Clinical laboratory measurement of serum/plasma creatinine concentration has been used to assess patient kidney function for well over 50 years. With incorporation of creatinine analyses to blood gas and other point-of-care platforms the test is now available outside the laboratory, at the bedside and in the clinic.

This is the first of two articles that highlight the clinical value of creatinine measurement in the radiology department. An ever-increasing number of patients submitted for X-ray and other body imaging examinations such as computed tomography (CT) and magnetic resonance imaging (MRI) scan are given image-enhancing contrast agents that can be associated with adverse effect.

Among these adverse effects are two conditions that are the focus of the two articles: nephrogenic systemic fibrosis (NSF) and contrast-induced nephropathy (CIN).

Consideration of the significance of serum creatinine measurement in CIN is reserved for the second article. Here the focus is NSF and how measurement of serum creatinine is used to identify those patients at risk of the condition. The article will include discussion of what is known about the pathogenesis of NSF, the triggering role of pre-existing renal disease along with the significance of MRI scanning. But it begins with a brief general consideration of the role of plasma creatinine measurement for assessment of renal function.

**Creatinine – a marker of renal function**

Creatinine is an endogenous product of muscle metabolism, specifically it is derived from creatine, a substance that in its phosphorylated state is involved in ATP-mediated energy transfer within muscle cells. The daily rate of creatinine production from creatine depends on total muscle mass and so varies greatly...
between individuals, but is of the order 0.5 g for children, 1.5 g for adult females and 2.0 g for adult males [1]. Although there is variability between individuals, for a given individual daily creatinine production remains pretty well constant so long as total muscle mass is unchanging.

Creatinine has no metabolic function and once released to blood from muscle cells, its fate is elimination from the body. This elimination is exclusively via the kidneys in urine.

The concentration of plasma creatinine thus reflects the balance between the rate of creatinine production by muscle tissue and the rate of elimination by the kidneys. In healthy adults plasma creatinine concentration is maintained within the approximate reference range 60-120 µmol/L (0.7-1.4 mg/dL) [2], with females having values at the lower end of this range and males at the higher end, reflecting their differing muscle bulk.

Most meat for consumption is muscle, so that diet is a potential source of creatinine, but by comparison with creatinine derived endogenously from muscle metabolism, the amount of exogenous (dietary) creatinine is usually slight and transitory.

Still, diet is a potential source of variability in plasma creatinine concentration [3] that can be eliminated by ensuring a meat-free diet during the 12 hours prior to measurement.

The value of plasma creatinine as a marker of renal function is based on the constancy of endogenous creatinine production. Given this constancy, increase in plasma creatinine concentration can only be due to reduced elimination in urine (if dietary effect is excluded) and therefore reduced renal function.

Irrespective of its cause, reduction in kidney function is associated with increased plasma creatinine concentration, although plasma creatinine concentration is an insensitive marker of early asymptomatic chronic kidney disease.

Loss of up to a half of renal function is required for there to be a discernible increase in plasma creatinine concentration. However, above this level of dysfunction, plasma creatinine concentration is reliably inversely correlated with renal function.

Among patients with the most advanced end-stage renal disease, when renal replacement therapy (either dialysis or transplantation) is required for survival, plasma creatinine typically exceeds 600 µmol/L (6.8 mg/dL) and may be as high as 1000 µmol/L (11.3 mg/dL).

In the context of rapid loss of function as in acute renal failure, in which progress from normal renal function to end-stage renal disease can occur over a period of days or weeks, the inability of plasma creatinine to detect minimal loss of renal function is not a problem; the loss of function is so rapid that plasma creatinine is always raised to some extent and normal plasma creatinine concentration excludes a diagnosis of acute renal failure.

However, in the context of the much more common chronic kidney disease (CKD), in which disease progresses slowly over months and years, plasma creatinine remains within the reference range in the early asymptomatic stages, implying incorrectly no loss of renal function.

The glomerular filtration rate (GFR) is the parameter that best defines kidney function and is a sensitive indicator of early CKD.

It is technically difficult to measure directly, but plasma creatinine concentration can be used to estimate this important parameter [4] and estimated GFR (eGFR) based on plasma creatinine concentration, age, gender and ethnicity has emerged in recent years as the internationally recommended means of assessing renal function and identifying those with CKD [5-7]).

The recommended equations for calculating eGFR in adults and children are described in Table Ia and Ib. The way eGFR is used to stage and monitor CKD is detailed in Table II.
eGFR (mL/min/1.73 m²) =
175 \times [\text{plasma creatinine (mg/dL)}]^{-1.154} \times [\text{age (yrs)}]^{-0.203} \times 1.212 (\text{if black}) \text{ and } \times 0.742 \text{ if female}

This equation should only be used if creatinine method has been recalibrated so that it is traceable to the GC-IDMS reference method and creatinine is measured in conventional units (mg/dL)

TABLE Ia: Equations for estimating GFR in adults from plasma creatinine concentration

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²) =</th>
</tr>
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<tbody>
<tr>
<td>186 \times [\text{plasma creatinine (mg/dL)}]^{-1.154} \times [\text{age (yrs)}]^{-0.203} \times 1.212 (\text{if black}) \text{ and } \times 0.742 \text{ if female}</td>
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<td>175 \times [\text{plasma creatinine (µmol/L) \times 0.01132}]^{-1.154} \times [\text{age (yrs)}]^{-0.203} \times 1.212 (\text{if black}) \text{ and } \times 0.742 \text{ if female}</td>
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</tr>
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This equation should only be used if creatinine method is not recalibrated so that it is traceable to the GC-IDMS reference method and creatinine is measured in SI units (µmol/l)

| TABLE Ib: Equations for estimating GFR in children from plasma creatinine concentration |
For the following discussion of nephrogenic systemic fibrosis, it is important to note that CKD is a common and growing health problem in the developed world, affecting predominantly those over 60 years.

In the US an estimated 19 million individuals (11% of the adult population) have some degree of CKD and the number progressing to end-stage renal disease increases at an annual rate of 5-8% in developed countries [8]. It is clinically silent in the early stages, and many individuals (40% in one study) are quite unaware of their diminished renal function [9].

**Nephrogenic systemic fibrosis (NSF)**

NSF is a relatively new disease. The first cases were reported just a decade ago [10] and the now accepted notion that it is an iatrogenic condition associated with magnetic resonance imaging (MRI) was first suggested only 4 years ago [11].

The original case study report in 2000 [10] described 15 patients with end-stage renal disease requiring dialysis, who had all developed a dermatological condition characterized by areas of hardening and thickening of the skin, visible as distinct orange/brown plaques.

Subcutaneous nodules were also evident. Skin of the face was unaffected and the torso was only occasionally affected. Disease was largely confined to the limbs. Loss of skin elasticity in the limbs was associated with joint stiffness that progressed to joint immobility (flexion contractures).

Although the condition resembled a very rare skin disorder called scleromyxedema, this and other diagnoses were excluded. The authors concluded that this was a novel “scleromyxedema-like” fibrotic condition, emphasizing that it had only been observed in patients who were receiving dialysis due to end-stage renal disease.

With more definitive clinical and histopathological characterization, the condition was given the name nephrogenic fibrosing dermopathy (NFD) a year later [12]. The systemic nature of the disease was subsequently demonstrated with autopsy of affected patients.

These revealed that fibrosis is not confined to skin but present in underlying muscle and other organs including heart, lung, liver and led to adoption of the current name nephrogenic systemic fibrosis (NSF) [13].

Since the initial description, more than 335 cases (as of October 2009) have been recorded at the NSF registry of the International Center for NSF Research [14] but this is likely to be an underestimate of the true prevalence [15].

These accumulating cases have allowed a clearer understanding of the disease. NSF is a condition that only affects those with severe renal impairment; either

<table>
<thead>
<tr>
<th>STAGE</th>
<th>GFR</th>
<th>DESCRIPTION</th>
</tr>
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<tbody>
<tr>
<td>Stage 1 CKD</td>
<td>≥90</td>
<td>Normal or increased GFR, with other evidence of renal damage (e.g. proteinuria)</td>
</tr>
<tr>
<td>Stage 2 CKD</td>
<td>60-89</td>
<td>Slight decrease in GFR, with other evidence of renal damage (e.g. proteinuria)</td>
</tr>
<tr>
<td>Stage 3 CKD</td>
<td>30-60</td>
<td>Moderate decrease in GFR with or without other evidence of renal damage</td>
</tr>
<tr>
<td>Stage 4 CKD</td>
<td>15-30</td>
<td>Severe decrease in GFR, with or without other evidence or renal damage</td>
</tr>
<tr>
<td>Stage 5 CKD</td>
<td>&lt;15</td>
<td>End-stage renal disease (renal failure)</td>
</tr>
</tbody>
</table>

*TABLE II: How e-GFR is used to stage chronic kidney disease (CKD)*

CKD may be stable or progressive. Progress is defined as decline in eGFR of >5mL/min/1.73 m$^2$ in one year or >10 mL/min/1.73 m$^2$ in 5 years.
acute renal failure (rarely) or CKD. Most diagnoses are made in patients with stage 5 CKD (eGFR <15 mL/min).

A minority have stage 4 CKD (eGFR between 15 and 30 mL/min). The condition has never been described in those with healthy kidneys or in those with e-GFR >60 mL/min. Most, but not all patients are dependent on dialysis when diagnosed.

The most common first symptom of NSF is bilateral ankle edema and ankle weakness followed by the appearance of the characteristic hard and thick "woody" skin lesions at this lowest extremity [16].

The skin lesions then "spread" upwards. NSF is an often painful, disfiguring and sometimes devastating disease that, due to severity of joint contractures, can leave affected patients immobile and wheelchair-bound, or even bedridden within a year of diagnosis [17].

Definitive diagnosis currently depends on deep skin biopsy of an affected area and there remains no cure or effective treatment. Reversal of renal disease and renal transplantation [17, 11] has been associated with improvement of skin lesions and halting of disease progression in some patients.

Although NSF is not of itself considered a fatal disease, many NSF-affected patients have died and the condition is thought to have been a contributory factor in these deaths. Although it was very soon appreciated that severe kidney disease is a necessary predisposing factor, the cause of NSF eluded researchers until 2006. In that year a significant breakthrough came with a case series report from Austria [11].

The author of this study described five cases of NSF that had arisen at his dialysis unit during the previous 2 years. In all cases the first symptoms of NSF appeared 2-4 weeks after the patients had undergone magnetic resonance imaging of blood vessels (MR angiography) enhanced with prior administration of gadolinium (Gd) containing contrast agent (Gd-CA). This was the first evidence of the now established link between Gd-CA and NSF.

MRI, Gd contrast agents and NSF

A history of Gd exposure during MRI has been reported in nearly all (95 %) cases of NSF [18]. Gd has been detected in the affected tissues of NSF patients but has never been detected in the tissues of patients unaffected by NSF who have received Gd-enhanced MRI.

Although the precise mechanism of its toxicity in NSF remains elusive, it is now widely accepted that Gd exposure is a necessary (but not sufficient) triggering cause of NSF. There must be other factors involved because only a small minority (5-7 %) of patients with advanced renal disease exposed to Gd-enhanced MRI develop NSF [19].

Gadolinium is the 64th element in the periodic table, a rare earth metal, one of the lanthanide series. It has seven unpaired electrons resulting in the strong paramagnetic properties that are exploited in its use as an image-enhancing agent in MRI [14].

Gd-CA is not necessary for all MRI procedures, but around half of all patients submitted for MRI are given Gd-CA, and Gd-CAs have been used in MRI evaluation of brain, spine, liver, kidneys, heart, pelvis, breast and blood vessels (angiography).

Gadolinium is not normally present in the human body, indeed is highly toxic to all tissues. To counter this potential toxicity the Gd contained in MRI contrast agents is bound to a non-toxic chelation agent [15].

The resulting complex keeps the Gd ion biochemically inert whilst preserving its diagnostically useful paramagnetic properties. Since the first Gd-CA, gadopentate dimeglumine (Magnevist®), was approved for clinical use in 1988, at least six further products have been released, each differing in chelate structure (Table III).

Not all of these products are associated with equal risk of NSF; indeed there are some that have no history of association with NSF [19]. The majority (85 %) of NSF cases to date have been associated with the use of Gd-CA, gadodiamide (Omniscan™) [15], most other cases being associated with the use of gadoversetamide (OptiMark®) or Magnevist®.
It appears that it is the relative stability of chelate binding of Gd that is significant. Those products associated with NSF have significantly lower stability constants than those not associated with NSF, and it is currently presumed that it is the release of Gd to tissues due to lower chelate stability that accounts for the differing risk of NSF associated with different products.

In those with normal renal function, even the least stable Gd-CA products do not pose a threat, because all are normally rapidly eliminated from the body (half-life of the order 1.5-2 hours). By contrast, in those with advanced renal disease half-life of administered Gd-CA is markedly prolonged (30-120 hours) [11], allowing the potential for accumulation in tissues and subsequent dissociation of free (toxic) Gd from protective chelate.

Just why administration of the same Gd-CA at identical dose to patients with advanced renal disease causes NSF in some but leaves the majority apparently unaffected, remains a mystery, but this has been the object of much speculative research that is recently reviewed [20].

**Prevention of NSF – a role for plasma creatinine measurement**

It is a cruel irony that the introduction of gadolinium-enhanced MRI in the late 1980s was hailed as the answer to the problem of nephrotoxicity associated with the use of iodinated contrast media (ICM). The perception was that with the new technique patients with renal impairment could now be safely submitted for enhanced diagnostic scan [21].

The emergence of NSF has proved that perception flawed, and it is now clear that consideration of patient renal function is as essential for the safe use of Gd-CA as it was and is for the safe use of ICM. In the absence of any effective treatment for NSF the focus has been on prevention. National guidelines for NSF prevention have been prepared in US, Canada, Europe and Japan [22].

They are all based on the accepted premise that the only individuals at risk of NSF following administration of Gd-CA are those with acute renal failure and those with stages 3-5 CKD (i.e. those with an e-GFR <60 mL/min/1.73 m2). The problem lies in accurately identifying this small subset of patients in the radiology department.

Clearly the only foolproof strategy for identifying those at risk of NSF is to measure plasma creatinine (and calculate eGFR) of all patients immediately prior to administration of Gd-CA.

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CHELATE CLASS **</th>
<th>ASSOCIATION WITH NSF††</th>
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<tbody>
<tr>
<td>Gadodiamide (Omniscan®)</td>
<td>Non-ionic linear</td>
<td>YES many unconfounded cases</td>
</tr>
<tr>
<td>Gadopentate dimeglumine (Magnevist®)</td>
<td>Ionic linear</td>
<td>YES some unconfounded cases</td>
</tr>
<tr>
<td>Gadoversetamide (Optimark®)</td>
<td>Non-ionic linear</td>
<td>YES some unconfounded cases</td>
</tr>
<tr>
<td>Gadobenate dimeglumine (Multihance®)</td>
<td>Ionic linear</td>
<td>??? No unconfounded cases</td>
</tr>
<tr>
<td>Gadoxetate disodium (Primovist®)</td>
<td>Ionic linear</td>
<td>??? No unconfounded cases</td>
</tr>
<tr>
<td>Gadobutrol (Gadovist®)</td>
<td>Non-ionic cyclic</td>
<td>??? No unconfounded cases</td>
</tr>
<tr>
<td>Gadoterate meglumine (Dotarem®)</td>
<td>Ionic cyclic</td>
<td>??? No unconfounded cases</td>
</tr>
<tr>
<td>Gadoteridol (Prohance®)</td>
<td>Non-ionic cyclic</td>
<td>??? No unconfounded cases</td>
</tr>
</tbody>
</table>

TABLE III: Gadolinium-based contrast agents used to enhance MRI scans

All GdCA products comprise a single Gd atom bound to a chelate molecule of variable structure.

** Linear chelate products are less stable than cyclic chelate products and therefore more likely to dissociate releasing free Gd ion.

†† An unconfounded case is defined as NSF occurring after exposure to only one GdCA Patients may be exposed to more than one GdCA and then it is impossible to attribute NSF to a particular product – such cases are referred to as confounded cases.
The opinion contained in all current national guidelines is that this is not necessary. US and Canadian guidelines suggest that the approach should be to identify those with renal disease and those at risk of renal disease by patient questionnaire and then establish plasma creatinine (and eGFR) only in these patients, either by interrogating recent medical records or blood testing.

A suggested sample questionnaire is contained in Fig. 2. A “YES” answer to any of the questions identifies an “at risk” patient and the necessity to establish e-GFR. The guidelines state that in the case of outpatients (whose renal status is presumed to be stable), eGFR obtained within 3 months is all that is needed.

For inpatients, whose renal status is possibly changing daily, eGFR must be obtained within 48 hours of scan. Clearly in some cases an appropriately timed eGFR result might already be available in patient or laboratory records, but in others it would be necessary to schedule fresh laboratory blood testing.

European guidelines represent a different approach that does not depend on patient questionnaire or patient selection but rather focuses on the variable risk of NSF associated with different Gd-CA products. These guidelines identify products (Omniscan, Magnevist, Optimark) for which plasma creatinine (eGFR) measurement is mandatory and those (Mulithance, Vasovist, Dotarem and Primovist) for which such testing is not considered necessary.

Guidance states that the three high-risk products should not be used in those whose eGFR is <30 mL/min and used “with caution” in those whose eGFR is between 30 and 60 mL/min.

All guidelines advise that alternative diagnostic procedures should be considered, but if absolutely necessary the lowest possible Gd-CA dose should be administered. In the case of dialysis patients, the advice is to schedule MRI scan immediately prior to the next dialysis appointment to enhance immediate elimination of Gd-CA.

Although both US/Canadian and European guidelines are a major step forward in NSF reduction, they may be logistically difficult to implement with the greatest intended effect in some institutions and therefore may not be sufficiently robust to identify all those at risk and entirely eliminate NSF.

All radiology departments must now have their own NSF-prevention policy, aimed at not merely reducing the incidence of NSF, but eliminating NSF. There is increasing acknowledgement that point-of-care testing for creatinine within the radiology department has a legitimate (perhaps necessary) role in identifying those at risk of NSF.

At least one department has adopted the policy that all outpatients scheduled for contrast-enhanced MRI scanning have point-of-care creatinine/eGFR measurement in the radiology department just prior to scan [23].

It is essential for such a policy to be maximally successful that point-of-care methodology allows the most accurate assessment of eGFR. Enzymic rather than the more traditional alkaline picrate methodology is considered the most accurate for routine measurement of serum creatinine [24].

Enzyme-based methods allow results that are most closely aligned to those obtained using the gas chromatography-isotope dilution mass spectroscopy (GC-IDMS) method, which is the internationally agreed reference method for determination of plasma creatinine [24].

Several studies [25,26] have demonstrated the reliability of point-of-care assays based on enzymic determination of creatinine to fulfill all the requirements for most accurate eGFR. Point-of-care measurement can certainly be as good and may be better than currently used laboratory-based methods for identification of those at risk of NSF.
Summary

- Nephrogenic systemic fibrosis (NSF), first described just 10 years ago, is a rare devastating condition that can leave affected patients permanently disabled and wheelchair-bound. There is no effective treatment.

- NSF is caused by exposure to gadolinium contrast agents (Gd-CA) used to enhance magnetic resonance imaging scans. There are six Gd-CA products – not all are associated with equal risk of NSF.

- Only those with renal impairment are at risk of NSF. Those with severe stage 5 CKD (GFR <15 mL/min) receiving dialysis are at greatest risk.

- NSF is not inevitable even in this patient group – the vast majority of patients with the most severe kidney disease who have been given “high-risk” Gd-CA have suffered no ill effect. The factor(s) that determine susceptibility to NSF among those with severe kidney disease are unknown so all must be considered at equal risk of NSF.

- Measurement of plasma creatinine/eGFR is necessary to identify those at risk of NSF, a necessary step for prevention.

- Point-of-care creatinine/eGFR testing in the radiology department allows all patients submitted for Gd-CA-enhanced MRI scan to be tested immediately prior to scan. This is a feasible and foolproof strategy for identifying all those at risk of NSF that has been adopted at some centers.
References


