

## Contrast Induced Nephropathy (CIN)

The development of acute renal failure (ARF) is a significant complication of intravascular contrast medium use and is linked with excess morbidity and mortality. The incidence of CIN is low (2%) in the general population, but increases significantly in high risk patients. Up to 50% of patients with renal impairment and diabetes will develop CIN<sup>1</sup>. The most common procedures associated with CIN are coronary angiography and contrast enhanced computer tomography (CT).

**Definition:** an acute decline in renal function (increase in serum creatinine >25% of baseline value) that occurs 24-48 hours after intravascular injection of contrast medium. Serum creatinine (Scr) usually peaks 2-3 days after contrast administration and returns to baseline within 14 days (however some patients progress to ARF requiring dialysis)<sup>2</sup>

**Assess risk:** Patients with GFR >60 ml/min are at very low risk of CIN and preventative measures are generally unnecessary. Patients with GFR 30-60 ml/min have not been well studied, however, their risk is low and therefore maintenance of hydration may be suitable prevention in this group. The risk of CIN is greatest in patients with GFR <30ml/min.

### Risk factors for acute on chronic renal impairment and/or development of CIN

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|---|---|
| <ul style="list-style-type: none"> <li>• Diabetes mellitus</li> <li>• Renal disease or solitary kidney</li> <li>• Sepsis or acute hypotension</li> <li>• Cardiovascular disease (HTN, HF, CVD, PVD)</li> <li>• Human immunodeficiency syndrome or acquired immunodeficiency syndrome</li> </ul> | <ul style="list-style-type: none"> <li>• Dehydration or volume contraction</li> <li>• Age &gt;70 years</li> <li>• Previous chemotherapy</li> <li>• Organ transplant</li> <li>• Nephrotoxic drugs (loop diuretics, amphotericin B, aminoglycosides, vancomycin, NSAIDs, chemotherapy)</li> </ul> |
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### Preventative measures:

- Consider alternative imaging which does not require contrast media
- Load with fluid volume – most important protective measure (administer to all patients with GFR <60 ml/min, except if on dialysis)
- Hold nephrotoxic medications 48 hours prior to the study
- Minimize the contrast medium volume and frequency of administration
- Use iso-osmolar or low-osmolar contrast media in patients with GFR <60 ml/min. Iso-osmolar agents are preferred in patients with chronic kidney disease who are undergoing angiography.<sup>2</sup> Avoid high-osmolar contrast in all patients with renal impairment
  - Note: RGH uses *Optiray 350*<sup>®</sup> contrast dye which is of low-osmolality
  - The average amount of dye used for a standard angiogram at RGH is 80 to 100 ml, and for an angioplasty is about 250 ml (range 90 to 400 ml)

**Fluid volume:** Many studies advocate for administration of IV isotonic saline, while some RCT's have shown favourable outcomes when isotonic sodium bicarbonate is used instead. Definitive duration and fluid composition have yet to be determined. Oral hydration may be utilized in low-risk patients and out-patients.

- Standard in-patient recommendation: 0.9% NaCl at 1ml/kg/h, 12 hours pre-procedure and continued for 12 hours post-procedure<sup>2</sup>
- May consider: NaHCO<sup>3</sup> 150 mEq in 850 ml D5W at 3 ml/kg/h for 1 hour before contrast administration and at 1 ml/kg/h for 6 hours after contrast administration<sup>2</sup>
  - Controversial: some studies demonstrate that NaHCO<sup>3</sup> is better<sup>4</sup>, but others say that it is no better<sup>5</sup> or worse<sup>6</sup>. Further study is required in order to make a firm recommendation.
- Patients on hemodialysis should not receive fluid loads prior to contrast studies, as intravascular volume expansion may pose risk to dialysis patients with increased cardiac filling pressures<sup>7</sup>

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## N-acetylcysteine (Mucomyst®, NAC)

### Clinical studies:

- First study investigating use of NAC in CIN was published in 2000<sup>9</sup>. Eighty-three patients undergoing CT scanning were studied, all had a Clcr <50 ml/min. Patients were randomized to either NAC 600 mg p.o. b.i.d. on the day before and the day of the procedure or placebo. All received concomitant hydration with 0.45 % NS and low osmolality contrast dye limited to a ≤75 ml total dose. ARF (an increase of Scr ≥44 umol/L) occurred in 21% of placebo compared to 2% in the NAC group (P=0.01). The results of this study caused an abrupt change in NAC use in clinical practice.
- Subsequently, more than 20 studies have attempted to replicate the above findings, often using different doses and routes of NAC. Numerous meta-analyses have also been published on the subject; however their usefulness is limited due to the marked heterogeneity in study results.<sup>10-16</sup>
  - The number of published NAC studies with negative results doubles those with positive results. Studies with negative effects are likely under-represented, since fewer negative studies would be expected to result in publication.
  - Most studies have had a primary endpoint of a relatively small increase in Scr and have had small sample sizes. This small change in Scr increases the susceptibility to inaccuracy of this outcome measurement and warrants the need for larger sample sizes. Studies have been underpowered to detect a difference in occurrence of CIN.
  - Studies measure the incidence of CIN, a surrogate outcome. The impact of NAC on important patient outcomes (all-cause mortality, doubling of Scr level and need for dialysis), is uncertain and yet to be thoroughly evaluated.
  - Variation in confounding factors which could affect the results: 1) dose and route of NAC, 2) type and amount of contrast dye used, 3) type, amount and route of hydration used
- A higher dose of NAC 1200 mg po bid was trialed in comparison to the standard dose of 600 mg po bid.<sup>17</sup> This study (n=223) included a similar patient population to *Tepel et al*<sup>9</sup>, but did not limit the amount of contrast dye used. Approximately 50% of patients received a total of ≥140 ml contrast dye. For the patients treated with low (<140 ml) amounts of contrast dye, there was no significant difference between the groups. However, of the patients who received larger amounts of dye (≥140 ml), those who received the double dose of NAC had less CIN (18.9% in the standard dose group vs 5.4% in the double dose group, p=0.039).
  - Canadian guidelines: recommend using the dose used in the initial trial (by *Tepel et al*<sup>9</sup>) along with minimization of dye amounts<sup>2</sup>

### Take home message:

- It is reasonable to consider NAC in patients at risk for CIN since it is safe, inexpensive, well tolerated and may offer benefit. However, its use is not mandatory and the procedure should not be cancelled or delayed if NAC has not been administered.
- No other medication besides NAC has been reliably shown to decrease the likelihood of CIN
- Recommended dose is based on the original trial which showed benefit:<sup>2, 9, 10</sup>
  - 600 mg p.o. b.i.d. the day before and the day of the procedure
  - Most evidence, most inexpensive, avoids the minor risk of anaphylaxis with IV
  - Note: at RQHR we administer the IV solution PO
- IV administration may be used in patients unable to take oral meds (less supporting evidence)<sup>2</sup>
  - 15 mg/kg in 500ml NS IV over 30 min immediately before contrast followed by 50 mg/kg in 500 ml NS IV over 4 hours
- The use of NAC is appropriate in dialysis patients with residual renal function, as it may offer benefit without known harm. However, there is no data on the value of “nephroprotective” strategies to reduce the potential risk of contrast nephropathy in these patients.<sup>4</sup>
- Follow up with serum creatinine in 48-72 hrs in patients with GFR < 30 ml/min (consider if GFR =30-60 ml/min)

#### Related Tidbit: Metformin dosing in CIN

- Glucophage®'s monograph states it “should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials” due to its risk of causing lactic acidosis in the setting of acute renal failure.<sup>18</sup>
- Canadian guidelines suggest to discontinue metformin at the time of contrast injection & for 48h after in:
  1. Patients with GFR >60 ml/min who are receiving more than 100 ml of contrast dye

All patients with GFR <60 ml/min. Only restart if renal function remains stable (<25% ↑ in Scr).<sup>2</sup>

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