Prevention of contrast-induced acute kidney injury

The number of interventional and diagnostic contrast procedures has increased year on year and contrast-induced acute kidney injury has become a leading cause of inpatient mortality and morbidity. This article summarizes how to identify the high-risk patient and gives a systematic approach to prevent contrast-induced acute kidney injury.

The number of radiological procedures performed in the UK has increased by 39% over the last 10 years to 4 million computed tomography scans and 250 000 angiograms (National Office for Statistics, 2013). This has resulted in contrast-induced acute kidney injury becoming the third most common cause of hospital-acquired acute kidney injury after impaired renal perfusion and nephrotoxic medications. Although the overall risk is low (0.6–2.3%), in certain high-risk groups this increases to over 20% (Mehran and Nikolsky, 2006). Contrast-induced acute kidney injury is independently associated with a higher inpatient mortality and longer hospital stay (Gupta and Bang, 2010). This highlights the importance of early identification of the high-risk patient and institution of preventative measures.

Definition

Three factors must be present to diagnose acute kidney injury in the context of contrast nephropathy:

1. A rise in the serum creatinine level by 44 mmol/litre or a 25% increase from baseline
2. An acute rise occurring 2–3 days post contrast administration
3. The rise must be solely caused by the contrast administration. Therefore, other causes of acute kidney injury such as infection, medications and dehydration should be actively looked for and treated before making this diagnosis (Mehran and Nikolsky, 2006).

A randomized trial looking at the prevention of contrast-induced nephropathy found that in 80% of cases of contrast-induced acute kidney injury serum creatinine level begins to rise 24 hours after contrast exposure and all patients with serious consequences, defined as mortality or dialysis, had a rise in their serum creatinine level within this time frame. Usually the serum creatinine level peaked at 3 days and returned to baseline within 2 weeks (Stevens et al, 1999).

Pathophysiology

The pathophysiology of contrast-induced acute kidney injury is summarized in *Figure 1* (Persson et al, 2005). There are no studies directly looking at the pathophysiology of contrast-induced injury, but it is likely that a complex interplay of direct toxic effects on tubular cells and poor renal perfusion are the main mechanisms responsible. As the renal medulla operates at near hypoxic oxygen concentrations adding highly viscous contrast can increase vascular resistance, causing reduced blood flow and hypoxic injury (Thomsen and Morcos, 2003). This in turn causes cytotoxic injury to the renal tubular cells. Production of reactive oxygen species, adenosine and endothelin leads to further renal vasoconstriction and an inflammatory response causing direct toxicity to the kidney.

Risk factors

The first step in the prevention of contrast-induced acute kidney injury is to assess for modifiable and non-modifiable risk factors to clarify the level of risk from a contrast procedure (*Table 1*).

Figure 1. The pathophysiology of contrast-induced acute kidney injury.

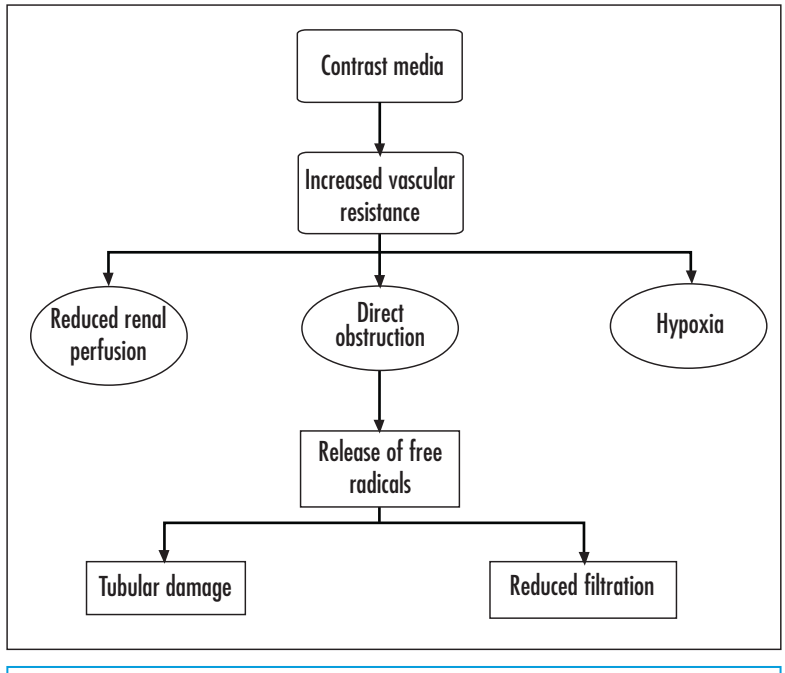

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Table 1. Risk factors for contrast-induced acute kidney injury

Modifiable	Volume of contrast media
	Sepsis
	Dehydration
	Nephrotoxic medications
	Anaemia
Non-modifiable	Age
	Diabetes
	Pre-existing renal disease
	Congestive cardiac failure

Non-modifiable risk factors

Many risk factors have been identified, but the only independent risk factors associated with contrast-induced acute kidney injury are pre-existing renal disease, diabetes and advancing age. The most important risk factor for contrast-induced acute kidney injury is the presence of pre-existing renal dysfunction. Those with an estimated glomerular filtration rate of greater than 60 ml/min/1.73m^2 have an extremely low risk of developing contrast-induced acute kidney injury and can be safely managed without the need for repeated blood tests and follow up (Stevens et al, 1999). Conversely, up to half of those with a baseline creatinine level of 170 mmol/litre have developed contrast-induced acute kidney injury. This risk increases exponentially with reducing estimated glomerular filtration rate (Mehran and Nikolsky, 2006).

The incidence of diabetes is growing rapidly and the incidence of contrast-induced acute kidney injury in those with diabetes and renal disease is 5.7–29% (Mehran and Nikolsky, 2006). This is only relevant in those with co-existing renal disease; those with normal renal function can be safely treated as the non-diabetic population.

Other risk factors such as sepsis, hypotension, nephrotoxic medications and congestive cardiac failure affect prognosis in contrast-induced acute kidney injury. These are thought to cause peri-procedural hypotension leading to ischaemic and direct nephrotoxic damage. The suspension of angiotensin-converting enzyme inhibitors that act to block the renin–angiotensin system is controversial as there is conflicting evidence regarding their association with contrast-induced acute kidney injury, as discussed later on (Mehran and Nikolsky, 2006).

Modifiable risk factors

The most significant modifiable risk factor in the development of contrast-induced acute kidney injury is the volume of contrast administration. Most non-interventional angiograms require a minimum of 100 ml of contrast media compared to 200–250 ml for intra-arterial stenting. Intra-arterial contrast administration is considered much higher risk then intravenous administration (Gupta and Bang, 2010). A maximum of 5 ml/kg has been suggested but the data are limited and an individualized approach in the context of risk *vs* benefits must be taken (Cigarroa et al, 1989). The risk increases by 12% for every 100 ml of contrast agent and those at highest risk should have the minimum amount necessary for the procedure. Those requiring less than 100 ml of contrast are at a very low risk of developing contrast-induced acute kidney injury and a negligible risk of needing renal replacement therapy (Mehran and Nikolsky, 2006).

Risk scoring systems

Risk scoring systems have been developed to stratify patients. Although this is impractical in all patients referred for a contrast procedure, especially in hospitals and clinics performing a high volume of procedures, three simple questions regarding age (>75 years), presence of diabetes and estimated glomerular filtration rate can quickly and easily identify those at high risk.

If the patient is highlighted as being at risk then a more detailed scoring system such as that developed by Mehran and Nikolsky (2006) can be used (this can be accessed at www.qxmd.com/calculate-online/nephrology/contrast-nephropathy-post-pci). This stratifies patients' risk of developing contrast-induced acute kidney injury using a validated scoring system from 0.04 to 12.6% (Mehran and Nikolsky, 2006). This will help stratify the highest risk candidates, allowing careful consideration of alternative imaging and medical management instead of interventional stenting. This is especially relevant in those in whom renal replacement therapy may not be a feasible option in the event of severe acute kidney injury.

Prevention of contrast-induced acute kidney injury

The most important way to prevent contrast-induced acute kidney injury is for the clinician to be aware of the high-risk patient and to take steps to reduce the risk of this occurring. Specific treatments to reduce risk are controversial and often lack robust evidence.

Alternative imaging

The first consideration in those with moderate to high risk of contrast-induced acute kidney injury is whether an alternative imaging modality can be used, such as non-contrast computed tomography imaging or magnetic resonance imaging. Unfortunately, because of the rare complication of nephrogenic systemic fibrosis, a severe, progressive fibrosis of the skin, joints and organs, most patients with moderate renal disease will be not be able to have gadolinium contrast for magnetic resonance imaging scanning (Gupta and Bang, 2010). Along with cost and availability this limits magnetic resonance imaging use at present but it may be a potential option in the future.

Nephrotoxic medications

The volume of contrast should be kept to a minimum as stated above and any nephrotoxic medication should be stopped at least 24–48 hours before the procedure and restarted 24–48 hours after the procedure. This may not be feasible in those with co-existing congestive cardiac failure who may require ongoing diuretic therapy to be able to tolerate the procedure. However, medications such as non-steroidal anti-inflammatory drugs and nephrotoxic antibiotics should be discontinued. This may not be feasible in the emergency situation where a best interest decision must be undertaken.

Renin–angiotensin system blockade

Controversy exists regarding renin–angiotensin system blockade. The general consensus is to withhold all renin–angiotensin system blockade 48 hours before administering contrast as this has been associated with progression to end stage renal failure in 29% of high-risk (elderly patients with coronary heart disease) patients as a result of intravascular vasoconstriction (Onuigbo and Onuigbo, 2008). However, there is some evidence that renin–angiotensin system blockade improves renal perfusion and protects against active uptake of contrast media. This is especially relevant in those with concomitant cardiac failure and moderate kidney disease (Kaplan and Kohn, 1992).

Metformin

The biguanide metformin should be withheld 24 hours before the procedure and can be restarted 48 hours post procedure. Although not nephrotoxic it is excreted via the kidney and can increase lactic acidosis. There is no clear consensus but it can be safely started 48 hours post procedure if there is no deterioration in renal function (Gupta and Bang, 2010).

Haemodialysis

Haemodialysis is an important tool in managing acute, severe kidney injury post procedure. However, this does not reduce the incidence of contrast-induced acute kidney injury if used immediately after a contrast procedure, despite filtering the contrast out of the systemic circulation. This likely represents the speed of acute kidney injury and the inflammatory nature of dialysis (Vogt et al, 2001). Furthermore, it is an invasive intervention with significant complications and therefore should not be undertaken.

Specific interventions to prevent contrast-induced acute kidney injury

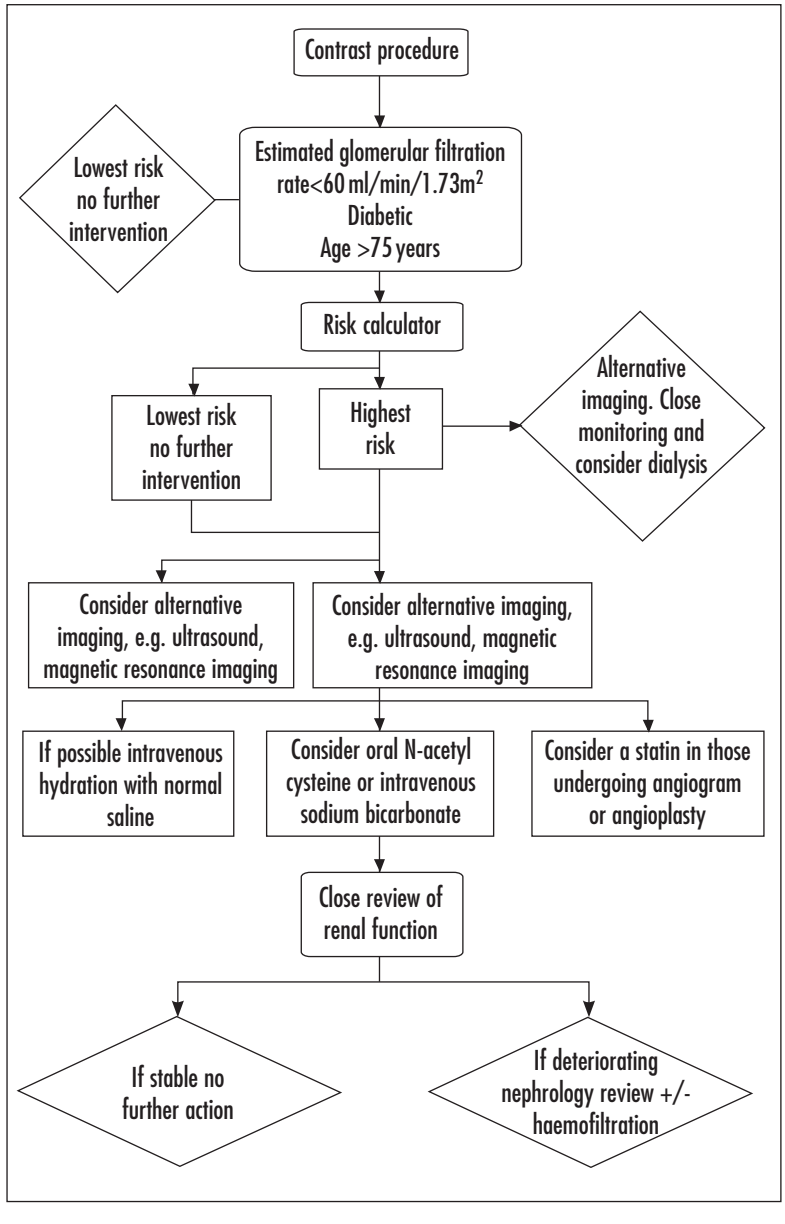
Figure 2 outlines methods for the prevention of contrast-induced acute kidney injury.

Hydration

Once all practical measures to prevent contrast-induced acute kidney injury have been taken, the most validated method of reducing the risk of a contrast-induced acute kidney injury is with pre-intervention hydration. It has been consistently found that intravenous hydration is superior to oral hydration (Mueller et al, 2002). The mechanism is thought to relate to improving renal perfusion and clearance of contrast media. The use of half normal saline *vs* normal saline has shown no additional benefit (Mueller et al, 2002). Normal saline is also safe, practical and cost effective.

There is no consensus on the protocol for administration of normal saline but a regimen of 1 ml/kg per hour has been suggested (*Table 2*), starting as early as possible and continuing for 12–24 hours post procedure (Bansal, 2014). This can be altered in those with concurrent dehydration or vasodilatory stress such as sepsis, and clinical judgement should be used in those with congestive cardiac failure.

Figure 2. Flow chart for the prevention of contrast-induced acute kidney injury.



N-acetyl cysteine

The use of N-acetyl cysteine in preventing contrast-induced acute kidney injury is controversial. Its sulfonyl group binds with high affinity to free radicals and this, coupled with a vasodilatory effect, allows it to theoretically protect against contrast-induced acute kidney injury (Gupta and Bang, 2010). Several clinical trials have been published with conflicting results and no consensus.

There have been 12 meta-analysis studies published with the majority showing a benefit of N-acetyl cysteine over standard treatment (Fishbane, 2008). However, there is significant variability in methodology with most studies being underpowered and all having heterogeneity in methodology and end points. One study showed a dose-dependent response of N-acetyl cysteine but this could not be reproduced in further trials (Fishbane, 2008).

Studies have suggested that N-acetyl cysteine interferes with serum creatinine measurement and this may artificially have shown benefit in previous studies. This has been further validated as studies that have used cystatin C measurement instead of creatinine have shown no benefit (Gupta and Bang, 2010).

Sodium bicarbonate

Sodium bicarbonate can be given either as an infusion or orally. It is thought that alkalinisation of the urine reduces free radical generation. Several systematic reviews have shown a benefit when compared to standard treatment but end points varied (Zhang et al, 2015). A meta-analysis of 20 randomized controlled trials found sodium bicarbonate to be more efficacious compared with intravenous hydration, but progression to dialysis and mortality was not changed (Zhang et al, 2015).

In one cohort trial that used a longer time frame of 7 days sodium bicarbonate increased the risk of developing contrast-induced acute kidney injury (From et al, 2008). A number of meta-analyses have shown an additive effect of N-acetyl cysteine in addition to sodium bicarbonate in preventing contrast-induced acute kidney injury, with subgroup analysis showing a more profound effect on those undergoing emergency rather than elective procedures.

Statin therapy

There is emerging evidence that statins have a renoprotective effect in those undergoing contrast procedures. Data from clinical trials are focused on statin use for angioplasty and angiograms only and do not include diagnostic computed tomography imaging. Meta-analysis data of over 5000 patients have shown the benefit of statin therapy in preventing contrast-induced acute kidney injury which is independent to the use of N-acetyl cysteine, type of contrast and pre-existing renal failure (Singh et al, 2014).

The mechanism is thought to relate to prevention of renal vasoconstriction. Statins have both antioxidant and anti-inflammatory properties, by down-regulation of angiotensin, reducing endothelin levels and by scavenging free radial oxygen species.

However, data are limited as there are still no large-scale double-blinded studies into this topic. As most of the exclusion criteria removed patients with an estimated glomerular filtration rate of less than 30 ml/min/1.73m^2, it is not clear whether statins only protect those with mild to moderate renal impairment.

Renal replacement therapy

Fewer than 1% of low-risk patients will need to undergo renal dialysis. However, the risk increases with increasing risk factors especially with pre-existing renal disease. Contrast media is rapidly removed from the circulating volume with high flux dialysis membranes able to filter up to 80% of contrast media in 4 hours (Gupta and Bang, 2010). Prophylactic haemodialysis is not useful, and is expensive and invasive as discussed previously.

Those who are already established on haemodialysis do not need any form of prophylactic filtration. However, the increase in intravascular volume may require an earlier dialysis session. Those with peritoneal dialysis or intermittent dialysis are likely to be at highest risk and therefore may benefit from post contrast dialysis. However, this would need additional vascular access and is limited by its invasive nature. Peritoneal dialysis itself offers no protection because of the speed of filtration (Gupta and Bang, 2010).

Conclusions

Contrast-induced acute kidney injury is an important and under-recognized cause of acute kidney injury that is associated with a high morbidity and mortality. By careful assessment and identification of the high-risk patient simple interventions can reduce this risk. Specific inter-

Table 2. Dose and duration of specific therapies for the prevention of contrast-induced acute kidney injury

Intervention	Dose	Time started before procedure	Time stopped after procedure
Normal saline	1 ml/kg/hr	As early as possible	12–24 hours
N-acetyl cysteine	600 mg twice a day	24 hours	24 hours
Sodium bicarbonate	3 ml/kg/hr	Day of procedure	6 hours
Statin	Depending on type of statin used	No clear consensus	No clear consensus

ventions are controversial and although the risk cannot be completely removed, by following a systematic approach the risk of acute kidney injury can be minimized. Further studies into this area are needed. BJHM

Conflict of interest: none.

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KEY POINTS

- Contrast-induced acute kidney injury is important and often unrecognized.
- Patients with diabetes, pre-existing renal disease and those >75 years of age should be considered as high risk.
- Reducing risk factors and intravenous saline are the most important preventative measures.
- Specific treatments are controversial and further research is needed to clarify their use.