NSW TAG

Minimising Medication-Related Complications in Patients Receiving Intravascular Iodinated Contrast

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NSW Therapeutic Advisory Group Inc.

Advancing quality use of medicines in NSW

Contents

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Purpose

The purpose of this guidance is to provide assistance to clinicians, guideline developers and policymakers in New South Wales (NSW) public hospitals, Local Health Districts and Specialty Health Networks regarding medication-specific considerations in the prevention and management of Contrast Induced Nephropathy (CIN). It is designed to be read in conjunction with and to complement information released in 2016 by the Royal Australian and New Zealand College of Radiologists (RANZCR)[1] and in 2017 by the Agency for Clinical Innovation (ACI).[2,3] The use of gadolinium-containing MRI contrast agents is not discussed in this guidance.

Definition

Contrast Induced Nephropathy (CIN) is a generally reversible form of acute kidney injury (AKI) indicated by a rise in serum creatinine of more than 25% that occurs soon (often within 48-72 hours)[3, 4] after the administration of intravascular iodinated contrast media in the absence of another aetiology. This type of AKI may persist for 3 to 21 days.[4, 5] The incidence of CIN requiring dialysis treatment is approximately 0.4%.[6]

Rationale for NSW TAG guidance

CIN prevention and management are areas of emerging evidence and changing clinical practice. In light of this, the NSW Therapeutic Advisory Group (TAG) Editorial Committee reviewed the currency of existing NSW TAG guidance, current NSW hospital and district policies and recent clinical guidelines by RANZCR and ACI. Significant variation in the approach to prevention of CIN was identified, including recommendations regarding concurrent medication use. Furthermore, some current local practices were not evidence based.

Our recommendations are informed by recent published evidence and best practice guidelines from expert bodies.[1-4, 7-15] At the time of publication, there were no conflicts of interest declared by the Working Party members.

Recommendations

Key messages

1. Contrast should not be withheld or delayed when it is deemed to be clinically essential for accurate diagnosis and subsequent appropriate timely care.
2. A carefully considered assessment of benefit versus harm for administering contrast should be made.
3. Evidence-based mitigation strategies to reduce risk of CIN should be implemented.
4. For those patients at **moderate to high** risk of CIN:
    a. Identify and consider withholding medicines that have the potential to cause or increase risk of nephrotoxicity (prior to contrast administration if feasible).
5. If no CIN develops, restart withheld medicines (as appropriate).
6. If CIN develops:
    a. Continue to withhold nephrotoxic medicines (as appropriate),
    b. Identify any renally cleared medicines, consult relevant guideline and/or recommendations in medicine reference texts for dosing in renal impairment, adjust and monitor.

Mitigation strategies to reduce risk of CIN

If contrast is clinically indicated, the mainstay of interventions to prevent CIN before and after contrast exposure is to (where possible):

- Ensure the patient is well hydrated and, if indicated, give hydration with intravenous isotonic sodium chloride.
    - *Current evidence does not support the use of oral N-acetylcysteine (NAC) or intravenous sodium bicarbonate as strategies to prevent CIN.*[1, 15]
- Use low osmolality* or iso-osmolar contrast media.[13, 16, 17]
- Use the lowest volume (dose) of contrast possible to complete the procedure.[13]
- Avoid repetitive or closely spaced studies within 48-72 hours.[13, 16, 17]
- Withhold nephrotoxic medications if appropriate – see below section ‘Medication considerations in patients receiving contrast’.

*E.g. Iopamidol (Isovue®), Iohexol (Omnipaque®), Iopromide (Ultravist®), Iodixanol (Visipaque®), Ioversol (Optitray®)

Medication considerations in patients receiving contrast

1. ASSESS A PATIENT'S LEVEL OF RISK OF DEVELOPING CIN using clinical judgment and relevant guidelines.

Consider comorbid risk factors as well as current renal function*. (Refer to references 1 and 2 for risk assessment information or consult your local guidelines (if any)).

IF LOW RISK

Patients are unlikely to develop medication-related complications

→ Proceed as intended

IF MODERATE TO HIGH RISK

2. BEFORE CONTRAST ADMINISTRATION

a) Identify patient's current medications that are potentially nephrotoxic or increase the risk of CIN.

- Consider referring to a clinical pharmacist for assistance.

Some significant examples of nephrotoxic medicines[9, 18] include:

- Non-steroidal anti-inflammatory drugs (NSAIDs);
- Anti-infectives (e.g. gentamicin, tobramycin, amikacin, vancomycin, amphotericin B);
- Immunosuppressants (e.g. ciclosporin, tacrolimus).

b) Withhold any implicated nephrotoxic medications or those that increase the risk of CIN if clinically appropriate and feasible.

- Withhold only after consideration of the patient's clinical condition and discussion with the treating specialist (e.g. careful consideration may be required for specialised medicines such as immunosuppressants).

NB1. Metformin is not considered a nephrotoxic medication and therefore, its concurrent use with contrast should not increase the risk of CIN. There is a rare increased risk of lactic acidosis if renal impairment is present. Current metformin dosing information recommends a dose of up to 500mg daily in adult patients with a creatinine clearance (CrCl) (Cockcroft-Gault equation) of 15-30 mL/min.[7]
There is no need to withhold metformin if renal function is stable and CrCl ≥15 mL/min in any patient receiving intravenous contrast or CrCl ≥45mL/min in any patient receiving intraarterial[1] contrast (increased risk of harm with intraarterial administration).
Withhold if: i) baseline renal function is unknown, ii) the patient is critically ill or severely dehydrated, or iii) patient's renal function is deteriorating.

NB2. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are contraindicated in patients with impaired renal function (dapagliflozin if CrCl <60 mL/min; empagliflozin and ertugliflozin if CrCl <45 mL/min) as efficacy is reduced (dependent on renal function) and renal function may worsen.[7]
SGLT2 inhibitors are associated with increased risk of euglycaemic diabetic ketoacidosis.[7]
Withhold if: i) pre-existing renal impairment present, ii) surgery is likely, iii) pre-existing volume depletion/dehydration is present, iv) restricted dietary intake (e.g. fasting) or v) active infection.[7, 19]

NB3. Angiotensin converting enzyme inhibitors (ACEIs) and Angiotensin-2 Receptor Antagonists are not regarded as nephrotoxic medications. There have been inconsistent findings regarding their putative role in CIN. It is not clear whether withholding them prior to contrast administration reduces the risk of CIN.[13, 20]

*An estimated glomerular filtration rate (eGFR) in patients who have a low body weight for their height (e.g. < 50 kg in > 150 cm tall individual) may be an over-estimate and further individual patient review should be undertaken.[21]

3. AFTER CONTRAST ADMINISTRATION

a) Check renal function 48 hours post contrast exposure.[5, 12] (It is the responsibility of the clinician ordering the imaging to check this.)

i. If no evidence of CIN is identified

- Resume any medications that were withheld.

ii. If CIN is evident

- Treat as per AKI management guidelines.
- Identify any nephrotoxic medications and/or renally cleared medications that may accumulate and cause adverse effects.

  Commonly used medications with potential to cause adverse effects in renal impairment are listed in Appendix 1.

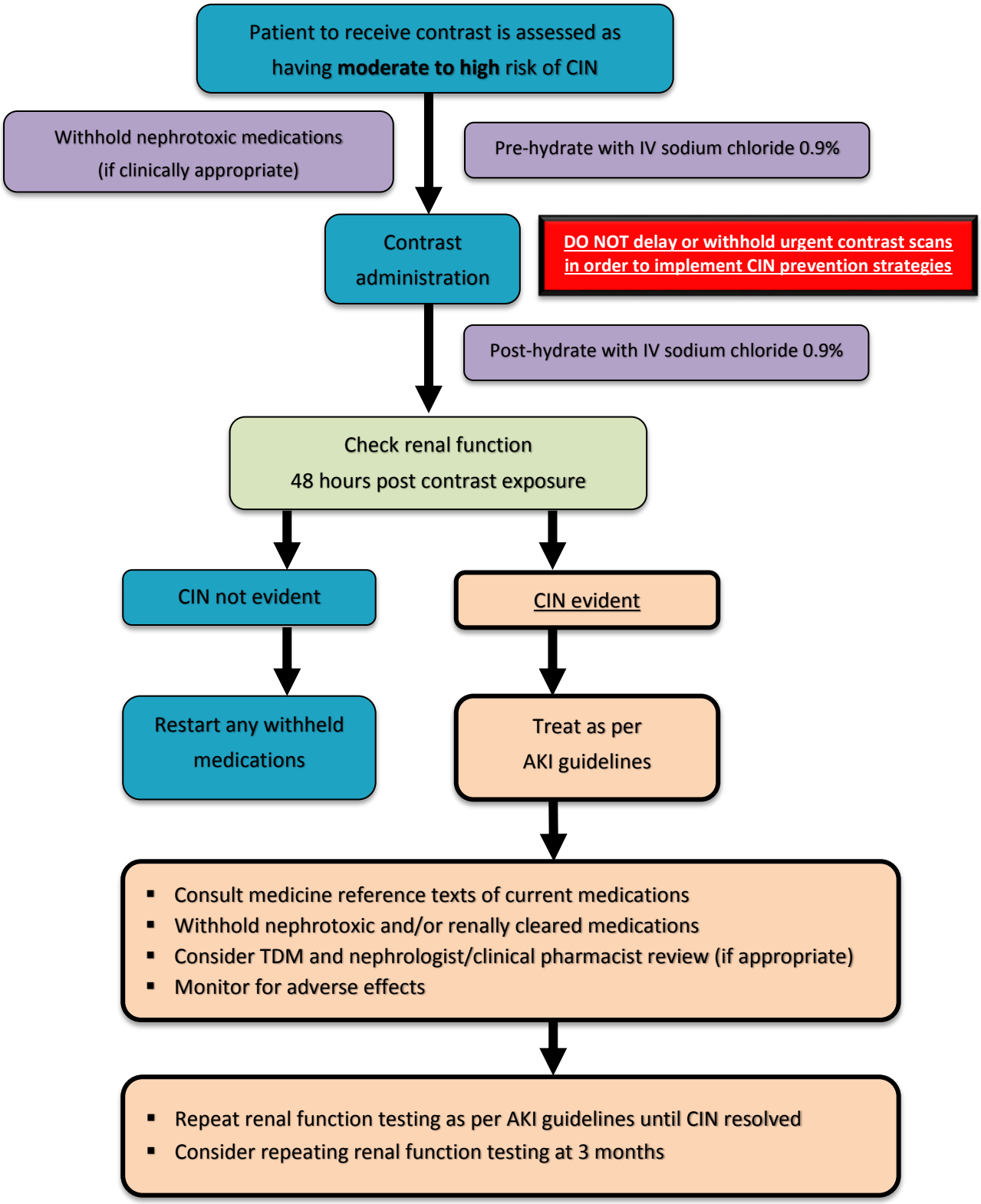
Some significant examples include[22]:

- Anticoagulants (e.g. apixaban, dabigatran, enoxaparin, rivaroxaban)
- Anti-infectives (e.g. gentamicin, tobramycin, vancomycin, antivirals)
- Digoxin
- Lithium
- Potassium sparing medicines (e.g. spironolactone)
- Opioids (most)

- Consult medicine reference texts of the implicated medication(s) for further information and management considerations.
- Consider referring to a nephrologist/clinical pharmacist/relevant specialty for assistance.
- Withhold implicated medications if clinically appropriate.
  - For example: the decision to withhold diuretic therapy in order to minimise the risk of intravascular depletion and worsening of nephrotoxicity should be made after assessment of fluid balance and the role of ongoing diuretic treatment for the underlying clinical condition.
- Monitor closely for any adverse effects from drug accumulation and conduct Therapeutic Drug Monitoring (TDM) where appropriate if concerned about reduced medication clearance.[23]
- Repeat renal function testing as per AKI management guidelines.
  - It is the responsibility of the clinician ordering the scan to consider whether outpatient renal function testing three months after a CIN episode is required to ensure the patient has not developed further AKI or CKD (long term risk of AKI).[6, 12]

Figure 1. Minimising risk of medication-related complications in patients at moderate to high risk of Contrast Induced Nephropathy

CIN = Contrast Induced Nephropathy, AKI = Acute Kidney Injury, TDM = Therapeutic Drug Monitoring



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Appendix 1: Commonly used medications with potential to cause adverse effects in renal impairment [8, 14, 22, 24, 25]

Disclaimer: The list provided is not exhaustive; for a more comprehensive list or further detailed information, please consult the medicine reference texts.

Anti-infectives	
Antiviral - Guanine analogues	Aciclovir, famciclovir, ganciclovir, valaciclovir, valganciclovir
Antiviral - Azoles	Fluconazole
Aminoglycosides	Amikacin, gentamicin, tobramycin, vancomycin
Carbepenem	Ertapenem, imipenem, meropenem
Cephalosporins	Cefazolin, cefepime, cefotaxime, ceftazidime, cefuroxime
Quinolones	Ciprofloxacin, norfloxacin
Penicillins	Piperacillin
Sulfonamides	Sulfamethoxazole
Other	Nitrofurantoin, trimethoprim
Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)	Captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril (See also NB3)
Angiotensin 2 Receptor Antagonists (ARBs or ARAs)	Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan (See also NB3)
Anticoagulants	
Direct thrombin inhibitors	Dabigatran
Factor Xa inhibitors	Apixaban, rivaroxaban
Heparins	Enoxaparin
Antidepressants	Desvenlafaxine, duloxetine, venlafaxine
Antidiabetic agents	Insulin Metformin (See also NB1)
Sulfonylureas	Glibenclamide, gliclazide, glimepiride, glipizide
SLGT2 inhibitors	Dapagliflozin, empagliflozin, ertugliflozin (See also NB2)
Benzodiazepines	Alprazolam, bromazepam, clobazam, clonazepam, diazepam, flunitrazepam, lorazepam, midazolam, nitrazepam, oxazepam, temazepam
NSAIDs	Celecoxib, Diclofenac, Ibuprofen, Indometacin, Ketoprofen, Ketorolac, Mefenamic acid, Meloxicam, Naproxen, Parecoxib, Piroxicam
Opioids	Codeine, hydromorphone, morphine, oxycodone, tramadol
Other/Miscellaneous	Allopurinol Atenolol Azathioprine Baclofen Colchicine Digoxin Eplerenone Fenofibrate Gabapentin and Pregabalin Levetiracetam Lithium Methenamine Hippurate Methotrexate Pramipexole Sotalol Spironolactone Topiramate Triamterene Zoledronic acid

Appendix 2: Acknowledgements

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