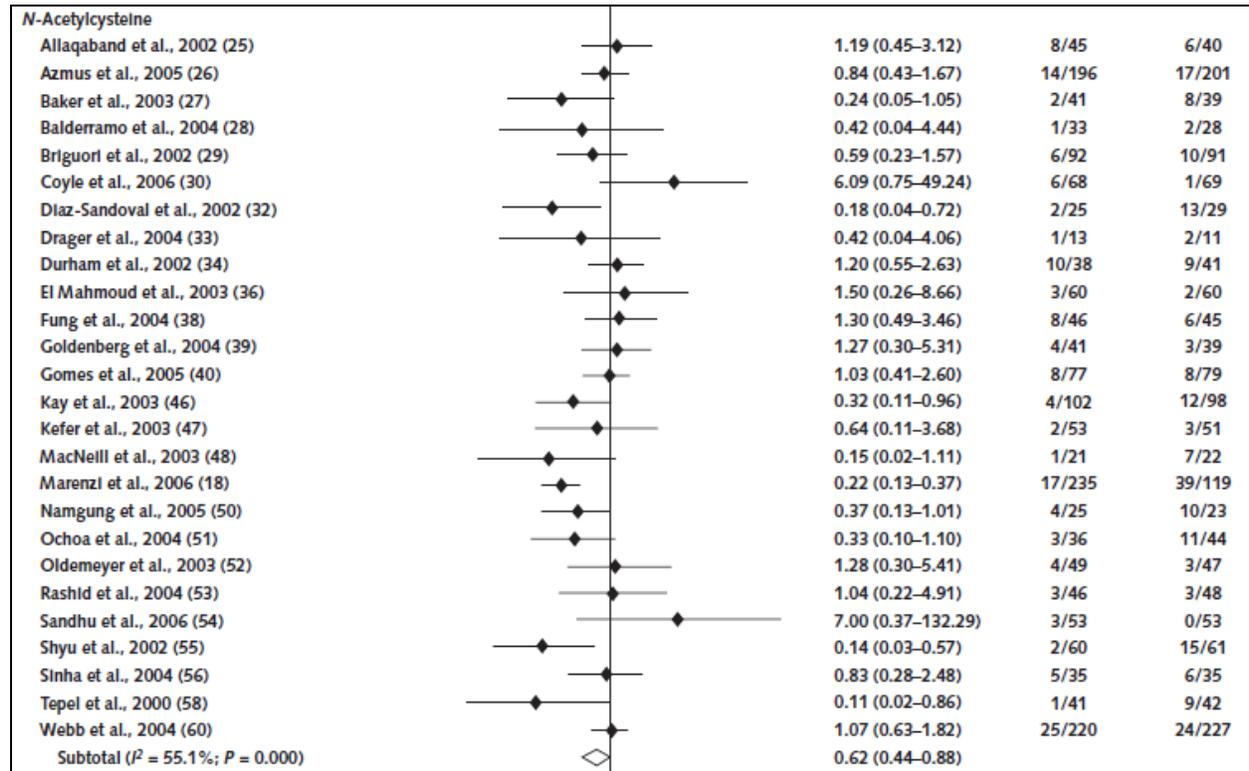
- Can I apply these results to my patient?
  - Comparison of my patient to trial patient?
    - His age was within the interquartile range for the study population. His CrCl was 44 mL/min by the Cockcroft-Gault formula, just below the study mean and well within the inclusion criteria for chronic renal insufficiency. He was also undergoing elective coronary angiography, without definitive plan for PCI, and in the absence of ACS.
    - My patient would NOT have qualified for this study due to changes in his medications, his new diagnosis of CHF (albeit euvolemic in good symptomatic control with diuretics) and associated low LVEF. Other studies would suggest his CHF places him at further increased risk of CIN.
    - These patients were taken from a Chinese center; my patient is Caucasian. Though there was no exclusion for overweight or obesity, the median BMI of study patients was 23.7 (!); my patient's BMI was >30.
  - All clinically important outcomes considered.

No, though the study was not established to address more definitive outcomes. CIN is used as a surrogate marker, but may represent minor, transient deterioration in renal function in many patients. Hospital length of stay is a useful endpoint, however. No patients required HD in this study; this reinforces the notion that the most severe forms of CIN are relatively uncommon after coronary angiography, though they may be more common in higher risk populations. A very large study, or targeted study of patients

believed to be high risk, would be best to assess for potential benefit in reduction of need for HD or in-hospital morbidity or mortality.

- o Likely benefits outweigh potential harms and cost?

Potential benefit in reducing risk of CIN and length of hospital stay, perhaps greater in higher-risk patients. Cheap; costs <\$30 for 3 liquid vials of acetylcysteine (23 cents for 500 mg tablet<sup>3</sup>). Well tolerated overall with minimal adverse effects (though my patient said it tasted terrible). Compared to costs of prolonged hospitalization, much less expensive; true morbidity and mortality benefit unclear, however. Recent meta-analysis suggestive of efficacy, but interpretation limited due to publication bias, study heterogeneity.



Kelly et al., Ann Intern Med, 2008

## References

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7. Bader BD, Berger ED, Heede MB, et al. What is the best hydration regimen to prevent contrast media-induced nephrotoxicity? *Clin Nephrol.* Jul 2004;62(1):1-7.
8. Fishbane S, Durham JH, Marzo K, Rudnick M. N-acetylcysteine in the prevention of radiocontrast-induced nephropathy. *J Am Soc Nephrol.* Feb 2004;15(2):251-260.
9. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA.* Feb 5 2003;289(5):553-558.