REVIEW

Contrast-induced nephropathy and nephrogenic systemic fibrosis: minimizing the risk

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Introduction: *Contrast-enhanced cross-sectional imaging is essential to the urologist's practice. Traditionally, patients with impaired renal function could not be imaged with a computed tomography (CT) scan with contrast due to the risk of contrast-induced nephropathy (CIN). These patients could alternatively be imaged by magnetic resonance imaging (MRI) with gadolinium. However, the recent identification of the association between nephrogenic systemic fibrosis (NSF) and gadolinium administration has created significant challenges for urologists and radiologists when faced with the need for evaluation with contrast-enhanced cross-sectional imaging. In this review, we summarize the most comprehensive articles discussing both NSF and CIN and present a straightforward, evidence-based algorithm to determine the appropriate approach to cross-sectional imaging for all patients, as well as future directions regarding cross-sectional imaging.*

Materials and methods: *A MEDLINE literature search for review articles from 1966 to August 2009 was performed. Selected additional articles for specific topics were also reviewed. This search yielded a total of 25 articles for NSF and 28 for CIN that were reviewed.*

Results: *The pathophysiology and risk factors of NSF and CIN are discussed, as well as potential interventions to decrease either morbidity or incidence. A multidisciplinary (urologist, nephrologist, radiologist) evidence-based algorithm is introduced for managing patients in need of cross-sectional imaging.*

Conclusions: *The associated risks of contrast-enhanced, cross-sectional imaging has created significant challenges for urologic evaluation. We propose an evidence-based approach to guide patient therapy, which can minimize patient risk and physician anxiety, while simplifying the decision-making process.*

Key Words: magnetic resonance imaging, end-stage renal disease, contrast-induced nephropathy, nephrogenic systemic fibrosis, computed tomography

Introduction

Contrast-enhanced cross-sectional imaging is essential to the urologist; particularly in the evaluation of hematuria and renal lesions. Computed tomography (CT) scanning and magnetic resonance imaging (MRI) have historically been the mainstays of contrast-enhanced cross-sectional imaging. The importance of contrast lies in its ability to differentiate between solid lesions which take up contrast (vascular structures) and are therefore more likely to be malignant, as compared to those lesions that do not (e.g. hyperdense renal cysts). Utilizing the measurement of Hounsfield units on pre and post contrast CT scans, one can more easily distinguish between the above entities, which has obvious implications for ultimate management decisions. The CT and MR urograms (CTU and MRU) allow for reconstruction of the excretory phase of the

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scan; providing a coronal three-dimensional image of the collecting system that can allow for evaluation of the urothelium. Enhancement remains the single most important criterion for determining malignant potential.

Although CT imaging provides urologists with vital information, there are a number of limitations to its routine use. Beyond the harms of ionizing radiation, one must consider the not insignificant proportion of patients that have allergic reactions to the intravenous (IV) contrast as well as those with pre-existing renal insufficiency. Until recently, MRI with gadolinium contrast offered a straightforward alternative imaging modality for patients with IV contrast allergy and/or renal insufficiency. However, with the recent recognition of the clinical entity of nephrogenic systemic fibrosis (NSF), a disease manifested following gadolinium exposure in patients with decreased glomerular filtration rate (GFR)[1] the use of MRI has been cautioned against from nephrologists and radiologists alike.[2]

Any intervention carries an associated risk to the patient. In this regard, cross-sectional imaging studies are similar to surgical procedures and their use should be considered within this same risk/benefit framework. Understanding the risks involved with each imaging modality and contrast agent is critical to be able to make appropriate clinical decisions and to assist patients in making informed choices.

Materials and methods

A MEDLINE literature search was performed for articles in the English language between 1966 and August of 2009 using the key words: contrast-induced nephropathy, nephrogenic systemic fibrosis, computed tomography scan, magnetic resonance imaging, management and recommendations. Two of the authors independently reviewed each returned article title and abstract to determine whether the article was appropriate for further review. The authors then met to discuss article selection and reconciled differences in selected articles. If deemed appropriate for further review articles were then read in their entirety and critically evaluated for inclusion. For the broad topics of "contrast-induced nephropathy" and "nephrogenic systemic fibrosis," search criteria were refined to return only review articles, which yielded a total of 137 articles for CIN and 113 articles for NSF. A MeSH database search was performed when combining these previous terms with "computed tomography scan," "magnetic resonance imaging," "management" and "recommendations." Selected additional articles for specific topics were suggested by the senior authors of each specialty and reviewed along with any pertinent original research articles cited in the review articles. This search ultimately yielded a total of 25 articles for NSF and 28 articles for CIN deemed appropriate for final inclusion.

Results

Nephrogenic systemic fibrosis (NSF)

First reported in the dermatopathology literature in 2000, NSF is a rare and difficult to diagnose disease, but one with potentially devastating consequences. Initially, the disease was linked to hemodialysis patients at a single institution, but cases started being reported elsewhere and included patients not undergoing hemodialysis. However, all NSF patients did have underlying renal insufficiency. Of note, no cases of NSF have been reported in patients with creatinine clearance (CrCl) greater than 30 mg/min, with incidence paralleling decreasing renal function below this cutoff.

It was not until 2006 that investigators linked NSF to gadolinium exposure.[2,3] Even at that time, only approximately 500 total cases had been reported worldwide.[4] Through pooled data analysis, the estimated incidence of NSF given a creatinine clearance less than 30 mL/min is approximately 2%-5%, however analysis of United States data suggests the incidence in this population to be approximately 1% or less. Furthermore, the incidence suggests a relationship to total dose, as a higher incidence has been noted with MR angiography studies, which require more concentrated doses of gadolinium.[5]

Clinically, the disease typically manifests itself in weeks to months as extensive thickening and hardening of the skin of the torso and limbs and has also been described as having a peau d'orange appearance. Often, the disease pattern is symmetrical and typically begins in the lower extremities, with the face being almost uniformly spared. The disease typically begins with edema and then the thickened skin appears and may progress to significant loss of function and disability.[6] Early symptoms include swelling, pruritus, joint stiffness, pain, parasthesias and burning.[4] Such dysfunction is in part due to collagen and fibroblasts causing contractures, pulmonary and cardiac fibrosis. The disease rarely spontaneously regresses, but typically stabilizes or improves with enhanced renal function.[5]

Though the exact mechanism for the development of NSF is unclear, a proposed pathway is via inadequate excretion of gadolinium-based contrast agents, which

allows prolonged tissue times for the molecule and free gadolinium tissue deposition. This in turn, activates a fibrotic reaction involving recruitment and activation of circulating fibrocytes and development of NSF.[5]

Prevention of NSF

Renal processing is the only route of detoxification and excretion of gadolinium and the typical half-life is 1-2 hours, which can be prolonged to up to 30 hours in the case of severe renal dysfunction.[7] Studies have shown that approximately 75% of gadolinium is removed by a single hemodialysis (HD) session and 99% by three sessions.[8] Peritoneal dialysis does not remove gadolinium effectively and the risk for NSF is 7.5 times greater than HD. However, despite the ability to clear gadolinium with hemodialysis, no studies have demonstrated the efficacy of immediate post-gadolinium administration hemodialysis. Therefore, this therapeutic practice is based on solely on intuition consistent with the pathophysiology of the disease process.

Should cross-sectional imaging using MRI be indicated, the urologist should consider working with a nephrology team to consider immediate post-exposure HD for 2-3 sessions. Some have even suggested that the best prevention strategy is the avoidance of MRI in patients with a CrCl of < 30 mL/min.[9] Given the large number of MRIs performed before the recognition of this entity, the overall risk is still extremely low, but greater for patients with a CrCl < 30 mL/min. Additionally, given that NSF is a potentially lifelong condition, minimizing this elevated risk seems prudent. Therefore, perhaps the best prevention strategy would be to reassess the need for cross-sectional imaging and if the team (urologist, nephrologist and radiologist) felt compelled to obtain contrast-enhanced, cross-sectional imaging, then the risks, benefits and alternatives of these different imaging modalities versus not obtaining imaging should be discussed with the patient. In the rare case of NSF development, consultation with Dermatology should be considered. Additionally, there has been limited success, much of it anecdotal, with the use of extracorporeal photophoresis, sodium thiosulfate, and pentoxifylline.[10]

Contrast-induced nephropathy (CIN)

The awareness of renal injury following the injection of contrast agents used for cross-sectional imaging has been increasing within the urologic community.[11] Contrast-induced nephropathy is seen as an abrupt (within 48 hours) reduction in kidney function, as evidenced by an increase in the serum creatinine concentration of at least 0.5 mg/dL, or at least 25% from baseline within 48-72 hours after exposure to contrast media.[12]

As the use of contrast agents is not limited to urology, there are additional data regarding CIN from other fields, most notably the interventional cardiology literature. Overall, the incidence in that population is around three percent.[13] Interventional cardiologists in reviewing CIN within their own field cite increased cost, length of stay, risk of failure to return to baseline renal function, and risk of mortality stemming from CIN associated with PCA and/or stenting.[13,14] Moreover, there has been evidence of a 15-times risk increase in major adverse cardiac events in patients after developing CIN.[15] Presumably, similar trends in both increased cost and adverse event expectations can be extrapolated to urologic patients whose hospitalizations are complicated by CIN.

Patients at risk for CIN include patients with renal insufficiency and as such, an increased overall risk for CIN is seen in patients with hypertension, diabetes, and cardiac disease, as well as any condition causing hemodynamic instability around the period of contrast administration.[16] Finally, the volume of contrast injected, the type of contrast agent used, and the presence of other nephrotoxic medications increase the risk of CIN.[17]

Prevention of CIN

Each patient at risk for renal insufficiency should have a screening estimation of renal function with serum creatinine. Then, using the modification of diet in renal disease (MDRD) calculation for glomerular filtration rate (GFR), they should have preprocedural GFR calculated. This includes patients with known renal disease or renal insufficiency, diabetic patients, those with cardiovascular disease or hypertension, and age greater than 65.[18] The use of the MDRD for estimation of renal function is due to the inherent errors associated with relying on serum creatinine in these patient populations.[19] The timing of the evaluation should be done in such a way that the test serves to aid in identifying those at risk for CIN, as well as to serve as a baseline prior to the test.

A number of medications and hydration protocols have been tested as preventive strategies for CIN. Data suggest, though not definitively, that N-acetylcysteine (NAC) might help to decrease the risk of CIN, although this is debated.[12,16,20-22] The typical dosage of N-acetylcysteine in these studies was either 600 mg or 1200 mg by mouth twice daily the day prior to and the day of the scan, with evidence suggesting that 1200 mg is better than 600 mg.[20,22] NAC given twice a day

for 48 hours following contrast administration during primary angioplasty resulted in a dose-dependent decrease in CIN from 33% in the control group to 15% and 8% in the 600 mg NAC and 1200 mg NAC groups, respectively.[22] NAC is well-tolerated and has minimal side effects at either dosage. Additionally, three other intervention strategies have proven beneficial in reducing the incidence of CIN after use of iodinated contrast.

Of all the intervention strategies to date, hydration has proven the most beneficial. Volume infusion in the form of isotonic normal saline for 24 hours total encompassing the before and after period surrounding the contrast load has been shown to be superior to 0.45% normal saline in reducing the rate of CIN.[23] Sodium bicarbonate infusion was first reported to be more effective when compared to saline in 2004.[24] This finding was subsequently confirmed in a double-blinded, randomized controlled trial in the REMEDIAL study group.[25] The suggested infusion rate is 6 mL/kg/hr for the hour prior to the procedure and then 1 mL/kg/hr during and for 6 hours post-procedure. In addition, the risk of CIN can be altered by the type of iodinated contrast used. Iso-osmolar and low-osmolar contrast agents are preferred over high osmolar contrast agents.[14] Interestingly, there is no evidence suggesting a difference between ionic and nonionic agents.[23,24] Investigators have found that limiting the contrast load to less than 140 mL improved the rate of CIN.[25] Finally, hemofiltration has been shown to be effective in high-risk patients in reducing the incidence of CIN from nearly 50% to approximately 20%. Hemofiltration's benefit was enhanced by beginning hemofiltration 6 hours prior to injection of contrast media and 18-24 hours afterward, thus bringing the CIN risk down to 3%.[15] Interestingly, neither hemodialysis nor peritoneal dialysis demonstrates clinical benefit in the prevention of CIN.[26]

Recommendations

Our algorithm builds on the work of Mehran et al who developed a 'risk score' to help counsel patients and guide physicians as to a patients individual risk of CIN, Figure 1.[27] We propose the use of this score along with GFR to guide patients through a decision tree incorporating both MR and CT imaging modalities, Figures 2 and 3.

Perhaps one of the more challenging issues faced by the urologist is how to proceed with the patient whose GFR is under 30 mL/min. The first question that must be answered is whether contrast-enhanced imaging is absolutely necessary. The factors that should be taken into account in order to answer this question sufficiently are the potential risks to the patient of not having the information that is gained from contrast-enhanced imaging in light of their medical comorbidities and life expectancy, as well as the patient's desire to obtain this information. A discussion of the risks inherent to each imaging modality should ensue so that the patient can be an informed participant. It should

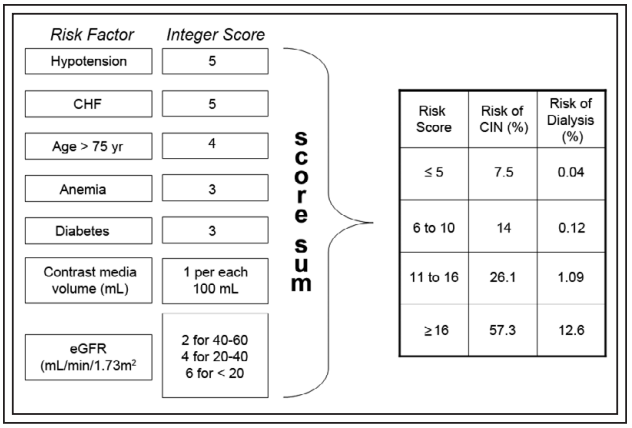

Figure 1. Algorithm based on patient risk factors for the chance of developing contrast-induced nephropathy (CIN) or subsequent need for dialysis. Hypotension = systolic blood pressure < 80 mm Hg for at least 1 hour requiring inotropic support; CHF = congestive heart failure class III/IV by New York Heart Association classification and/or history of pulmonary edema; Anemia = baseline hematocrit value < 39% for men and < 36% for women; eGFR = estimated glomerular filtration rate.

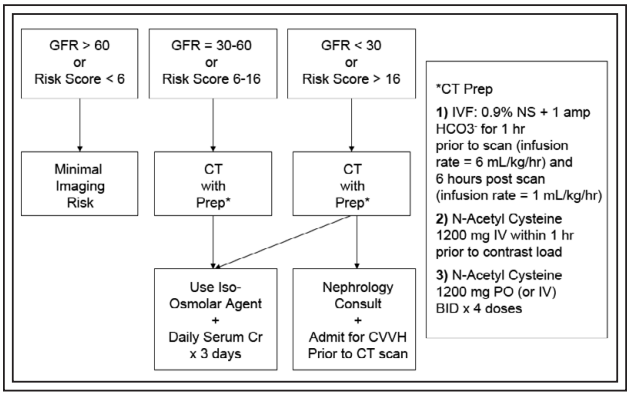

Figure 2. Proposed algorithm for computed tomography (CT) that requires intravenous contrast administration. GFR = glomerular filtration rate (measured in mL/min); Cr = creatinine; IVF = intravenous fluids; $HCO3^-$ = bicarbonate; CVVH = continuous veno-venous hemofiltration.

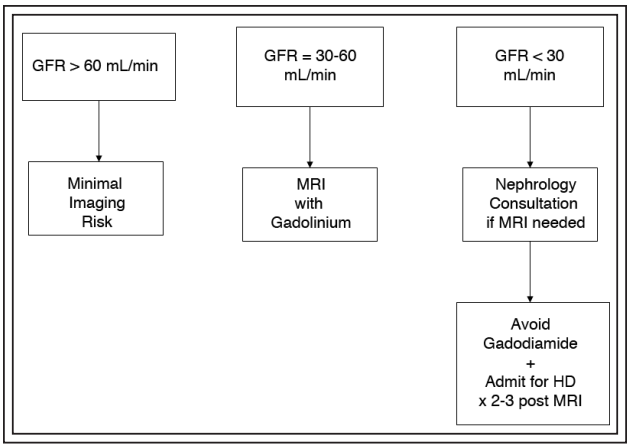

Figure 3. Proposed algorithm for magnetic resonance imaging (MRI) that requires intravenous contrast administration. NSF = nephrogenic systemic fibrosis; HD = hemodialysis

be explained to the patient that the risk of NSF post gadolinium-enhanced MRI is approximately 1% and that although strategies do exist to limit its potential development, none have been rigorously studied and are based mainly on the perceived pathophysiology of the disease process. In addition, central venous access for temporary hemodialysis comes with its own set of complications, with over 15% of patients acquiring a mechanical, infectious, or thrombotic complication during and after placement.[28] Likewise, the risk of developing CIN and ultimately requiring HD post contrast-enhanced CT imaging in these high-risk patients is over 50% and 12.6%, respectively, with up to 2% of these patients remaining dialysis-dependent.[27] Therefore, the worst case scenario of each imaging modality (NSF versus remaining dialysis-dependent) should be discussed with each patient so that they can make an individualized choice of which option is best for them.

In a patient with a GFR above 30 mL/min, the decision between contrast-enhanced CT or MRI becomes somewhat less problematic, especially if MRI is chosen.

As noted above, the risk for NSF above a GFR of 30 is essentially zero. Should CT be the modality of choice, one can proceed according to the algorithm outlined herein, Figure 2. The urologist need only to make a few simple calculations to arrive at a risk score which will help determine a patient's course through the care pathway, Figure 1. Additionally, by reviewing a patient's risk factors, the physician can obtain a clearer picture of an individual's risk of developing CIN and for the potential need for hemodialysis.[17,27]

A few groups have addressed the follow up after developing CIN and have advocated for a repeat creatinine 24-48 hours after CM injection in high-risk populations.[29] Nephrology consultation should be considered in order to help manage these high-risk patients. During the acute phase of renal insufficiency, daily creatinine levels should be followed. During this time, attention should be paid to blood pressure with a goal of normotensive levels. Physicians should be cautioned against potentially nephrotoxic medications like NSAIDs and metformin and should seek alternatives. Those medications which are renally-cleared should be dose-adjusted for current GFR. For all patients that have had CIN, optimization of cardiac risk factors, including dyslipidemia, hyperglycemia, and hypertension, should be aggressively pursued given the increased risk of cardiovascular morbidity and mortality in this population.

Future directions

In lieu of treating the complications of acquired renal injury following cross-sectional imaging, the idea of utilizing renal protective strategies remains a central tenet in the management of at-risk patients. Below we discuss some contemporary strategies and emerging techniques to reduce the risks associated with contrast-enhanced imaging.

Targeted renal protection

Selective vasodilation of the renal arteries is not a novel concept. Over a decade ago, the use of dopamine to target the renal vasculature was evaluated as having a potential renal-protective effect in surgical intensive care unit patients.[30] A more recent line of investigation has been undertaken with the drug fenoldopam. However, much like the prior dopamine studies, multiple studies addressing fenoldopam have resulted in conflicting results.[31,32]

The systemic administration of a vasodilator agent to augment renal perfusion may secondarily redistribute flow to non-vital organs and thus be counterproductive. To address this problem, a novel intra-renal arterial drug delivery system has been developed.[33] It involves placement of a very small bifurcated infusion catheter directly into the renal arteries. This system allows drug infusion at significantly higher doses than would otherwise be achievable through systemic administration. Early results show a clear dose-dependent effect with a significantly lower incidence of CIN among patients receiving higher drug doses.[34]

Direct intra-arterial therapy is ideal for patients already undergoing catheter-based procedures. The

question that remains is the role that this intervention may have as a stand alone therapy on patients at high risk of acute kidney injury that are not undergoing imaging or catheter angiography with iodinated contrast. This line of investigation is currently being pursued.

Dual head contrast injectors

Historically, IV contrast needed to be delivered continuously, in part, in order to propel the contrast load itself.[35] In effect, the contrast load required for image generation was less than what was given, as some of the volume was utilized as a driving force to deliver the true bolus load.

Recently, the utilization of dual cylinder injectors has reduced the total volume of contrast that is required for imaging while simultaneously improving image quality.[36] By allowing a two-stage injection, the contrast bolus is driven into the central venous circulation using saline rather than continuous contrast injection. This makes use of contrast that would otherwise be unused as it remains in the peripheral circulation. As a result there is a tighter delivery of a smaller volume of contrast, increasing both the efficiency of contrast medium utilization and the level of enhancement.[37]

Whole organ imaging using wide area detector CT

As imaging technology has continued to advance, the load of contrast required to generate an adequate CT image study is now a moving target. With the development of CT scanners using multi-detector technology, imaging can now be performed with incredible temporal, spatial and contrast resolution. Scanners with arrays as large as 320 detectors are now available which allows entire organs to be imaged with a single rotation of the CT gantry. As a result, the volume of IV contrast required can be significantly reduced.[38]

Contrast-enhanced ultrasound

This technology uses injection of microbubbles to generate an acoustic reflection which is altered by the level of blood flow to the area. Improved sensory equipment can then decode these signals to generate an enhanced image.[39] This technology remains at an experimental stage and its use as a replacement or adjunct to current cross-sectional imaging (MRI and CT) remains untested. The initial focus for urologic applications has been in the area of prostatic imaging and results are encouraging.[40] Potential hurdles include lack of generalizability and operator dependence, as well as concern over microbubble safety.[41] However, one expects continued improvement of this novel concept and represents a substantial effort toward minimizing the potential risks of current contrast-enhanced imaging, as well as decreasing the exposure of patients to ionizing radiation.

Advanced MRI non-contrast imaging

Advanced MRI imaging offers a wide array of functional contrast mechanisms, which do not require injection of gadolinium while providing for potential perfusion information analogous to the information provided by gadolinium-based tumor enhancement. Arterial spin labeling (ASL) is an attractive functional contrast mechanism because it provides direct quantitative perfusion measurement.[42] ASL has been used to assess the presence of blood flow in metastatic RCC and has been suggested as a potential biomarker for RCC.[43,44] Problems with respiratory motion and poor signal to noise ratio continue to limit the widespread use of this technique.

Diffusion MRI has been also shown to be a promising technique in differentiating cyst from tumor, although there is significant overlap between the apparent diffusivity of tumor and renal tissue.[45] The use of these techniques individually or in concert to assess renal masses remains an active area of radiological research.

Conclusions

Contrast-enhanced cross-sectional imaging is heavily relied upon by the modern day urologist. The urologist's familiarity with the risks, benefits and alternatives associated with contrast-enhanced cross-sectional imaging is essential to providing conscientious care. By following the outlined care pathway and using it as a discussion point for patients and between physician specialties, uncertainty regarding imaging modalities can be minimized and potential morbidity decreased, while obtaining the requisite information to guide patient care. □

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