

# Prevention Strategies of Contrast Medium Induced Nephropathy (CIN): A Review of the Current Literature

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## Abstract

Contrast medium induced nephropathy is the third most common cause of renal failure for inpatients and represents the 10% of all acute kidney injury occurring during hospital-stay. It is associated with prolonged hospitalization, cost increase and, above all, an unfavourable short- and long-term prognosis. Here, the authors discuss about the contrast medium induced nephropathy prevention strategies, from the identification of patients at risk and drugs potentially nephrotoxic, to the hydration with possible administration of drugs that appeared to be, in some contexts, nephron-protective, and finally we analyze the radiological procedure aimed at the correct choice of type and administration modality of the contrast medium according to current literature.

## Keywords

Contrast Medium, Acute Kidney Injury, Hydration

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## 1. Introduction

Contrast medium Induced Nephropathy (CIN) is the third most common cause of renal failure for inpatients and represents the 10% of all Acute Kidney Injury (AKI) occurring during hospital-stay. It is associated with prolonged hospitalization, cost increase and, above all, an unfavourable short- and long-term prognosis with acceleration of chronic renal disease [1]-[3]. The imaging techniques most frequently associated with CIN are coronary angiography and Computed Tomography (CT) acquired after Contrast Medium (CM) administration. Both these exams are extensively required in

the current clinical practice [4].

Prospective studies of hospitalised patients with AKI demonstrate that CM administration is directly responsible or concurrent to renal failure development in the “11% - 14.5% of cases” [5]-[7]. Therefore, the AKI development is considered a significant complication of CM and it has been related to an increase both in morbidity and mortality despite the fact that the recent use of low osmolarity or iso-osmolar CM has significantly reduced the risk [8] [9].

## 2. Definition

To date, CIN is defined as an acute alteration of the renal function resulting in an increase of serum creatinine level greater than 25% compared to the basal values (pre-exam) or an absolute increase of creatinine level equal or superior to 0.5 mg/dl occurred within 48 - 72 hours following the patient exposition to CM, in absence of other possible causes of AKI [10].

CIN represents the development of renal damage that may verify after the CM administration, in absence of other identifiable causes, and it is widely recognised as one of the main causes of acquired renal insufficiency [10].

The exact pathophysiology of CIN development is still unknown but it is assumed that hypoxia, oxidative stress and free radicals produced in the renal medulla cause acute vasoconstriction, which determines renal hypo perfusion. In addition, it seems that there is direct CM toxic effect on the tubular epithelium (Figure 1) [11] [12].

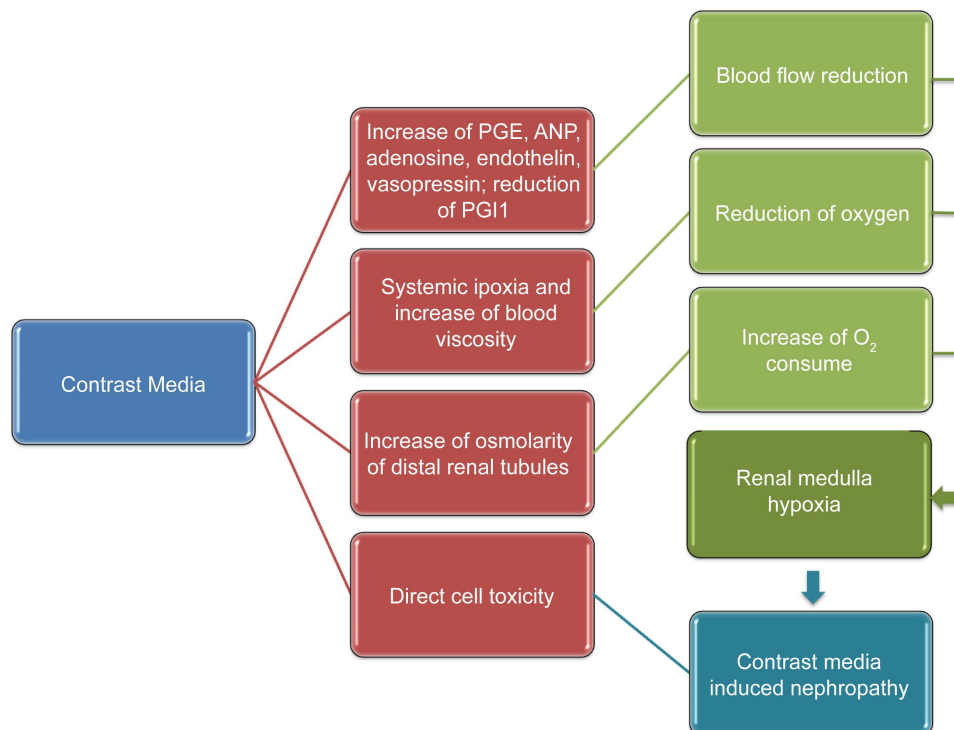


Figure 1. CIN pathogenesis.

### 3. Risk Factors

The development of CM nephrotoxicity has a significant impact on the duration and costs of hospitalization and on the short and long-term mortality [3]. Therefore, it is necessary to identify conditions that are thought to increase the risk of developing AKI in patients who need to be exposed to diagnostic exams and/or percutaneous procedure with CM administration.

Among predisposing conditions related to the patient, it is widely recognised the pre-existing kidney injury. There have been also associated (**Table 1**) advanced age and diabetes mellitus. In addition, numerous studies demonstrated that heart failure is a risk factor for patients undergoing percutaneous coronary intervention [13].

There are factors connected to the procedure such as type, quantity, administration modality (intra-arterial or intra-venous) of CM and interval between multiple administrations. The concurrence of these factors, associated with the population ageing, has been responsible for an increased CIN incidence, which could be avoided by adopting effective preventive measures. Before CM administration, patients should be adequately evaluated, in order to undertake the best preventive strategies to reduce CIN incidence [10].

Thus, it is important to identify the patients who might be particularly exposed [14] [15]. Fortunately, most of the patients who develop CIN have got identifiable risk factors and the results of many studies suggest that CIN onset is directly related to the number of pre-existing risk factors [16]-[18].

### 4. Strategies of CIN Risk Prevention

Here, we discuss about CIN prevention strategies, from the identification of patients at

**Table 1.** CIN risk factors.

Known risk factors	
Modifiable	Not modifiable
High dose of CM	Age > 65 years
Use of iodinated CM	Diabetes mellitus
High osmolarity CM	Pre-existing renal impairment
Short time interval between two injections of CM	Heart failure (NYHA III-IV)
Hypovolaemia	E.F. < 50%
Use of nephrotoxic drugs	
Presumptive risk factors	
Modifiable	Not modifiable
Arterial hypertension	Acquired immunodeficiency syndrome
Hypercholesterolemia	Previous kidney surgical interventions
Hyperlipidemia	Vasculitis
Hypoalbuminemia	Race

risk and drugs potentially nephrotoxic, to the hydration with possible administration of drugs that appeared to be, in some contexts, nephroprotective, and finally we analyse the radiological procedure aimed at the correct choice of type and administration modality of the CM.

#### 4.1. Identification of Patients at Risk

Strategies to reduce CIN incidence first suggest identifying patients at risk and finding for them, when possible, alternative examination tools. They can be identified through the use of questionnaires, the collection of complete anamnesis and the evaluation of glycaemia and, most of all, the assessment of renal function before the CM administration [10].

The glomerular filtration rate (GFR) through either MDRD or Cockcroft-Gault formulas correlates with the renal function better than the serum creatinine [19]-[21].

The GFR estimate should be obtained within 3 months before a radiological exam with CM in stable day hospital patients, and within 7 days in the hospitalized ones. The measurement should be the latest possible in patients likely to be affected by a recent modification of the renal function (haemodynamically unstable patients, recent chemotherapy, recent use of nephrotoxic drugs, etc.) [21].

When it is not possible to obtain GFR in due time, for example in Emergency room, the presence of multiple risk factors might indicate patients susceptible of glomerular filtration reduction and therefore renal damage induced by CM [21].

Patients with a GFR  $\geq 60$  ml/min have an extremely low CIN risk and, generally, do not require preventive measures or follow-up. Using preventive measures when the GFR is  $<60$  ml/min is considered worthwhile. In particular, several studies suggest that GFR cut-off for CIN risk is 40 - 45 ml/min and efforts to reduce the CIN risk should be concentrated on patients with GFR  $< 45$  ml/min, with a specific attention to patients with a serious renal dysfunction (GFR  $< 30$  ml/min) and additional risk factors [22] [23].

#### 4.2. Potentially Nephrotoxic Drugs When Associated with CM

Drugs that may exacerbate CIN can be divided into three categories:

1) FANS, aminoglycosides, cyclosporine, tacrolimus and amphotericin, which act with a direct nephrotoxic mechanism and which is better to suspend at least 24 hours before CM administration [24].

2) Some antihypertensive drugs, among which ACE-inhibitors, angiotensin II receptor antagonists and aliskiren interfere with the renin-angiotensin system and decrease the renal perfusion, particularly when it is based on the renin-angiotensin system (in case of hypovolemia, dehydration, heart failure or renal artery stenosis). It has been recently demonstrated that these drugs represent a risk factor for CIN in patients undergoing coronarography [25]. Nevertheless, there is no evidence that the suspension of these drugs is useful for preventing CIN; hence, to date, it is not recommended their routine interruption [21].

3) Metformin, which itself do not increase the CIN risk, may generate lactic acidosis in case of worsening of renal function and it is cause of acute cell damage. For this reason, it is recommended metformin interruption 48 hours before the CM administration in case of pre-existing renal failure (GFR < 60 ml/min) and restart 48 hours later, after evaluation of renal function [26]. The European Society of Urogenital Radiology (ESUR) adopts a conservative approach and recommends to continue the therapy with metformin until the CM injection in patients with normal serum creatinine levels and to suspend it 48 hours before the injection in patients with a compromised renal function [21].

### 4.3. Detraction or Dose Reduction of Iodinated CM

Obviously, the risk of CIN onset might be completely avoided obtaining necessary diagnostic data without intravascular administration of iodinated CM [26]. However, in some cases the use of CM is essential but it could be used an inferior dose as the renal toxicity of the iodinated CM is dose-dependent [27].

The CIN prevalence is connected with the CM volume administered, and it has been observed that the lowest rates of CIN risk affect patients receiving less than 100-140 ml of CM. CM administered in volumes higher than 5 ml/Kg is strongly predictive of a serious acute renal insufficiency, which needs a dialysis treatment [28]. Recent studies found that by using only 50% of normal dose of CM it is possible to acquire appropriate diagnostic images of peripheral arteries, but reducing CIN development in patients at risk [29].

Moreover, Leheti *et al.* showed how complications after endovascular aneurism repair appear to be acceptably imaged using only half dose of CM in patients with weight < 90 Kg or BMI < 35 Kg/m<sup>2</sup> [30]. It has been also demonstrated a significant increase of the CIN risk among patients who received a second CM dose within 48 hours after the administration of the first [31]-[33].

It should be reduced the CM volume to the bare minimum, avoiding repeated injections by 72 hours. Moreover, it should be used the minimum amount of iodinated CM which allows satisfying image quality, as it could be often diluted with physiological solution without compromising the image quality [33].

### 4.4. Choice of Low-Osmolar Contrast Medium

One of the advantages of the use of low-osmolar instead of high-osmolar CM is the reduction of CIN incidence in patients at risk [34]. The mechanisms that determine the CIN risk reduction with low-osmolar CM have not been clarified yet. Possible explanations concern the reduced osmolarity itself, the different ionization, and/or other chemical-physical properties [35]. High-osmolar CM are related to more systemic adverse events, including CIN, than low- or iso-osmolar CM. Therefore, the use of CM with higher osmolarity should be avoided in patients with chronic renal insufficiency. In particular, iso-osmolar CM has been demonstrated to be related to low nephrotoxicity, therefore, it has been widely recommended for patients with renal failure [36].

#### 4.5. Hydration

Hydration is the only accepted prophylactic strategy for CIN and it is strongly recommended by the Guidelines, as it is effective in reducing the risk and severity of the nephropathy [37]-[39]. All the patients considered at CIN risk should receive hydration. The crystalloids generally used are saline isotonic solution and bicarbonate (154 sodium bicarbonate mmol per 0.85 liter of dextrose at 5%), which are low-cost and harmless for the patients. The possible physiopathological explanation about the hydration efficacy in reducing the CIN risk could be related to the fact that, if correctly completed, it increases the intravascular volume and induces diuresis. Consequently, there is CM dilution in the renal tubules resulting in reduction of its contact time with the tubular epithelium inside the kidney. Moreover, diuresis increase leads to vasodilatation at the level of renal medulla, which is a region more vulnerable to the CM action, probably increasing the prostacyclin production. Furthermore, the volume expansion suppresses the renin-angiotensin system and the anti-diuretic hormone (ADH) production with a vasoconstrictor effect [21]. Particularly for patients with left ventricular dysfunction is important to improve renal blood flow to prevent CIN, as recently demonstrated by Kawatani *et al.* in a group of patients undergoing endovascular stent graft positioning [40]. Both intravenous and oral hydration have been proposed, however, to the best of our knowledge, there are not strong evidences to consider the oral administration as effective as the intravenous infusion in patients at CIN risk [35] [41]. The most widespread intravenous hydration regime are: 2 ml/Kg/h 2 hours before CM administration and 1 ml/Kg in the following 6 hours; or 1 ml/Kg/h 12 hours before and 12 hours after the procedure [42].

#### 4.6. Premedication

Pharmacological prophylaxis for preventing CIN would represent the best result to achieve, however, no medication offers a certain efficacy. In particular, several studies showed the possible role of N-Acetylcysteine (NAC) to prevent CIN due to its double role as vasodilator and antioxidant or because its effect on urine alkalinisation [43]-[46]. Numerous protocols have been proposed for NAC use. Actually, CIN incidence has been significantly reduced with oral administration of 600 mg of NAC 24 hours before CM injection instead of hydration alone [47]. Another study proposed intravenous NAC 7 hours instead of 20 min before CM injection to prevent CIN after coronary angiography [45]. In a randomized study, Li *et al.* compared pre-medication with probucol and hydration. They demonstrated that oral intake of 500 mg of probucol twice a day for 3 days before and after coronary intervention procedure was associated with lower serum creatinine levels than the hydration group [48]. Another study showed that administration of 3 g of ascorbic acid before and 2 g after the procedure markedly reduced the CIN incidence [49]. However, high doses of NAC seem to be more effective than ascorbic acid [50]. Lee *et al.* attested that a short pre-treatment of 2 mmol/L of NAC for 15 min before CM injection and a supplementary dose of NAC 12 hours after reduced CIN more than pre-treatment with probucol or ascorbic acid [51]. Neverthe-

less, data about the efficacy of NAC and other drugs in reducing the incidence of CIN are divergent, therefore, usefulness remain unproven and their use cannot be recommended [52] [53].

#### **4.7. Haemodialysis and Hemofiltration**

The sense of haemodialysis in patients at high risk for CIN is the early removal of the CM from the blood [54]. Several studies have been published in order to determine if haemodialysis post-administration of CM reduces CIN rate [55]-[57]. A systematic literature review has highlighted that haemodialysis, even if performed after CM administration, is not effective in reducing CIN rate, probably due to the very early CIN development after CM administration [55]. Moreover, haemodialysis simultaneous with CM administration has not been effective in reducing the damage. In addition, haemodialysis is related to risks connected to the procedure itself, and it can be in some cases nephrotoxic because of phlogosis activation and volume depletion [56].

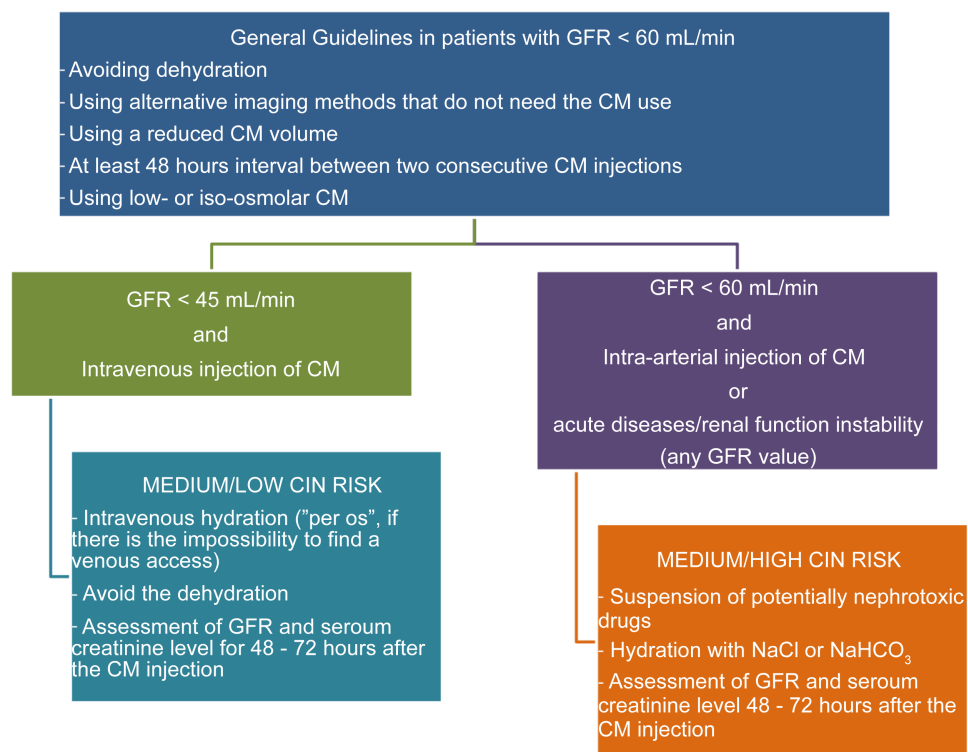
The hemofiltration is a continuous form of renal replacement therapy. When solutes and water are removed from blood, fluids are substituted by big volumes of isotonic fluid, which help maintaining the hemodynamic stability [58]. With this procedure, most of the CM is removed from blood with the hemofiltration while the isotonic fluid dilutes the remaining CM [59].

The hemofiltration is an expensive procedure, which is performed in intensive care. Even though it may be effective for highly selected patients at extremely high risk of CIN, evidence of its efficacy remains poor [60].

### **5. Conclusions**

To date, CIN is one of the most serious adverse reactions to iodinated CM. Since there is no specific therapy for CIN and the disease is iatrogenic, prevention is of paramount importance [45]. The patients at highest risk have a GFR below 60 ml/min. GFR measurement is particularly recommended before intravascular administration of iodinated CM in patients affected by renal disease, positive familiar anamnesis, renal insufficiency, diabetes under medical therapy, vascular collagen diseases, previous renal surgery or which are under treatment with metformin or nephrotoxic drugs like aminoglycosides and nonsteroidal anti-inflammatory [61] [62]. All patients should be persuaded to freely drink water 12 hours before and after CM injection, when possible. Intravenous hydration, which expands the blood volume, is the only intervention to limit hypoxic damage and direct toxic effect of CM and to prevent CIN. The hydration protocols consider 1 - 1.5 ml/kg/h intravenous saline isotonic solution administration 6 - 12 hours before the CM administration and for 6 - 24 hours after. For hospitalized patients, it should be applied a 24-hour protocol which includes 1 ml/Kg/h of saline solution administration, beginning 12 hours before and continuing for 12 hours after CM injection [63].

No pharmacological prophylaxis (with vasodilators that have a renal action, receptor antagonists of endogenous vasoactive mediators, cytoprotective drugs) has been



**Figure 2.** Guidelines for patients with GFR < 60 ml/min modified from Owen RJ *et al.* [64].

demonstrated to be useful in preventing the nephropathy caused by CM. The hydration pre- and post-CM administration represents the only prevention therapy strongly recommended by the guidelines for patients at risk (Figure 2) [10] [21] [64].

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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### Abbreviation Note List

CIN: Contrast medium Induced Nephropathy

AKI: Acute Kidney Injury

CM: Contrast Medium

GFR: Glomerular Filtration Rate

ADH: Anti-Diuretic Hormone

NAC: N-AcetylCysteine



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