

Contrast-induced Acute Kidney Injury: A Contemporary Review

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Abstract

Clinically significant Contrast-Induced Acute Kidney Injury (CIAKI) is a severe complication of interventional contrast-based procedures of all kinds. It involves high morbidity, mortality, social and financial losses. Acute renal damage after coronary angiography or percutaneous coronary intervention may occur in 1-2% of cases in the general population or 50+% of cases with high CIAKI exposure. It is essential to detect high-risk patients with renal damage as a major and frequent CIAKI predisposing factor. There are novel biomarkers with rapid or nearly instant response to acute subclinical contrast-induced renal damage, which are highly valuable in CIAKI diagnosis and for this reason desire deeper clinical research. Despite a number of controversies, prophylactic and therapeutic measures are practically the same in a vast majority of guidelines. An intravenous 0.9% NaCl solution remains the only proven measure in CIAKI prophylaxis and treatment, while the use of other pharmacological approaches still needs more relevant prospective clinical research. The aim of this paper was to review contemporary evidence-based CIAKI data.

Keywords

Nephropathy; Renal injury; Contrast media; Renal injury biomarkers

Introduction

Contrast-Induced Nephropathy (CIN), or Contrast-Induced Acute Kidney Injury (CIAKI), is acute damage to the renal parenchyma, caused by the intravascular administration of iodinated Contrast Media (CM) without other alternative reasons [1]. CIAKI was first described by clinicians in a 1950s case history, clinically proceeding as a lethal acute renal failure after intravenous pyelography in myeloma patients [2,3]. The incidence of CIAKI may be as low as 2% in patients without risk factors, but in those with risk factors, such as diabetes, the rate rises to 9%, and even as high as 90% in patients with diabetic nephropathy or preexisting chronic kidney disease [4,5]. Therefore, the number and the type of preexisting risk factors directly influence the incidence of renal insufficiency. Incidence rates are also procedure dependent, with reports in the literature ranging from 1.6-2.3% for diagnostic interventions to 14.5% overall in patients undergoing coronary intervention [4,5]. Renal damage after coronary angiography or percutaneous coronary intervention may develop in 1-2% of cases in the general population and almost 50% of patients with high CIAKI exposure [1,6]. A major CIAKI factor is existing nephropathy, especially in diabetic patients [5,7].

Every year, the growing number of patients receiving percutaneous cardiac care increases CM consumption and consequently CIAKI incidence. CIAKI entails an increased frequency and number of cardiovascular complications, extended admission, need for substitutive renal therapy, and fivefold increase in hospital mortality [8]. CIAKI's fully iatrogenic and predictable nature makes this disease available for a comprehensive study with focus on its pathophysiology, risk stratification, prophylaxis and treatment.

CIAKI meets one of the following criteria of acute kidney injury, regardless of etiology [9]:

- Serum Creatinine (SC) increase by 26.5 $\mu\text{mol/L}$ within 48 h;
- SC increase by 1.5+ times above its known or estimated level in previous 7 days;
- Lower diuresis (oliguria $<0.5 \text{ ml/kg/h}$) for 6 h (cannot be regarded as a reliable diagnostic criterion, since it rarely develops after CM administration for a variety of reasons).

The key factor in diagnosing and determining nephropathy severity is relative or absolute SC growth in the first 48-72 h after CM injection.

The downside of this definition is hyposensitivity to small oscillations of plasma creatinine, related to renal parenchyma damage, and the absent functional estimation of renal function condition [10-12].

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Under recommendations by Kidney Disease Improving Global Outcomes (KDIGO), CIAKI is classified into 3 groups [13] (Table 1).

The problem of using SC as a renal damage biomarker is that SC increase after CM injection characterizes a preexisting decrease in Glomerular Filtration Rate (GFR), not cellular damage. Creatinine increase is only observed 48-72 h after CM injection and has no clinical value during preexisting AKI [14]. However, a study by Ribichini et al. [15] has proved that SC increase by 5% 12 h after CM injection is an AKI marker with 75% sensitivity and 72% specificity. In addition, such SC growth dynamics may be used to estimate a 30-day nephropathy prognosis [15].

However, clinical practice and most studies on CI nephropathy prefer the first definition as a simpler one with superior correlation with clinical outcomes [1,7,16-21].

Based on the fast or nearly instant response by some biomarkers to subclinical AKI, measuring their urine or plasma concentration is now a promising research trend. Significant AKI biomarkers include Neutrophil Gelatinase-Associated Lipocalin (NGAL), Cystatin C, Kidney Injury Molecule-1 (KIM-1) and Interleukins-6, 8, 18 (IL-6,8,18).

1. Urine or plasma NGAL. Used both for early detection (within 4 h) and prognosis of AKI progression [22-26].
2. Plasma Cystatin C. The plasma level of this biomarker accurately reflects renal function change - 10% increase within 24 h highly likely eliminates AKI presence after CM injection [27-31].
3. Kidney Injury Molecule-1, a Type I transmembrane protein normally absent in the urine, is a sensitive and specific AKI biomarker, under some studies [29,32-36].
4. Measuring concentrations of IL-6,8,18 released by glomerular mesangial cells in response to CIAKI can help detect CIAKI shortly (within 24 h) after contrast X-ray [37-40].

Despite reliable correlation between changes in these markers' concentrations and AKI presence, their routine use is not yet included in current guidelines on CIAKI prophylaxis and treatment for lack of major multicenter studies [6,7,18,41-45] and evidence of the relevant novel biomarker response in contrast-induced acute kidney injury.

Contrast media

As to CI nephropathy, radiopaque iodinated substances as the prime AKI cause, widely used in modern interventional radiology, cannot escape consideration. The first CM works were published in 1896 by E. Haschek and O. Lindenthal [46]. At that time, bismuth, plumbic and barium salts were used in stump vessel angiography but were unsafe for lifetime diagnostics. In the early 1920s, Osborne et al. [47] found that a syphilis patient's urine, after long-term treatment with iodinated drugs, acquires radiopaque properties. This observation led the researchers to the first successful pyelogram taken at Mayo Clinic in 1923. Intravascular iodinated CM were introduced into clinical practice by urologist Moses Swick [48] in 1928, thus initiating long-term experiments with structural CM modification so as to reduce their toxicity and increase efficiency.

In present-day interventional radiology, iodinated CM remains frontline therapy, despite the significant nephrotoxic effect, due to almost totally absent alternatives.

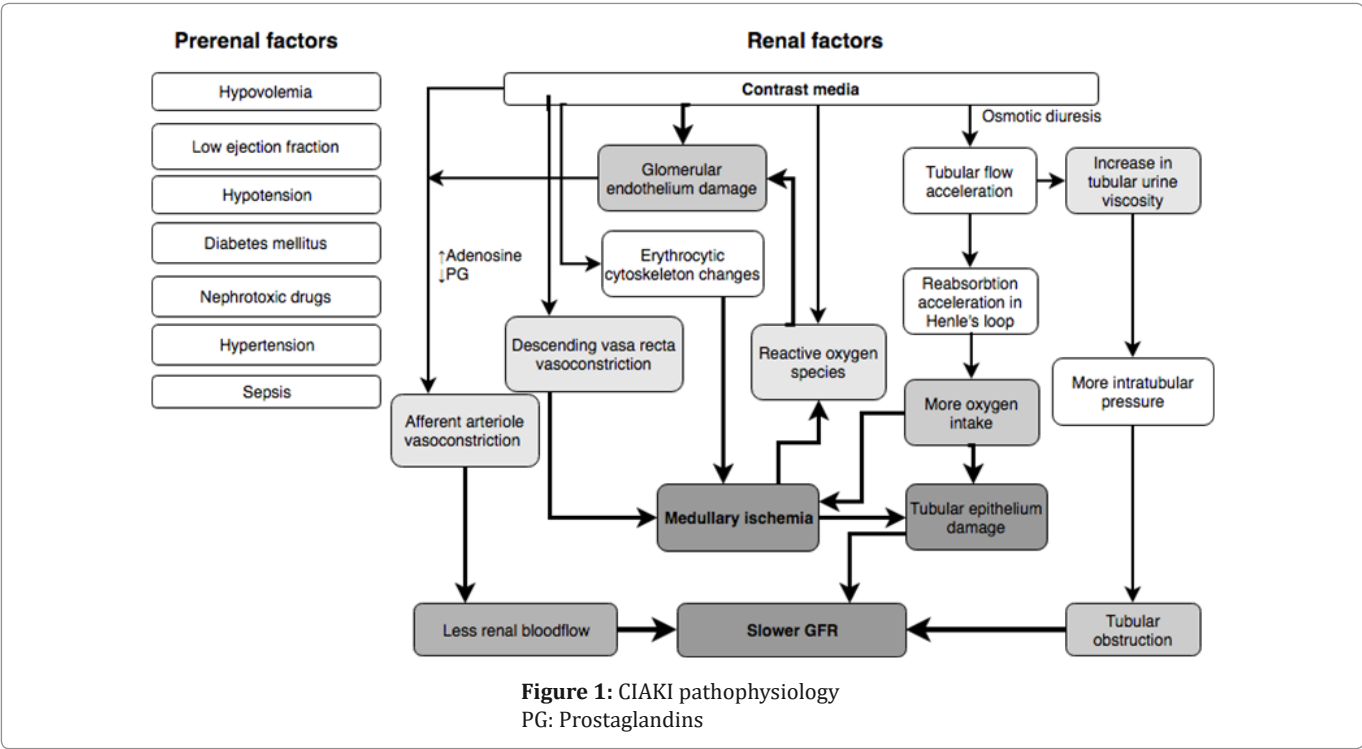
CM's damaging effect on the renal parenchyma is conditioned by 2 main mechanisms (Figure 1):

1. CM's direct cytotoxic effect on the glomerular endothelium with a developing vasoconstriction of afferent arterioles and the tubular epithelium.
2. CM's indirect effects on blood and urine viscosity, followed by increased intratubular pressure and reduced GFR [49-52] (Figure 1).

CM's ability to damage, renal tissue results from such factors

CIAKI Stage	SC	Diuresis
1	1.5-1.9x up or ≥ 26.5 mcmol/L (0.3 mg/dL) above baseline	<0.5 ml/kg/h for 6-12 h
2	2.0-2.9x upt	<0.5 ml/kg/h >12 h
3	3x up above baseline or ≥ 353.6 mcmol/L (4.0 mg/dL) above baseline or need for substitutive therapy or GFR reduction <35 ml/min/1.73 m ²	<0.3 ml/kg/h >24 h or anuria ≥ 12 h

Table 1: CIAKI severity under KDIGO Clinical Practice Guidelines for Acute Kidney Injury, 2012



as ion composition, osmolality, and viscosity (Table 2). Low- or isosmolar CM are recognized standards in interventional cardiology, which is confirmed by a number of studies, while ionic CM is used rarely nowadays due to frank nephrotoxicity [17,49,53].

A NEPHRIC study comparing use of isosmolar Iodixanol to low-osmolar Iohexol in cohorts of high-risk nephropathy, diabetic patients with initial nephropathy showed ninefold lower CIAKI risk in the Iodixanol cohort [41]. A RECOVER study also showed a lower CIAKI incidence in the cohort administered with isosmolar Iodixanol versus low-osmolar Ioxaglate [54].

Although apparent benefit from using Iodixanol is not confirmed by the majority of clinical studies, the use of low- or isosmolar CM is most encouraged in clinical practice, especially in high-risk patients with strict contraindications against using high-osmolar CM.

CM injection amount is an independent CIAKI risk factor and even in small doses (30 ml) may trigger adverse effects in high-risk patients. Therefore, contrast-using procedures should be done on the "As Low As Possible" (ALAP) principle, using the precise CM amount to achieve satisfactory image quality. For example, diagnostic coronary angiography requires optimal CM amount at <30 ml, with minimum of 100 ml for Percutaneous Coronary Intervention (PCI) [8,55]. The Maximum Allowable Contrast Dose (MACD) is calculated by the formula "5 ml CM x body weight [kg]/initial plasma creatinine [mg/dL]" [56] and must not exceed allowable values.

Speaking about iodinated CM alternatives, first of all we should mention a gadolinium CM, usage of which did not show superiority to iodinated media in patients with moderate renal function impairment [57,58]. According to some researchers, gadolinium CM rises the incidence of nephrogenic systemic sclerosis (also known as nephrogenic fibrosing dermopathy) - serious invalidizing skin and internal organs sclerosis [59,60], however a series of multiple studies showed no evidence of that statement [61,62].

A promising yet controversial iodinated CM, alternative carbon dioxide is contraindicated in intra-arterial injection above the diaphragm (coronary and brachiocephalic arteries, thoracic aorta). CO₂ is currently used only in diagnostic endovascular procedures below the diaphragm (abdominal aorta, lower limb vessels) through an introduction system (CO₂mmander) and portable tanks with

carbon dioxide [63-65] (Table 2).

Risk factors

The patient's CIAKI risk during contrast X-ray must be measured before preoperative assessment and selecting the CM type.

There are several proved CIAKI risk factors:

1. Initial nephropathy is the strongest CIN predictor, as proved by most studies [6,7,18,41-45]. Specifically, patients with very low creatinine clearance before the procedure (<40 ml/min) are 10 times more likely to suffer from CIAKI versus the cohort with a normal renal function [45].
2. The presence of diabetes mellitus with diabetic nephropathy predisposes to developing adverse renal complications during CM injection, while diabetes mellitus with a normal renal function hardly affects CIAKI development [9,45,66]. Other major CIAKI risk factors are in the Table 3.

Risk Assessment

Given that patients with chronic kidney disease (CKD) and GFR<60 ml/min/1.73 m² are predisposed to a high CIN risk, all CM procedure candidates must have their GFR measured. Since CIAKI results from many factors, isolated GFR measurement does not reliably identify nephropathy risk, so risk assessment systems are developed based on the cumulative effect of many factors [67-69]. Clinical practice prefers several systems for measuring perceived CIAKI risk.

As calculated by Maioli et al. [44] risk stratification should factor in 7 basic parameters (Table 4) [70]. Availability of each parameter is assessed in points resulting in patient distribution into low, medium, high and very high-risk cohorts. CM injection in previous 72 h, low LVEF, difference between SC before the procedure and initial creatinine, higher initial creatinine, diabetes mellitus, 73+ age and lower GFR are factored in Table 4.

Mehran et al. [68] developed a calculation system with 8 variables (Table 5). In addition to patient distribution into low, medium, high and very high-risk cohorts, dialysis probability and death risk are also estimated. Points are awarded for hypotension, CKD, IABP, CHF, diabetes mellitus, 75+ age, anemia, and administered CM amount.

	Blood plasma	Isosmolar CM (Iodixanol)	Low-osmolar CM (Iohexol)	High-osmolar CM (Diatrizoate)
Osmolality, mosm/kg H ₂ O	290	290	890	2,100
Viscosity, mPa.s	3-4	8.8	6.8	4.1
Ion composition		Nonionic	Nonionic	Ionic
Molecular composition		Dimer	Monomer	Monomer
CIAKI exposure	-	Low	Low	High

Table 2: CM comparison

CM : Contrast Media; CIAKI: Contrast-induced Acute Kidney Injury

	Non-modifiable	Modifiable
Patient factors	Age Female Diabetes mellitus Hypertension Renal damage CHF Myeloma Albuminuria	Anemia Hypovolemia Nephrotoxic drugs Hypoalbuminemia Higher glucose level Higher low-density lipoprotein level
Procedure factors	Manipulation urgency	Periprocedural hypotension Intra-arterial injection Large CM amount High-osmolar ionic CM Intraoperative hemorrhage IABP

Table 3: CIAKI risk factors

CHF: Chronic Heart Failure; IABP: Intra-Aortic Balloon Pump

The most up-to-date, though uncommon, system in clinical practice is the one by Tziakas et al. [18] (Table 6), using 5 variables, including the presence of previously detected CKD, permanent metformin introduction, previously done PCI, obliterating atherosclerosis of peripheral arteries and intraoperative injected CM amount. The score is distributed among 3 CIAKI exposure cohorts: low, medium and high-risk. (Table 6)

Having assessed perceived CIAKI exposure, it is necessary to start preparing the patient for the procedure, based on the standardized prophylaxis and treatment protocol (Figure 2) [71].

Prophylaxis

CIAKI prophylaxis should begin with the cancellation of the patient's nephrotoxic drugs among non-steroidal anti-inflammatory, antifungal, antiviral, antitumoral, immunosuppressants and antibiotics, especially aminoglycosides, 24 h before the study. In diabetic patients, metformin introduction must be canceled 48

h before and limited 48 h after CM injection. ACE inhibitors and angiotensin receptor blockers, due to possible harm and inadequate data on their positive effects on renal hemodynamics and GFR, should be excluded from therapy 1 day before the study, although, under the KDIGO consensus, this allegation has not been fully proved [13,72].

To date, intravenous loading with a 0.9% NaCl solution is the only proved efficient CIAKI prophylactic measure [9,41,42,45,73-76]. Despite the aforesaid superiority of using intravenous sodium bicarbonate, its role in nephropathy prophylaxis is comparable to 0.9% NaCl, based on the findings of some randomized studies [66,73,75,77]. Although one study did show the benefits of high sodium bicarbonate concentrations (833 mEq/L) [78], clinical guidelines for nephropathy prophylaxis have not supported this fact.

N-Acetyl Cysteine (NAC) was widely used in CIAKI prophylaxis in high-risk patients, based on some positive observations, in a dose of 600 mg twice a day, 2 days before the planned study [79]. Subsequent studies (~40 clinical trials and 13 meta-analyses) using both high

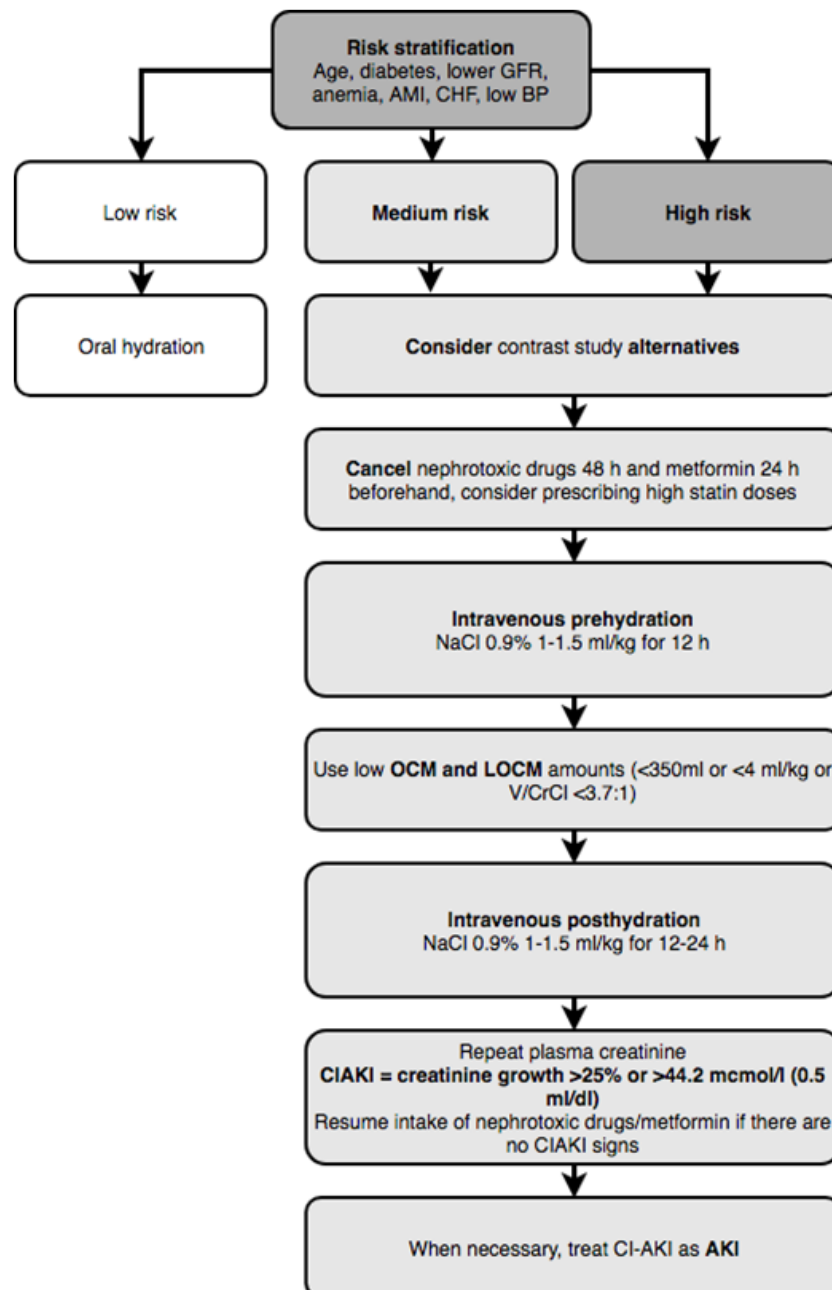


Figure 2: Algorithm of prophylaxis and treatment of patients with different CIAKI exposure [71]

AMI: Acute Myocardial Infarction; BP - Blood Pressure; NaCl: Sodium Chloride; IOCM: Isosmolar Contrast Media; LOCM: Low-Osmolar Contrast Media; V/CrCl - Ratio of Injected CM to Creatinine Clearance

Risk factor			Score
CM injection in previous 72 h			3
LVEF <45%			2
Preprocedural SC >initial SC			2
Initial SC >132.6 μmol/L (1.5 mg/dL)			2
Diabetes mellitus			2
GFR<44 ml/min			2
Age >73			1
Result	0-3	4-6	7-8
CIAKI risk	Low 1.1%	Medium 7.5%	High 22.3%
			Very high 52.1%

Table 4. CIAKI risk stratification [70]

CM: Contrast Media; LVEF: Left Ventricular Ejection Fraction; SC: Serum Creatinine; GFR: Glomerular Filtration Rate;

CIAKI: Contrast- Induced Acute Kidney Injury

Risk factor			Score
Hypotension (SBP<80 mmHg or >1 h of inotropic support)			5
IABP			5
CHF (NYHA III/IV or recent pulmonary edema)			5
Age >75			4
Diabetes mellitus			3
Anemia (M: HCT <0.39, F: HCT <0.36)			3
GRF <20 ml/min			6
GRF <20-40 ml/min			4
GFR <40-60 ml/min			2
CM amount			1 point per 100 ml
Result	0-3	4-6	7-8
CIAKI risk	Low 7.5%	Medium 14%	High 26.1%
Dialysis risk	0.04%	0.12%	1.09%
			12.6%

Table 5: CIAKI exposure stratification [68]

SBP: Systolic Blood Pressure; IABP: Intra Aortic Balloon Pump; CHF: Congestive Heart Failure; NYHA: New York Heart Association;

HCT: Hematocrit; GFR: Glomerular Filtration Rate; CM: Contrast Media; CIAKI: Contrast-Induced Acute Kidney Injury

Risk factor			Score
CKD			2
Metformin administration			2
Previously performed PCI			1
Presence of obliterating atherosclerosis of peripheral arteries			2
CM amount ≥300 ml			1
Result	0-1	2-3	>4
CIAKI risk	Low 3-11%	Medium 11-27%	High 27-83%

Table 6: CIAKI exposure stratification [18]

CKD: Chronic Kidney Disease; PCI: Percutaneous Coronary Intervention; CM: Contrast Media; CIAKI: Contrast-induced Acute Kidney Injury

oral NAC doses and intravenous drug injection showed contradictory results. NAC use causes no side effects (except for anaphylactoid reactions to high intravenous and oral doses) and is generally not contraindicated in CIAKI prophylaxis [42,45,80].

The most recent, major and well-designed PRESERVE (Prevention of Serious Adverse Events Following Angiography) study comparing intravenous 1.26% sodium bicarbonate, intravenous 0.9% sodium chloride and 5 days, oral acetylcysteine and oral placebo showed no benefit of intravenous sodium bicarbonate over intravenous sodium chloride or of oral acetylcysteine over placebo for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days or for the prevention of CIAKI [81].

Atrial natriuretic peptide, dopamine, fenoldopam as well as theophylline and ascorbic acid have not demonstrated positive effects in CIAKI prophylaxis, whereas forced diuresis with mannitol or furosemide is contraindicated due to its damaging action [42,45].

Using prostaglandin E1 and statins has shown clinical benefits, but insufficient observation still prevents their adoption. Targeted therapy with the infusion system Benefit™ for selective fenoldopam delivery and using the RenalGuard™ infusion system demonstrated a lower CIAKI incidence only in few minor clinical trials [82-84].

Patients already under hemodialysis do not require volume support before a contrast study, and dialysis after the procedure is necessary only with frank liquid overload. As to hemofiltration, benefits in high-risk cohorts were not confirmed, despite some authors' successful use in very high-risk patients with Stage 5 CKD before and after the radiographic contrast study [19,21,85,86].

Safe CM reinjection time is not exactly defined, but, according to the average renal function recovery time with CIAKI (3 weeks), this period is recommended for a repeated contrast study.

For high-risk patients, daily SC control for 5 days is indicated, and in case of oliguria, patient treatment is the same as with other

AKI reasons including monitoring of acid-base, electrolyte and fluid balances. Severe cases may require temporary hemodialysis and permanent one in exceedingly rare cases [87,88].

Conclusion

Clinically significant CIAKI is a major complication of endovascular radiographic procedures, associated with high morbidity, mortality rates, and consequent socioeconomic losses. Despite few guideline differences, there are several strict positions in CIAKI prophylaxis and treatment. Early detection of high CIAKI exposure in patients is crucial for timely initiation of preventive measures and reducing likelihood of renal parenchyma damage and further nephropathy. In interventional cardiologist's and radiologist's practice, preference must be given to using only low-and isosmolar CM as less as possible. Based on the rapid or nearly instant reaction of some biomarkers to subclinical AKI, measuring their urine or plasma concentration is now a promising research trend, although their routine usage is not yet featured in current guidelines for CIAKI prophylaxis and treatment. Intravenous loading with a 0.9% sodium chloride solution is the only proven efficient CIAKI prophylactic measure, whereas other pharmacological support is either damaging or requires further research and more prospective studies.

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