Contrast-induced nephropathy: Preventive measures.

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Learning objectives

To review the literature on contrast-induced nephropathy (NCI). To analyze the different prevention measures, and propose a prophylaxis protocol .

Background

INTRODUCTION

Contrast induced nephropathy (CIN) is a generally reversible decrease in renal function, defined as an increase a rise of 25% in the serum creatinine when the baseline is less than 1,5 mg/dl, or an absolute rise of 0.5 mg/dl when the baseline is greater than 1,5 mg/dl in serum creatinine within 3 days of the intravascular administration of a iodinated contrast medium (ICM) in the absence of an alternative aetiology for the renal impairment.

CIN is the third most common cause of hospital-acquired renal failure. The incidence of the NCI varies widely depending on renal function prior to the administration of contrast, the presence or absence of risk factors, the amount and type of radiocontrast agent administered and the exact radiologic procedure. In patients with preserved renal function the incidence is between 2 - 3 %, and those who present values of serum creatinine greater than 1.5 or creatinine clearance less than 50 the incidence increases to 13% (50% in high-risk patients).

CIN is usually mild, transient and nonoliguric although it may persist in patients with pre-existing advanced underlying disease, particularly in diabetics. It usually begins within 12 - 24 hours of contrast administration, with creatinine peaks at 3-5 days and normalization with 1-3 weeks.

It is important to make the differential diagnosis with renal atheroembolic disease, in these cases the presence of other embolic lesions, transient eosinophilia e hypocomplementemia and a delay in the onset of renal failure and the prolonged course of renal alteration are frequent.

There is no etiological treatment of this pathology, so it it should be managed as any cause of acute tubular necrosis, focusing on fluid maintenance and electrolyte balance.

PATHOPHYSIOLOGY

There are intrinsic factors of the renal physiology responsible for renal susceptibility to contrasts iodinated injury such as the corticomedullary gradient (the renal cortex receives 90% of the renal flow and performs 10% metabolic work, instead these percentages are reversed in the renal medulla), medullary hypoxia (PaO_2 in the cortex is 50 mmHg in the medulla of 10-20 mmHg) and the small diameter of the vasa recta (reduction in medullary blood flow occur due to contrast media, that increase blood viscosity).

The exact pathogenic mechanism of CIN is not well understood. The two major theories that have been suggested include:

1) Renal hemodynamic changes (vasoconstriction), resulting in medullary hypoxia, possibly mediated by vasoactive mediators such as endothelin and adenosine, and by reduction of the release of vasodilators factors (nitric oxide, prostaglandins). Diabetes mellitus and heart failure increase the risk of contrast-induced kidney injury in humans and these disorders are associated with impaired nitric oxide generation, which could contribute to the susceptibility to contrast agents

2) Direct tubular toxicity, as a direct result of the cytotoxic effects of the contrast agents or by the release of oxygen-free radicals.

In addition, it is possible that prerenal factors or intratubular obstruction contribute to the pathogenesis.

TYPES OF RADIOCONTRAST AGENTS

Iodinated radiocontrast agents are either ionic or nonionic and, at the concentrations required for different imaging techniques, are of variable osmolality:

First generation agents are ionic monomers; they are highly hyperosmolal (1400 to 1800 mosmol/kg) compared with the osmolality of plasma.

Second generation agents, such as iohexol, are nonionic monomers with a lower osmolality than the first generation radiocontrast media; however, they still have an increased osmolality (500 to 850 mosmol/kg) compared with plasma. There is an ionic low osmolal contrast agent (ioxaglate).

The newest nonionic contrast agents are iso-osmolal, being dimers with an osmolality of approximately 290 mosmol/kg (iodixanol is the first such agent).

RISK FACTORS FOR CONTRAST MEDIUM-INDUCED NEPHROPATHY

There are several factors that are associated with an increased risk of CIN: pre-existing renal failure (particularly as a result of diabetic nephropaty), dehydration, class III/IV congestive heart failure, age > 70 years, gout, administration of nephrotoxic drugs, the use of hyperosmolal ionic contrast agents, high total dose of contrast agent, or multiple contrast studies within a 72 hour period. The risk of CIN associated with intravenous CM administration may be lower than with intra-arterial administration.

Several potential new markers of CIN risk have been identified in patients undergoing coronary intervention. These include metabolic syndrome, prediabetes, hyperuricemia, hypertriglyceridemia, impaired fasting glucose and women #65 years of age.

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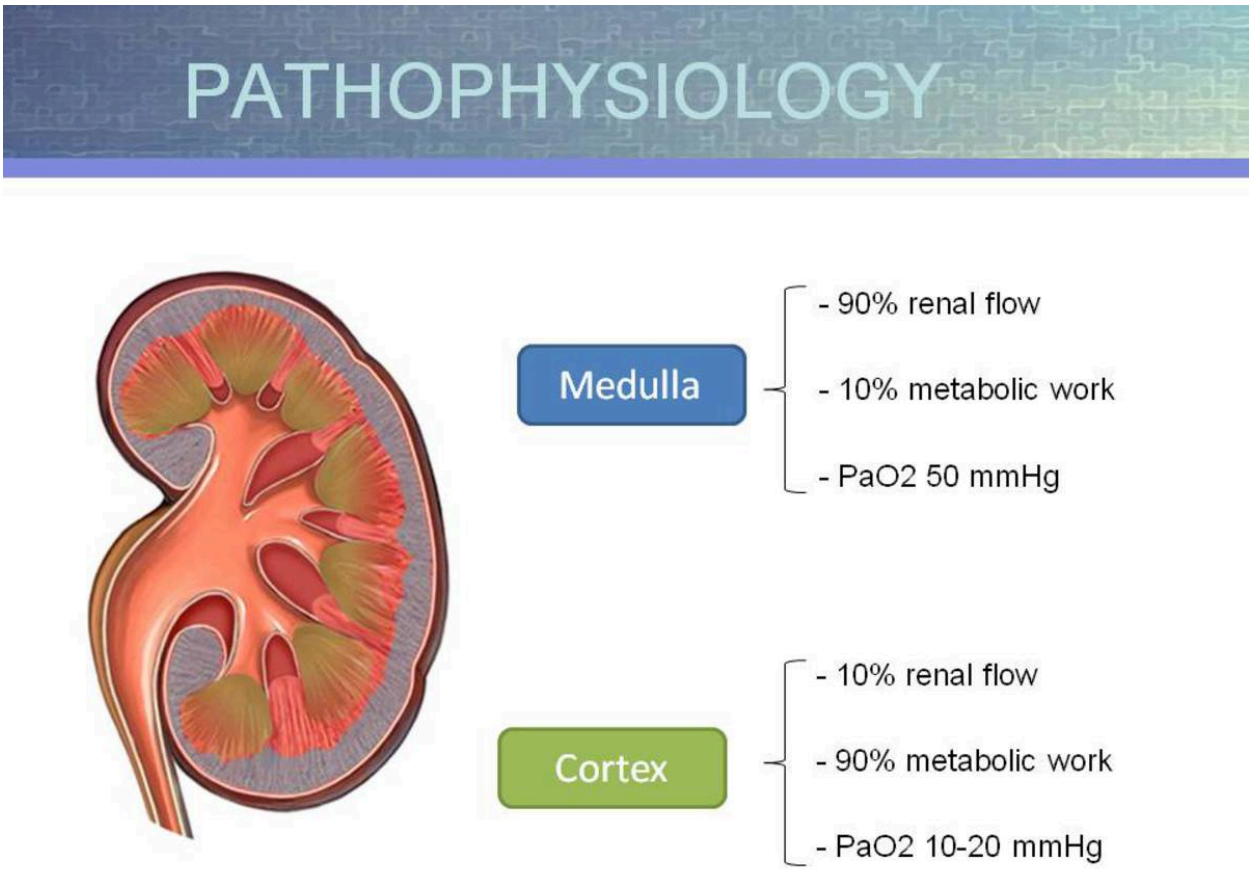

Fig. 1: Pathophysiology

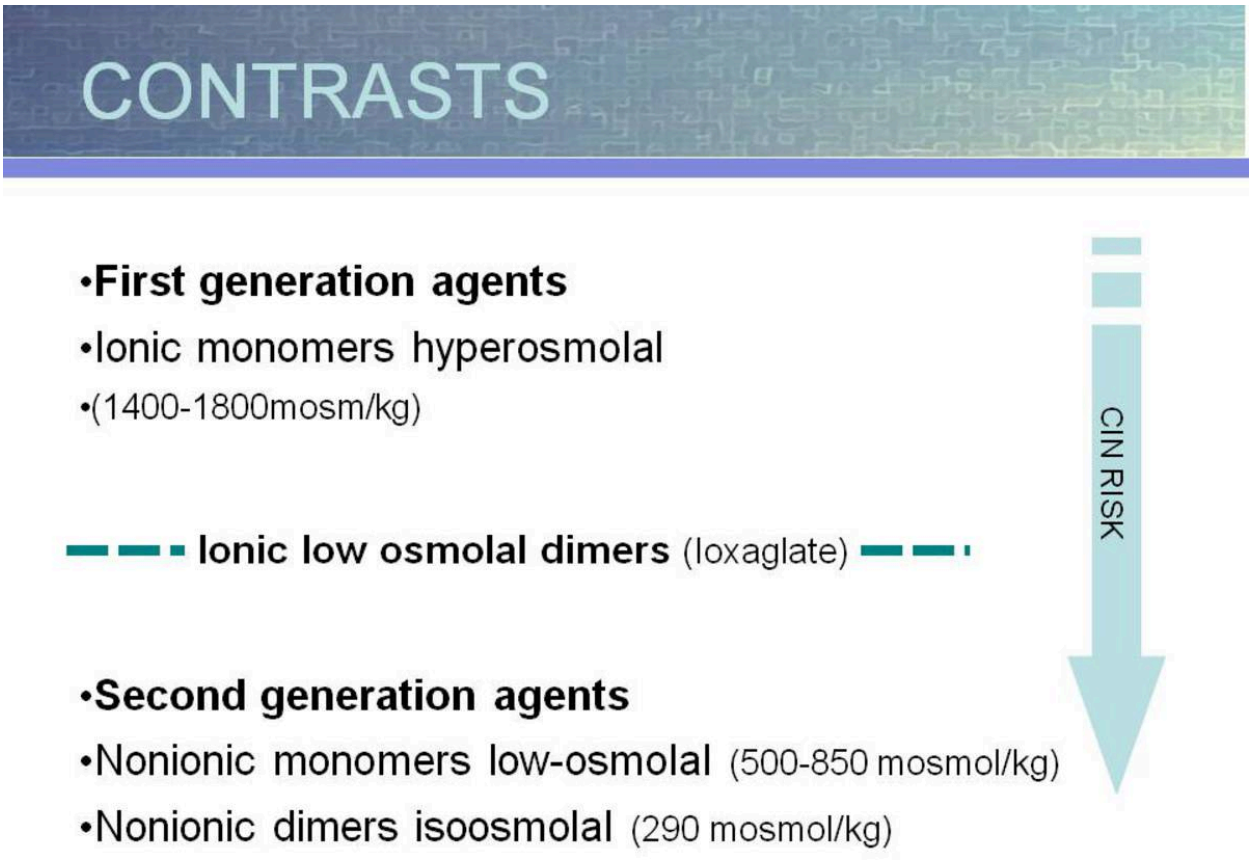

Fig. 2: Contrasts

Risk Factors

Patient-related	Procedure-related
eGFR less than 60 ml/min/1.73 m2 before intra-arterial administration eGFR less than 45 ml/min/1.73 m2 before intravenous administration	Intra-arterial administration of contrast medium
Known or suspected acute renal failure	
Age over 70	High osmolality agents Large doses of contrast medium
Concurrent administration of nephrotoxic drugs	
Diabetic nephropathy, Dehydration	Multiple contrast medium administrations within a few days
Congestive heart failure (NYHA grade 3-4) and low LVEF	
Recent myocardial infarction (< 24 h), Peri-procedural hypotension, Low haematocrit level	
Intra-aortic balloon pump	

Fig. 3: Risk factors

Imaging findings OR Procedure details

Data were mainly extracted from the most actual and representative articles as the research basis, and recommendations of practice guidelines of official organizations of radiology and nephrology (ESUR, ACR, NKF).

GENERAL PREVENTION MEASURES:

Alternative diagnostic techniques that do not utilize iodine contrast media must be considered in high risk patients. Other measures include limiting contribuitory risk factors (like hypovolaemia, NSAIDs and certain antibiotics) and limit both the total dose and the number of doses administered in a 48 - 72 hour period. Different autors have tried to establish the optimal dose, and determinate that it should be less than or equal to 100 ml when the TFGe is less than 60, and 5 mlkg of maximum weight when the creatinine exceeds 1.8 mldl; although even a volume less than 30 ml may cause NCI in high-risk patients.

CONTRASTS

Many trials have evaluated the relative effectiveness of non-ionic, low osmolarity agent related to ionic hyperosmolar agent, showing reduced risk of NCI with the use of the low osmolal, but in patients with preserved renal function, the difference is not so relevant. Ioxaglato, an ionic low osmolal, agent is also associated with low risk of nephropathy by contrast compared to the ionic hyperosmolar agents. There was no significant difference between Ionic, low osmolal agent, and isoosmolal in patients with normal renal function, but in high-risk population data are heterogeneous, the greater part of the trials not found differences between these two type of agents in terms of incidence of NCI (CARE, IMPACT, PREDICT), in others this pathology is less frequent in patients who has been administered isoosmolal agents (NEPHRIC, RECOVER) or hipoosmolal agents(ACTIVE).

This heterogeneity in the results of different studies is due to differences in standardization of the monitoring of creatinine values, different proportion of patients with risk factors, chronic renal insufficiency and diabetes, variety of clinical situations (coronary angiography CT), different protocols of prophylaxis, volumes and doses of contrast.

Gadolinium was proposed as an alternative contrast agent in angiographic procedures but the dose needed to avoid nephrotoxic injury (< 0.3mmol) not allowed to obtain satisfactory images.

Non-ionic low osmolarity agents are the most used in the most radiological, as a result of the reduction of costs, the patient tolerability, decrease of hypersensitivity reactions and less incidence of NCI in high risk patients.

SPECIFIC STRATEGIES

The hydration has proven to be the only major preventive action against CIN. It would appear that intravenous hydration is superior to oral hydration. The optimal fluid choice, infusion rate and volume are unclear. Different patterns of intravenous hydration (table)

Before selecting the solution (isotonic normal N-saline; ½ N-saline, and isotonic sodium bicarbonate) and the rate of administration it must be taken into account the peri-operative hydration policies of each centre, the patient's ability to tolerate a fluid load and alkalinisation; and the degree of risk for nephropathy.

None of the pharmacological measures (renalvasodilators, receptors antagonists of endogenous vasoactive mediators or cytoprotective drugs) have shown consistent protection against the NCI.

The use of acetylcysteineis based on its potential vasodilator capacity and reduce oxygen-free radical generation and although the results from clinical trials have been inconsistent (fig table), the trend is suggestive of benefit and it is well tolerated and relatively inexpensive, so it is usually administrated to high risk patients. The preferred dose is 1200 mg administered orally twice daily on the day before and the day of the procedure to patients at risk for CIN. It must not be administred intravenous because of potential risk of anaphylactoid reactions.

All gadolinium and iodinated contrast media may be removed by hemodialysis or peritoneal dialysis, however there is no evidence that hemodinalisis protects patients with impaired renal function from NCI or Nephrogenic Systemic Fibrosis. So correlation of time of the contrast medium injection with the hemodialysis session and extra hemodialysis session to remove contrast medium is unnecessary.

METFORMIN AND CONTRAST NEPHROPATHY

Metformin does not cause kidney failure per se, but in the case of pre-existing or iodinated contrast-induced kidney failure, can cause lactic acidosis.

Therefore, when eGFR is equal to or greater than 60 ml/min/1.73m2 can continue to take metformin normally. Patients with eGFR 30-59 ml/min/1.73 m2 and receiving intra-arterial contrast medium, and those receiving intravenous contrast medium with an eGFR between 30 and 44 ml/min/1.73 m2, should stop metformin 48 h before contrast medium and should only restart metformin 48 h after contrast medium if renal function has not

deteriorated. Metformin is contraindicated and iodine-based contrast media should be avoided for patients with eGFR less than 30 ml/min/1.73 m2, or with an intercurrent illness causing reduced liver function or hypoxia. In emergency patients metformin should be stopped from the time of contrast medium administration and should be restarted 48 h after.

PROTOCOL

To study the clinical guidelines for the use of iodinated contrast, published by American and European Radiology societies there were some problems: do not cover all aspects of patient managenment (for example there specificity by technique), is not suitable to use a unique algorithm for all patients given the variety of clinical settings as limited space, human resources, etc.

One of the main difficulties is to set the parameter that should be used to recommend prophylaxis measures. Several measurements have been proposed: serum creatinine concentration, calculated creatinine clearance, and estimated glomerular filtration rate (eGFR).

- Serum creatinine concentration, (cutoff of 1.5mg/dL) , is a parameter that does not detect the 40% of risk patients because this parameter is affected by factors independent of the glomerular filtration rate .

- The clearance of creatinine, calculated using Cockcroft-Gault formula, takes into account the age, weight and gender as variables.

- Glomerular filtration rate (GFR) is the best index of kidney function, and can be calculated as estimated by the MDRM formula. It has been shown useful especially in obese patients, older and with diabetes mellitus.

It is essential to determinate a baseline serum creatinine before the hydration. In emergencies we should determine eGFR if the procedure can be deferred until the result is available without harm to the patient. There is no universally agreed upon acceptable interval between the baseline serum creatinine measurement and contrast medium administration but some autors accept a 30-day interval as adequate.

Cystatin C seems to be a promising marker of kidney function, is independent of sex, body mass index and less influenced by external factors. It constitutes a more accurate marker of renal damage in patients with diabetes mellitus early. Its cut-off point is 1.2 mgdl.

Discussed other biomarkers of renal function, both serum and urinary needing more studies for validation.

Based on the most actual and representative articles as the research basis, and recommendations of practice guidelines of official organizations of radiology and

nephrology (ESUR, ACR, NKF) we have proposed the following algorithms of NCI prevention in those patients that undergo a radiologic technique that requires intravascular administration of contrast iodized depending on the type of procedure, renal function of the patient and urgency of the procedure.

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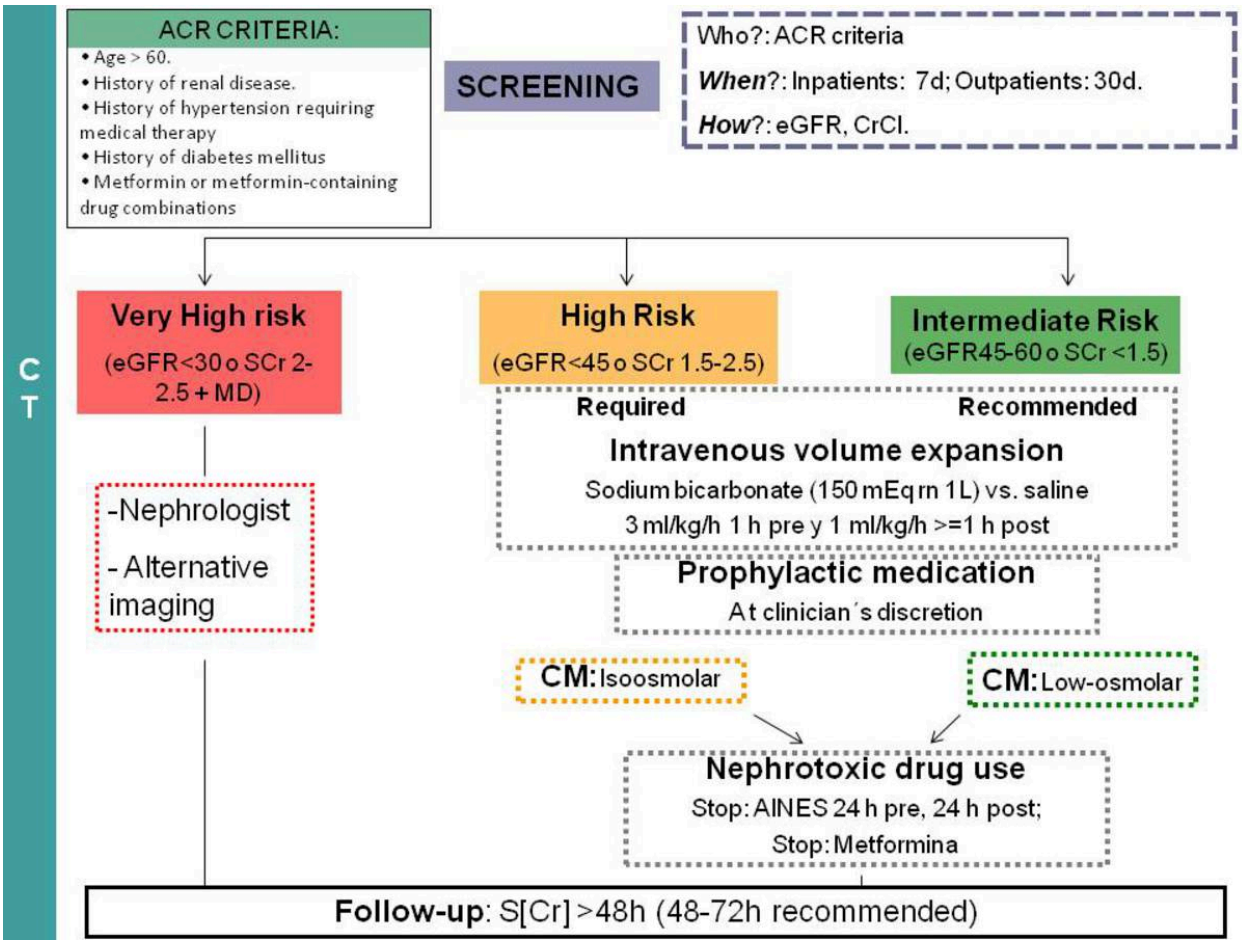

Fig. 4: TC algorithm

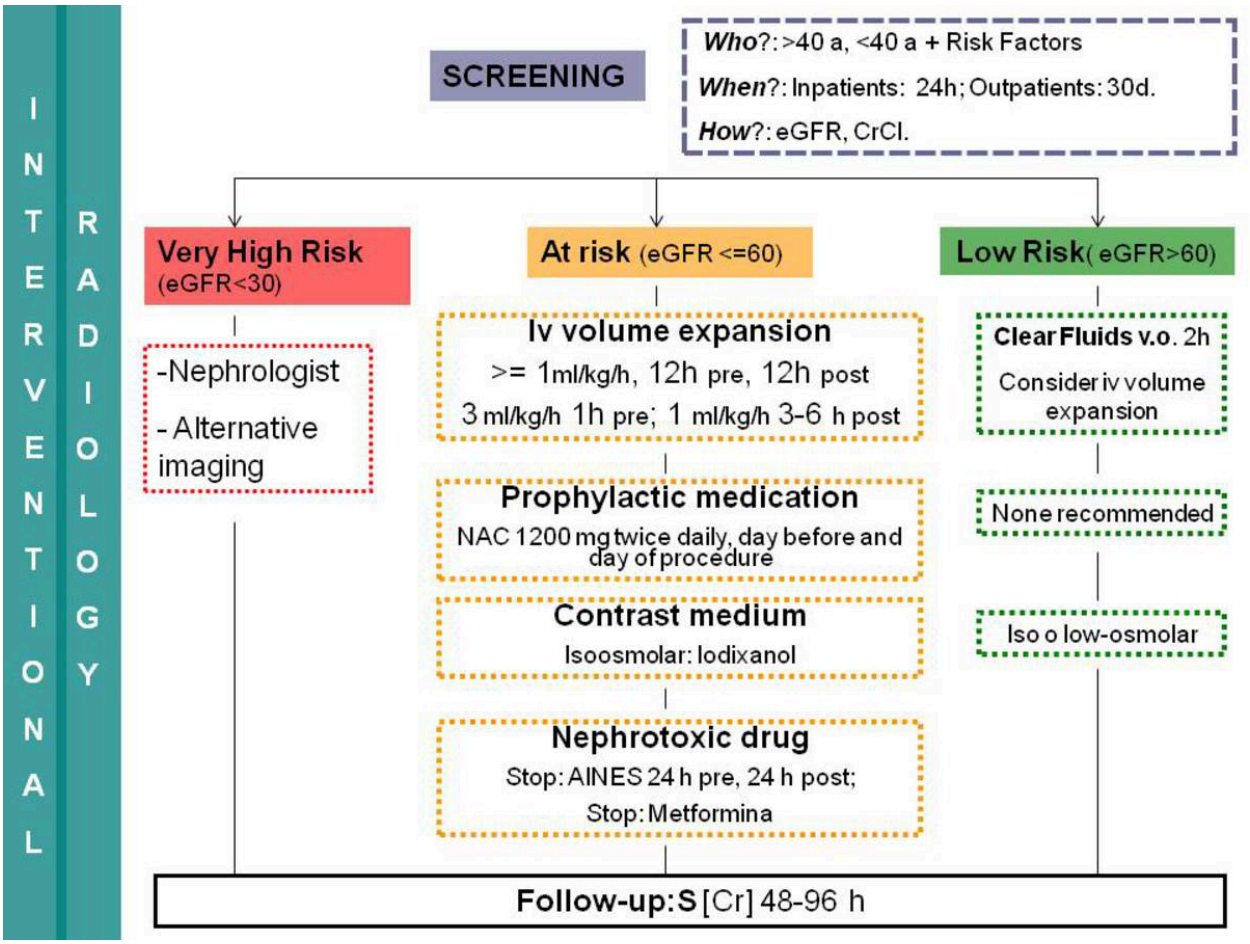

Fig. 5: Interventional radiology algorithm

Conclusion

CONCLUSIONS

The best index of kidney function is the GFR which can be estimated using the MDRM formula. The measure that has shown greater efficiency is intravenous hydration, no drug provides consistent protection against the NFC, studies on acetylcysteine show inconclusive results, although it tends to his administration

Patients with near-normal renal function are at little risk and few precautions are necessary other than avoidance of volume depletion.

In those patients who are at high risk of contrast nephropathy, more effective preventive measures, are as follows:

-Use, if possible an alternative technique without radiocontrast agents.

-Not using high osmolal agents (1400 to 1800 mosmol/kg) (Grade 1A). Preferably iodixanol or nonionic low osmolal agents such as iopamidol or ioversol rather than iohexol (Grade 1B).

-Use lower doses of contrast and avoid repetitive, closely spaced studies.

-Avoid volume depletion and nephrotoxic drugs.

-Volume expansion with isotonic intravenous fluids prior to and posterior to contrast administration (Grade 1B).

-Acetylcysteine the day before and the day of the procedure (1200 mg orally twice daily rather than 600 mg twice daily the day before and the day of the procedure) (Grade 2B).

-Among patients with stage 3 and 4 CKD, it is not necessary to perform prophylactic hemofiltration or hemodialysis after contrast exposure (Grade 1B).

-Among patients with stage 5 CKD, prophylactic hemodialysis can be done after contrast exposure if there is already a functioning hemodialysis access (Grade 2C). Although the benefit is questionable.

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