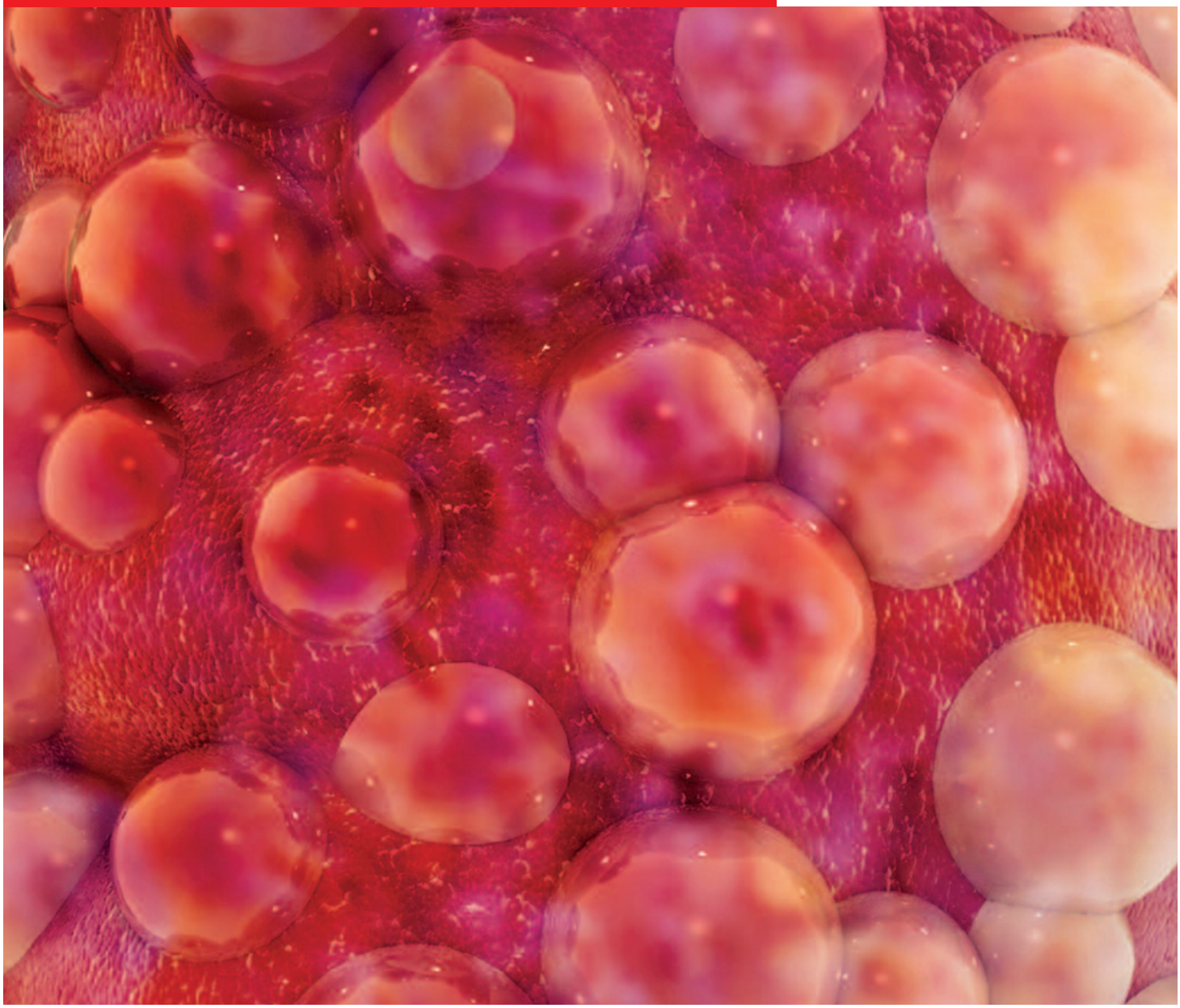
British Journal of
Renal Medicine



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* Cure of hepatitis C virus (HCV) infection=sustained virologic response, the primary end point in all studies, defined as HCV ribonucleic acid (RNA) less than the lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment (SVR12).[1,3]

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HCV genotype	Treatment and duration
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1b	ZEPATIER for 12 weeks
4	ZEPATIER for 12 weeks ZEPATIER for 16 weeks plus ribavirin should be considered in patients with baseline HCV RNA level >800,000 IU/ml to minimise the risk of treatment failure.

No dose adjustment required in patients with mild, moderate, or severe renal impairment (including patients receiving haemodialysis or peritoneal dialysis).
CONTRA-INDICATIONS: Hypersensitivity; moderate or severe hepatic impairment (Child-Pugh B or C); co-administration with OATP1B inhibitors or CYP3A inducers or P-gp inducers.
PRECAUTIONS: Assess hepatic function prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, also assess hepatic function at week 12. Advise patients to seek medical advice immediately if they have fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discoloured faeces. Consider discontinuing therapy if ALT levels >10 x ULN. Discontinue therapy if ALT elevation is accompanied by signs or symptoms of liver inflammation, increased conjugated bilirubin, alkaline phosphatase, or INR. Not recommended in genotypes 2, 3, 5 and 6. Perform HBV screening in all patients before initiation of Zepatier treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should be monitored and managed according to current clinical guidelines. Contains lactose and 69.85 mg of sodium per dose. *Drug interactions:* Co-administration with strong CYP3A inhibitors not recommended. Concentrations of dabigatran may increase when co-administered with elbasvir, with possible increased bleeding risk. Clinical and laboratory monitoring is recommended. When co-administered with vitamin K antagonists, monitor INR. When co-administered, the daily dose of atorvastatin, fluvastatin, lovastatin or simvastatin should not exceed 20 mg and the daily dose of rosuvastatin should not exceed 10 mg. When co-administered, monitor tacrolimus whole blood concentrations, changes in renal function, and for tacrolimus-associated adverse events. When co-administered, use with caution as dose adjustment of sunitinib may be required. *Children and adolescents:* not recommended. *Pregnancy and lactation:* Use in pregnancy only if the potential benefit justifies the potential risk to the foetus. When used with ribavirin, women of childbearing potential must use effective contraception during treatment and for a period post-treatment. Breast-feeding should be discontinued during Zepatier therapy.
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Date of review of prescribing information: November 2017.

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Comment

See one, do one, teach one

The adage 'see one, do one, teach one' is thought to originate from William Stewart Halsted, who became the first Chief of Surgery at Johns Hopkins Hospital in 1890, and transformed surgical training by creating a surgical residency programme.[1,2] While learning through experience remains an essential part of healthcare training, medical educators have a wealth of tools available today to enhance learning. In particular, simulation-based learning often provides a safe environment to gain procedural experience.

Learning to be safe

A meta-analysis of studies comparing simulation-based medical education with deliberate practice found that skills acquired in medical simulation laboratory settings improved patient care across a range of outcomes.[3] Simulation-based training in central venous catheter insertion in the intensive care setting improves success rates and reduces complications, including catheter-related infections.[4,5]

Insertion of temporary haemodialysis catheters is a procedural competency required to achieve a certificate of completion of training (CCT) in renal medicine in the UK.[6] Simulation-based education improves performance during temporary haemodialysis catheter insertion by nephrology fellows, although the skills acquired may subsequently decline.[7] Indeed, both trainees and consultants may benefit from simulation-based learning over time.[8] In contrast, renal biopsy is an optional procedural competency in the UK, although in the US the Accreditation Council for Graduate Medical Education (ACGME) programme[9] still requires nephrology fellows to develop competent biopsy skills for native and transplanted kidneys.[10] Simulation-based training for renal biopsies is less readily available, although simple models using porcine kidneys have been described[11,12] and appear to increase both the confidence and competence of trainees, with a higher level of success and lower biopsy-related blood loss.[13]

The right place

As the importance of simulation training for patient safety becomes widely recognised, the scope to develop novel approaches becomes more evident. In this issue, Kathryn Watson and colleagues describe the impact a multi-disciplinary simulation *in situ* training programme for the management of medical emergencies in haemodialysis units can have across professions.

John Bradley, Editor

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Spontaneous renal artery dissection: a cautionary tale of a young male with loin pain

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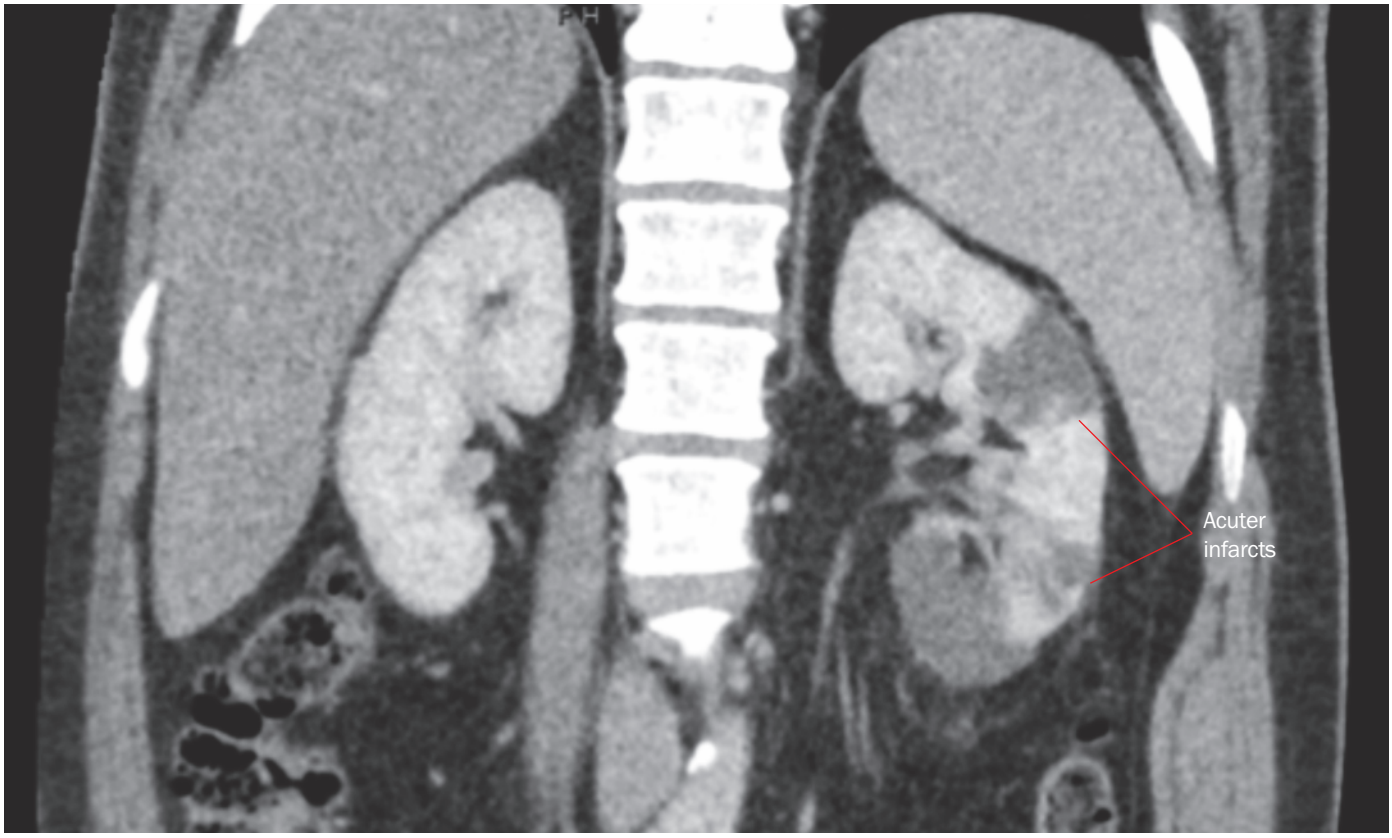
Spontaneous renal artery dissection (SRAD) is an uncommon condition, which often mimics other pathologies; therefore, delayed diagnosis is a problem among physicians. It has a 10:1 male predominance, most commonly occurring between 40 and 60 years of age. Patients present with signs and symptoms suggestive of pyelonephritis or renal colic, with a constant loin-to-groin pain, pyrexia, nausea and vomiting; importantly, they are also markedly hypertensive. Confirmation of the diagnosis requires CT renal angiography, as a conventional CT can be inconclusive. Management is mainly conservative, with antihypertensive agents and anticoagulants, but there is an emerging role for endovascular stenting.

Case study

A previously well, 45-year-old male lorry driver presented to his GP after waking with a constant, severe, sudden-onset, left-sided abdominal pain, associated with vomiting, dizziness and pyrexia. The GP sent him to A&E and when he was questioned further about his symptoms on arrival,



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■ **Figure 1.** Coronal reconstruction CT image of kidneys in portal venous phase

he described pain radiating from loin to groin and declining excruciatingly slowly from its peak at onset. He also suffered with malaise and shivering. He had no frank haematuria or other urinary symptoms. He reported no past medical history, apart from an episode of gout.

Examination revealed moderate guarding and tenderness in the left iliac fossa, with marked renal angle tenderness. Observations exposed a temperature of 38.3°C and a remarkably raised blood pressure of 193/82 mmHg.

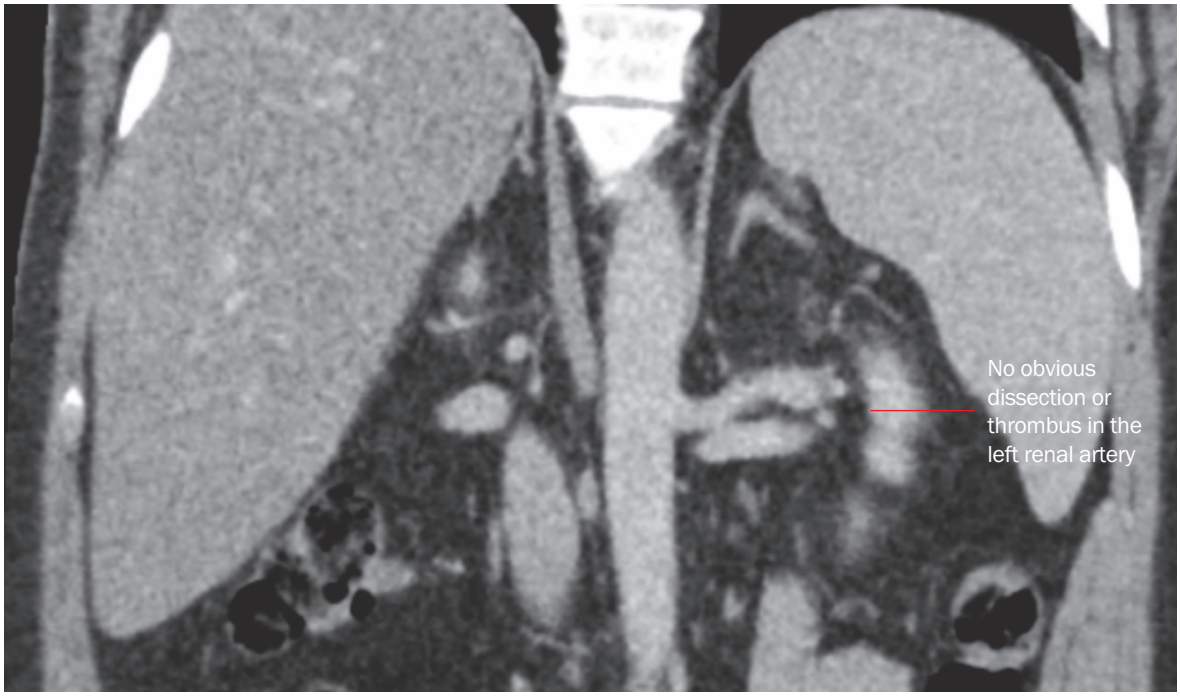
A surgical opinion was sought by A&E clinicians, and a provisional diagnosis of diverticulitis/renal colic was made. A urine dipstick analysis was strongly positive for glucose and protein, moderately positive for ketones and mildly positive for blood. Blood tests were largely unremarkable, with results for full blood count, clotting screen and kidney function in the normal range. Lactate levels were 1.8 mmol/l and glucose levels were 17–18 mmol/l with a glycated haemoglobin (HbA1c) of 12% as well as mild hypertriglyceridaemia. At this point, a medical opinion was requested and pyelonephritis was the lead differential diagnosis, alongside a diagnosis of new-onset diabetes mellitus. Management comprised of continuing broad-spectrum antibiotics and analgesia. At this stage, he was commenced on gliclazide 40 mg BD. Lipid-lowering treatment (simvastatin) was added five days later.

Three days after onset of symptoms, a CT scan showed an infarcted left kidney (see Figure 1) with a patent renal artery (see Figure 2). Vascular risk factors consisted of obesity, hypertension and diabetes mellitus. Nephrologists requested thrombophilia and vasculitis screens, a midstream urine sample for protein:creatinine ratio (PCR) and an echocardiogram, which were all unremarkable. Therapeutic enoxaparin and perindopril were started, with CT renal angiogram as the next step, which showed a dissection flap, subintimal thrombus and further thrombus extending into the segmental branches in the left kidney (see Figure 3). A multidisciplinary team discussion with vascular surgeons and interventional radiologists was organised upon discovery of the dissection flap and concluded that, in light of stable renal function, conservative management would be appropriate. The patient continued to be prescribed anticoagulant and antihypertensive treatment, with perindopril and amlodipine for BP, enoxaparin followed by warfarin on discharge, and the search for a precipitant began; however, tests for anticardiolipin, anti-double-stranded DNA, antinuclear and antineutrophil cytoplasmic antibodies and anti-extractable nuclear antigen, were all negative.

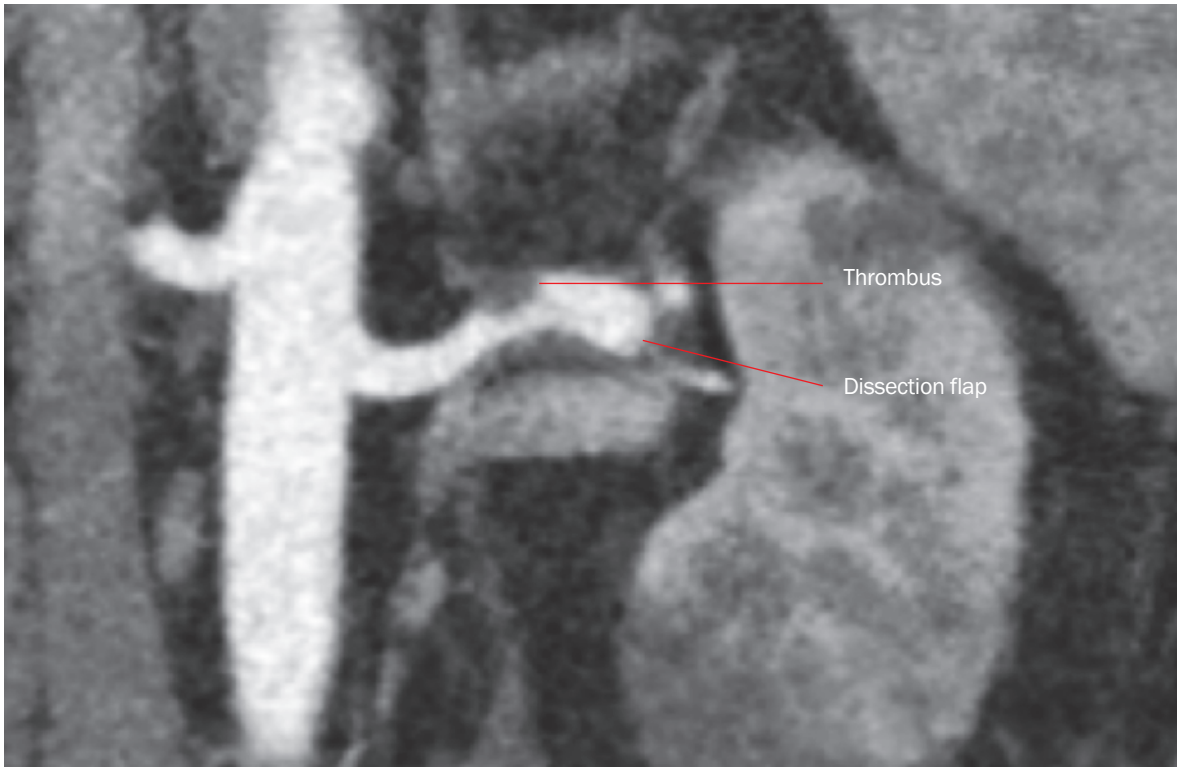
One year later, the patient is well, with normal renal function. He is still on antihypertensive medication, a statin and treatment for diabetes mellitus. Blood pressure readings in the outpatient clinic are still moderately high, at 150/100 mmHg, and he has been encouraged to lose weight to reduce this further.

Discussion

Around 200 cases of SRAD have been reported in the literature. The condition is up to ten times more prevalent in men than women and predominantly affects those aged between 40 and 60 years.[1,2] There is no evidence to suggest that one kidney is affected more than the other.[1] Multiple risk factors have been associated with its



■ **Figure 2.** Coronal reformatted CT image of the portal venous phase



■ **Figure 3.** Coronal reformatted CT image of the arterial phase

development, including fibromuscular dysplasia, severe atherosclerosis, subadventitial angiomas, malignant hypertension, Marfan and Ehlers–Danlos syndromes, cystic medial necrosis, extracorporeal shockwave lithotripsy and cocaine use.[1,3] Unfortunately, in the vast majority of cases, no cause is found.

In a young, previously well male, pyelonephritis is a rare occurrence. Symptoms of pyelonephritis in a man with high blood pressure should arouse suspicion of SRAD, which commonly mimics the former.[1] A severe, constant, unilateral pain, often in the flank and radiating to the groin, is the most common presentation, occurring with or without headache and/or macroscopic haematuria.[2,4] The presence of hypertension is almost universal.[1]

As highlighted by this case, confirming a diagnosis can be a challenge. Clinically, SRAD is a rare event that mimics renal colic; vertical thinking will result in missing the diagnosis. Ultrasound scanning is not beneficial, and while an abdominal CT scan may show an infarcted kidney, it may not expose the vascular correlate. CT angiography is, therefore, the gold standard for diagnosis and a renal angiogram may also allow for endovascular treatment simultaneously.[1]

No randomised controlled trials have evaluated the management of SRAD. Management must, therefore, be

guided on an individual basis. Options include conservative management, endovascular intervention with stenting or coiling, and surgical revascularisation. In a study of eight patients, conservative management resulted in normal renal function in seven patients and control of blood pressure was achieved with a single antihypertensive in six of the eight patients. The study concluded that surgical management should be considered only if malignant hypertension or renal failure are present acutely, or refractory hypertension is present chronically.[5]

Other case reports [2,3,6,7] promote endovascular stenting in the subacute setting as a successful method of revascularisation and normalisation of blood pressure and renal function. A study of 16 patients reports successful outcomes after endovascular stenting, with seven patients taking no medication at all and the rest taking only one or two antihypertensive agents at a mean follow-up of eight years.[7] Mean blood pressure was 118/78 mmHg, while plasma creatinine levels were all in the normal range and complications were minimal. Use of endovascular stenting can obviate the need for long-term pharmacological therapy; however, one should be confident that SRAD was causative of high blood pressure if using this approach as an antihypertensive measure ■

Patient consent
Patient consent was obtained for publication of this case report.

Declaration of interest
The authors declare that there is no conflict of interest.

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Key points

- In a presentation with signs and symptoms of pyelonephritis or renal colic, renal artery dissection (spontaneous or otherwise) is a differential diagnosis.
- Furthermore, if the patient is male and/or has a high blood pressure, consideration of spontaneous renal artery dissection is imperative. CT renal angiography is required to confirm the diagnosis.
- Management can be conservative, with antihypertensive medications and anticoagulants, or interventional, with endovascular stenting. The latter is an option for patients with resistant hypertension or declining renal function.

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Figure 1. The high-fidelity manikin receiving haemodialysis via a permacath

A novel patient safety initiative: interprofessional *in situ* simulation for the management of medical emergencies in hospital and community haemodialysis centres

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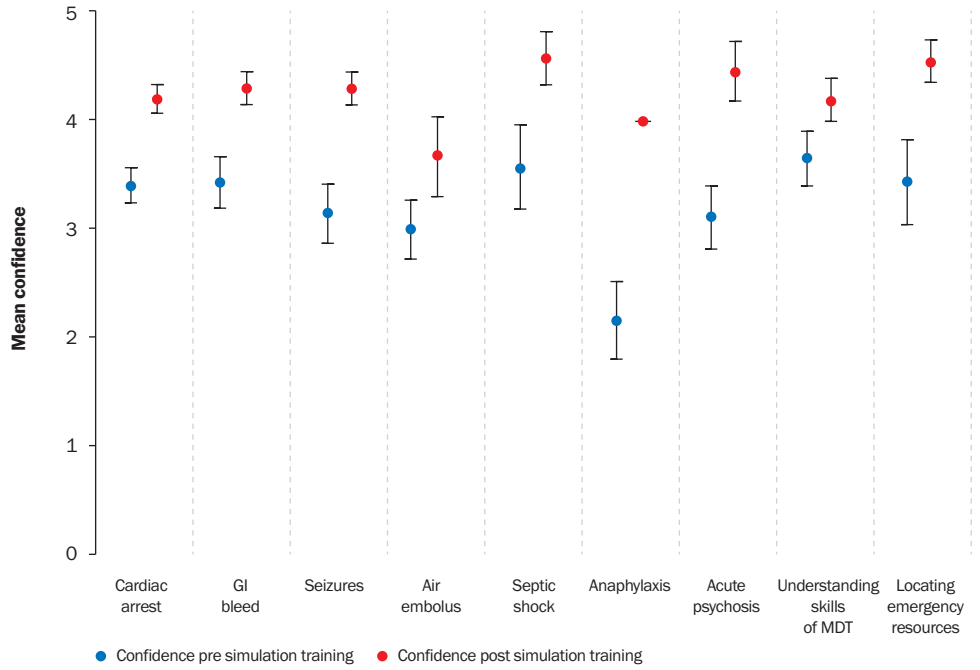
Interprofessional *in situ* simulation is an educational tool designed for multidisciplinary healthcare teams (MDTs) to consolidate and advance their knowledge of the management of a simulated clinical problem in their work environment. Being *in situ*, it provides an opportunity for reflection on practice within the clinical environment, therefore providing a means of detecting latent safety threats, such as clinical error waiting to happen, and highlights areas for clinical development.[1] In this article, we present a novel patient safety initiative through the development of an interprofessional simulation training programme designed for the management of medical emergencies in kidney patients on main and satellite haemodialysis units.

Simulation provides experiential and contextualised learning in a safe and controlled setting, and can be of particular benefit when dealing with life-threatening emergencies – it also raises awareness of rare but serious specialty-based clinical problems.[2] While it offers an opportunity to practise the clinical management of a specific scenario, it also focuses on how the team achieves this. In this way human factors, including teamwork, communication and leadership skills, are enhanced.[3]

The haemodialysis unit is a unique environment. It is run by specialist dialysis nurses and medical support may be available on site only at scheduled times, particularly in community-based satellite haemodialysis units. Nursing teams therefore require knowledge of and confidence in managing various emergency situations prior to further medical support arriving. Conversely, junior doctors called to a hospital-based haemodialysis unit in an emergency

■ **Figure 2.** Confidence pre and post interprofessional simulation training on the main King's haemodialysis unit



Confidence in managing various medical emergencies was assessed using a five-point Likert-type scale questionnaire before simulation training and after simulation training. Cardiac arrest: n=5 Mean confidence pre 3.40 (SD 0.49) post 4.20 (SD 0.40) p=0.035; Gastro intestinal (GI) bleed: n=7 Mean confidence pre 3.43 (SD 0.73) post 4.29 (SD 0.45) p=0.031; Seizures: n=7 Mean confidence pre 3.14 (SD 0.83) post 4.29 (SD 0.45) p=0.012; Air Embolus: n=6 Mean confidence pre 3.00 (SD 0.82) post 3.67 (SD 1.11) p=0.303; Septic Shock: n=7 Mean confidence pre 3.57 (SD 1.18) post 4.57 (SD 0.73) p=1.02; Anaphylaxis: n=6 Mean confidence pre 2.17 (SD 1.07) post 4 (SD 0) p=0.003; Acute psychosis: n=9 Mean confidence pre 3.11 (SD 0.87) post 4.44 (SD 0.83) p=0.006; Understanding skills of MDT working on the dialysis unit: n=46 Mean confidence pre 3.67 (SD 0.78) post 4.26 (SD 0.62) p=0.002; Knowledge of location of emergency resources: n=46 Mean confidence pre 3.46 (SD 1.17) post 4.53 (SD 0.63) p<0.001

may be less familiar with this patient population, the dialysis machine and the unit setting, and may therefore approach the situation with increased apprehension. Emergencies on the haemodialysis unit are often highly stressful situations for team members.

A potentially valuable resource to support MDT members in managing clinical scenarios is *in situ* renal simulation training. This novel training method provides an opportunity for the renal MDT to practise their specific roles within the team in their place of work during the management of a medical emergency on a manikin. Not only can individuals consolidate their knowledge of both common and rare medical emergencies, but they can learn more about the roles of their MDT colleagues, practise effective communication and teamwork, and also strengthen their knowledge of the local environment and location of emergency resources.

Methods

A high-fidelity Susie-Gaumard® manikin was used for simulation training. This manikin can simulate heart, breath and bowel sounds, pupillary reactions and peripheral pulses, and can be intubated, cannulated and catheterised. It can be attached to monitoring devices and defibrillated in a cardiac arrest; it was adapted to allow attachment to a dialysis machine by re-vascularising the cannulation training arm, stripping the veins and replacing them with a looped vein of silicone tubing to recreate a fistula graft; alternatively, a permacath could be attached to the chest wall, depending on the scenario (see Figure 1).

Scenarios were written by the King's College Hospital Postgraduate Department of Medical Education in collaboration with the renal team and were based on perceived learning needs, real patient scenarios and previous adverse incidents. They included septic shock from tunnelled line sepsis, acute gastro-intestinal bleed, sustained ventricular tachycardia with haemodynamic compromise leading to cardiac arrest, seizures, air embolism, anaphylaxis and acute psychosis.

Simulation training was 75 minutes long and held monthly for seven months on the main haemodialysis unit, with each session comprising one scenario. Two sessions were held in community satellite units, where specific training for nurses was provided as there are no resident doctors on site. The faculty included a senior nephrology trainee or consultant, an experienced renal nurse, an education fellow and a simulation technician. Healthcare staff were rostered to participate in each session.

Each session included an orientation to the manikin and haemodialysis unit. This was followed by a scenario performed in real time, then a debrief discussion to facilitate reflection on the experience. The debrief was structured using the diamond model.[4] Learning points and application to future practice were highlighted, and this

■ *In situ* simulation training on the haemodialysis unit can increase confidence across the multidisciplinary team and their management of medical emergencies

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learning was shared by email with other relevant members of the renal team. Any latent safety threats detected were discussed immediately with the learning group, then escalated and discussed among haemodialysis clinical leads with a collectively agreed intervention proposed.

Simulation sessions were evaluated using a pre- and post-session questionnaire, with individuals rating their confidence against a five-point Likert-type scale. Questions included confidence in managing the emergency scenario, knowledge of the skill sets of colleagues from the interprofessional team and confidence in locating emergency resources. Free text boxes were included to provide qualitative data on what was liked and disliked and suggested improvements. A non-parametric paired t-test, the Wilcoxon signed rank test, was used to analyse the results and determine statistical significance.

Results

Fourty-seven healthcare professionals consisting of 18 doctors and 29 nurses participated in seven interprofessional simulation training sessions on the main haemodialysis unit and 26 nurses participated in two satellite haemodialysis unit sessions. Individuals were included in the evaluation if they had completed the matched pre-and post-course questions. Complete response rate was 98% in the main dialysis cohort and 100% in the satellite unit cohort. Of the 73 healthcare professionals who participated, 100% found the course worthwhile.

> “*in situ* inter-professional simulation training improves healthcare workers’ confidence in managing specific medical emergency scenarios”

Mean confidence levels in managing various medical emergencies pre and post interprofessional simulation training on the main haemodialysis unit are shown in Figure 2. The mean confidence level of the participants increased after simulation for all emergency scenarios and was statistically significant for cardiac arrest on dialysis (mean confidence increased from 3.40 to 4.20; p=0.035); gastro intestinal bleed (mean confidence increased from 3.43 to 4.29; p=0.030); seizure management (mean confidence increased from 3.14 to 4.29; p=0.012); anaphylaxis (mean confidence increased from 2.17 to 4.00; p=0.003); and acute psychosis (mean confidence increased from 3.11 to 4.44; p=0.007). Furthermore, participants’ understanding of the skill set of their colleagues working in the MDT increased from a mean of 3.67 to 4.26 (p=0.002), and confidence in locating emergency resources on the dialysis unit increased from a mean of 3.46 to 4.53 (p<0.001).

On the nurse-led satellite unit, a statistically significant increase in confidence was demonstrated in management of a cardiac arrest from 3.33 to 4.58 (p<0.001) and in seizures from 2.79 to 3.93 (p=0.021) – data not shown.

The latent safety threats discovered with *in situ* simulation training, along with interventions to improve patient safety, are shown in Table 1.

Table I. Areas for development in patient safety with proposed solutions

In hospital main unit (interprofessional training)	
Latent safety threats discovered	*Proposed solutions*
• Lack of knowledge of location of oxygen/cardiac arrest trolley and defibrillator • Inefficiencies; e.g., ECG machine not available as shared with another department • Revealed knowledge gaps unknown by both faculty and participants, e.g., 'Can you defibrillate a patient while they were attached to the dialysis machine?'	• *In situ* simulation training • Additional ECG machine has been purchased for the haemodialysis unit • Literature search/review of trust guidelines; education of the team and circulation of learning points to the whole department
Satellite unit (nurse training)	
Latent safety threats discovered	*Proposed solutions*
• Highlighted that staff were not confident managing an acutely unwell patient, e.g: – attaching patient to the defibrillator – giving effective CPR • Highlighted need to improve the quality of referrals from the satellite unit nurses to the doctors in the main renal department	• Regular *in situ* simulation training in the satellite units, including workshops on A to E approach, basic life support and using the defibrillator. The mandatory intermediate life support (ILS) training has been increased to alternate years. Laminated emergency algorithms now displayed to provide guidance • Simulation training now includes handover workshop based on the 'SBAR-D' framework

Discussion

In this report, we show that *in situ* interprofessional simulation training improves healthcare workers' confidence in managing specific medical emergency scenarios in the haemodialysis patient, including cardiac arrest, acute gastro-intestinal bleed, seizures, anaphylaxis and acute psychosis. The training also increased the confidence of the participants' understanding of the skill sets of the MDT and their confidence in locating the emergency resources on the dialysis unit.

While this educational tool is still being piloted and patient outcome measures have therefore not yet been studied, other published reports have demonstrated that simulation can be associated with improved patient outcomes – for example, Theilen *et al.* reported that an *in situ* simulation programme for the emergency paediatric healthcare team resulted in improved recognition and management of deteriorating patients and was associated with significantly reduced hospital mortality.[5]

This study has also highlighted that *in situ* simulation can uncover latent safety threats, leading to initiation of measures to improve patient safety. The simulation training sessions have been instrumental in identifying knowledge gaps and unrecognised learning needs. Performing further regular simulation training can provide a tool to meet these learning needs.

Further research is required to determine if *in situ* simulation does alter key outcome measures, such as patient morbidity and mortality. Future challenges include the sustainability of the programme and consideration of transfer of this training across other haemodialysis programmes in the region and nationally. As the high-fidelity manikin is expensive, a key question would be whether lower-fidelity options could be used with similar results (for example, is it the technology, the scenarios or MDT group training that are the key learning enablers?).

Conclusion

In situ simulation training on the haemodialysis unit can increase confidence in the MDT management of medical emergencies as well as improve their understanding of the skill sets of their colleagues; it can identify latent safety threats and form the basis of clinical improvement projects. This training can offer highly valuable contextualised learning with potential benefits not only for the individual, but also for MDT team-working and patient safety ■

Key points

- An *in situ* interprofessional simulation course was set up on the haemodialysis unit with the aim of improving confidence in managing medical emergencies occurring in the kidney patient on haemodialysis and to improve multidisciplinary team-working on the dialysis unit.
- The training demonstrated increased confidence of individuals in the interprofessional team in managing certain emergencies, in understanding the skill sets of colleagues from the MDT and in locating emergency resources.
- This *in situ* training offers an opportunity to identify latent errors and represents an effective patient-safety initiative.

Acknowledgements
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Declaration of interest
The authors declare there is no conflict of interest.

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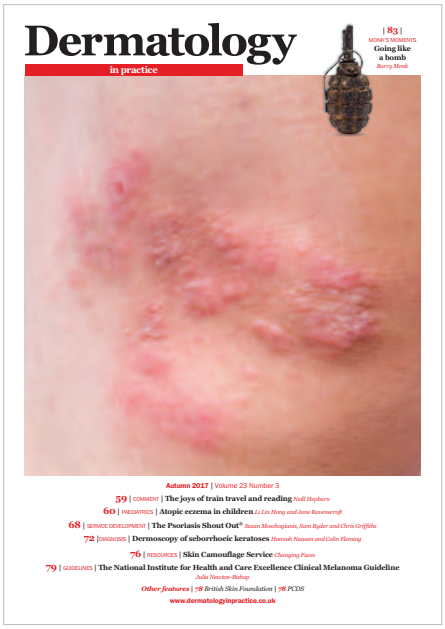

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Caring to change

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Aneurin Bevan's book in *In Place of Fear* describes the background to the foundation of the NHS in 1948. It was an expression of a core national value of compassion: a post-war generation made a commitment to providing free health care for all those who needed it, regardless of status, wealth, ethnicity, age, gender or any other characteristic. Indeed, Bevan even makes the point that 'the cost of looking after the visitor who falls ill cannot amount to more than a negligible fraction of £399,000,000', the total cost of the NHS at its inception. The NHS is our most prized institution and the nation has demonstrated its commitment to this value of a free and inclusive NHS by its fierce and sustained protection of the system over the subsequent 69 years.

Compassion is also fundamental to the work orientation of front-line NHS staff who deliver healthcare in the UK. Virtually all NHS staff have dedicated a major part of their lives to caring for others in their communities, with compassion being their core work value. When NHS and social care professionals work in organisations that mirror that core value, their motivation, well-being and creativity are sustained and nurtured, and they demonstrate compassion in their interactions with patients and carers. Care that is compassionate, rather than uncaring or disempowering, has a positive effect on patient satisfaction and health outcomes. Compassionate care is what patients want and need. The challenge then, in these austere and challenging times, is to nurture a strong culture of compassion in health and social care.

Ahead of the budget, all the major health think tanks, NHS providers, staff unions and Royal Colleges have come out pressing for more money for the NHS. Even Simon Stevens, Chief Executive of NHS England, strayed into the political debate, with his slide of the Brexit bus and its '£350 million a week' more for the NHS, to make the point that the excuse that the cost of Brexit means less for the NHS will not wash with the electorate. However, it is also clear that more money on its own, without transformative change, will not be enough for the NHS to meet the rapidly changing needs and expectations of the communities we serve. While adequate financial support is a necessary precondition, only radical and sustained innovation can enable modern healthcare organisations and systems to meet the current and future needs of our population.

> "The NHS is our most prized institution."

In *Caring to Change*[1] Michael West, a professor of work and organisational psychology at Lancaster University, and colleagues from the King's Fund argue that the evidence of links between psychological safety, supportiveness, positivity, empathy, leadership and innovation is deep and convincing. They challenge the prevailing perspective in economics about the factors influencing innovation, which is based on a somewhat simplistic view of human motivation, far less relevant to the NHS than it is to (at least some) private sector

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organisations. West argues that compassion needs to run through our NHS from top to toe. He makes the point that compassionate leadership enhances the intrinsic motivation of NHS staff and reinforces their fundamental altruism. That it helps to promote a culture of learning, where risk-taking within safe boundaries is encouraged and where there is an acceptance that not all innovation will be successful – an orientation diametrically opposite to a culture characterised by blame, fear and bullying.

Compassion creates psychological safety in our patients and in our colleagues and co-workers. When staff feel confident in speaking out about errors, problems and uncertainties, they also feel empowered and supported to develop and implement ideas for new and improved ways of delivering services. In such an environment, NHS professionals thrive; they work more co-operatively and collaboratively in a compassionate culture, in a climate characterised by cohesion, optimism and efficiency. Compassionate leadership is seen as an enabling condition for innovation across sectors. West proposes it is particularly salient and a cornerstone for sustained innovation in health services because of the need for coherence between the values and behaviours within health care organisations and how they engage with service users.

The aim of innovation is improvement. It's the introduction and application of processes, products, treatment or procedures, new to the team, department, ward, pathway, organisation or system that are intended to benefit patients, staff, the organisation or wider system and society. The same skills and attributes needed for quality improvement and improvement science that result in system-wide learning are necessary prerequisites for a healthcare system that is eager to pull new innovations into its ways of working in order to drive improvement. Innovation includes the implementation of ideas adopted from other organisations and adapted to fit the different context. We need to learn as a whole NHS and from international experience.

Creating the conditions for innovation means giving front-line teams the autonomy to experiment, discover and apply new and improved ways of delivering care. In kidney care it involves creating space and freedom for teams to work across organisational boundaries in networks, to co-operatively work together to listen, to learn and to support improvements and innovation in the care of people with kidney disease.

Caring to Change highlights the need to let go of a command-and-control leadership style and give way to a model of collective and compassionate leadership aligned to the core values of the NHS front-line staff and the public. One that encourages creativity and innovation, that motivates and builds capacity for developing new and improved ways of delivering healthcare.

For innovation and quality improvement to be the texture of NHS organisations, compassion is the golden thread ■

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Ducks not in a row

For a number of years now, governments of all persuasions have favoured devolving power to regional administrations, to councils or to other more local bodies. This might seem strange considering that when entering politics you are perceived to be seeking power – not handing it over. The answer, of course, is that by devolving power, you are removing yourself from any accountability. This is very apparent within the health field, particularly within renal.

It is well reported that A&E departments are overstretched, that the ambulance service is not meeting its 999 attendance targets, and that NHS trusts claim that there is insufficient funding to meet their targets.

But the government (who apportions available funding) claim that A&E departments could manage if people used chemists and GPs more often, that the ambulances would be on time if there were fewer unnecessary calls, or that trusts needed to be more efficient – everybody's fault but their own.

> "it has long been accepted that transport to and from dialysis is an essential part of treatment"

In renal, it has long been accepted that transport to and from dialysis is an essential part of treatment – indeed The National Institute for Health and Clinical Excellence (NICE) guidelines said so in 2006. Anything else is simply unthinkable – dialysis patients are very sick people who are unable to drive themselves, too poorly after dialysis for public transport, and unable to afford taxis as they cannot work and exist on benefit payments.

Why oh why then has Kernow Trust in Cornwall flirted with the crazy decision to ignore NICE guidelines and impose charging on those dialysis patients who do not meet their own brand of 'means testing'? And why is Somerset engaged in a consultation to see whether they might follow suit?

This nonsense must stop before patients choose food and heating rather than dialysis and die. The government should take the lead, halt this dangerous practice and provide sufficient funding so that trusts do not act in this absurd manner ■

Timothy F Statham OBE
Chief Executive
National Kidney Federation

The Renal Association

The Renal Association (RA) has produced guidance on best practice in the management of patients with kidney disease since 1995. These guidelines help identify the data to be collected by the Renal Registry. In January 2016, the RA was successful in regaining The National Institute for Health and Care Excellence (NICE) accreditation for its guidelines. This means that the guidelines will be seen as being produced by rigorous processes as detailed in the guideline development manual. The RA Clinical Practice Guidelines (CPG) committee oversees the development of guidelines. In recent months, the composition of this committee has evolved and it currently comprises three adult nephrologists, a manager, a patient representative, a paediatric nephrologist and a trainee adult nephrologist. We hope that a renal pharmacist will join the committee soon. The role of this committee is to consider which guidelines the RA should continue to produce and which new ones should be commissioned, taking into account feedback from RA members and existing guidelines from other organisations. Expressions of interest in being authors are invited from RA members for all new guidelines or commentaries. All guideline author groups will include a patient representative and many will also include a paediatric nephrologist and pharmacist. Other multidisciplinary team members will be sought when it is relevant for the guideline. The committee monitors the progress of guidelines and oversees their peer-review prior to publication.

The CPG committee has recently developed a strategy that sets out a plan of the work of the committee for the next three years. This strategy was informed by a survey sent to RA members last year. National and International guideline bodies, such as NICE and Kidney Disease Improving Global Outcomes (KDIGO), have significant resources to help authors, with teams of people dedicated to literature search, analysis and writing. RA guideline authors do not have this level of support, although they do now have administrative support with a CPG committee manager. In order to avoid unnecessary duplication, we thought it was important to define the place of RA guidelines in relation to documents produced by these other bodies. In future, the RA will not usually produce a guideline on a topic that is covered by KDIGO or NICE but will produce a commentary stating which recommendations the RA endorses and which it does not. Audit standards may be contained in this commentary. An exception to this may be made if the committee think that the recommendations in a KDIGO or NICE guideline is significantly at variance with UK practice or there are gaps in the scope of the NICE or KDIGO guideline that need to be addressed. Full guidelines will continue to be produced on topics not covered by KDIGO and NICE. These will include smaller topics thought to be important in UK nephrology. New topics will be considered by the guidelines committee if suggestions are received, and we will continue to write joint guidelines with partner professional bodies.

Three guidelines have been published this year, covering peritoneal dialysis, anaemia of chronic kidney disease (CKD) and post-operative care of the kidney transplant recipient (jointly with the British Transplantation Society). A number of guidelines are in progress, including haemodialysis, nutrition in CKD and blood-borne viruses. A commentary on the recent KDIGO guideline on CKD- mineral and bone disorder is also in progress, and a commentary on the imminent KDIGO guideline on evaluation and management of candidates for kidney transplantation will be produced. New RA guidelines on monitoring children and young people with, or at risk of developing, ADPKD, medical management of stone disease, and pregnancy and renal disease are planned. The RA continues to produce regular guidelines and commentaries, usually written in the authors' spare time – a testament to the hard work and commitment of professionals in the UK renal community ■

Michael Robson Chair of the Renal Association Clinical Practice Guidelines Committee and Senior Lecturer and Honorary Consultant Nephrologist, King's College London and Guy's and St Thomas' NHS Foundation Trust.

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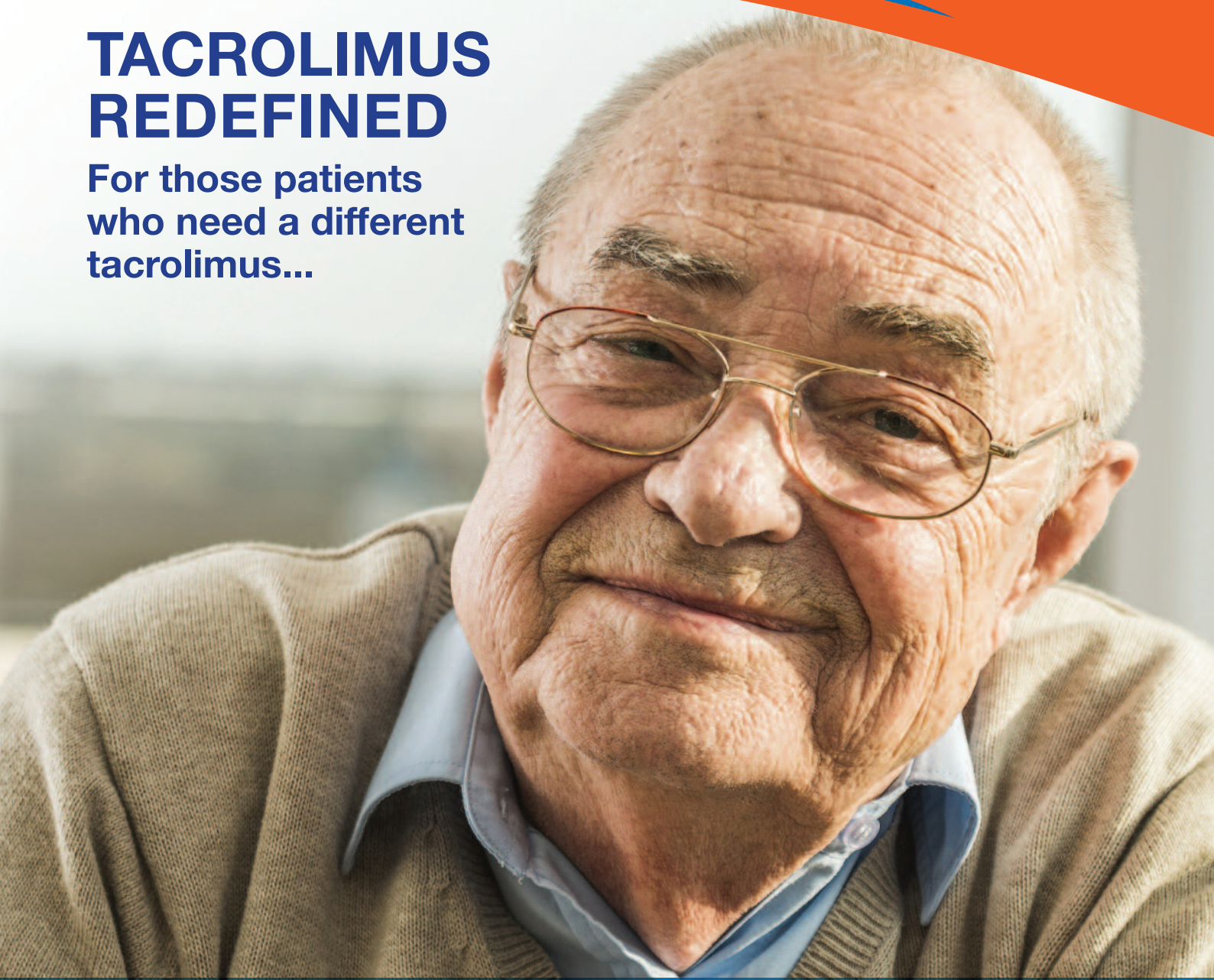

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Chiesi

Prescribing information and references can be found on reverse. Date of Prep: July 2016 CHENV20160322b

Envarsus® 0.75mg, 1mg, 4mg prolonged-release tablet Tacrolimus (as monohydrate) Please refer to Summary of Product Characteristics (SmPC) before prescribing **Prescribing information** **Presentation** Envarsus prolonged-release tablets containing 0.75mg, 1mg and 4mg of tacrolimus (as monohydrate) **Indications** Prophylaxis of transplant rejection in adult kidney or liver allograft recipients and treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients **Dosage and administration** Envarsus is a once-a-day oral formulation of tacrolimus. Envarsus therapy requires careful monitoring by adequately qualified and equipped personnel. This medicinal product should only be prescribed, and changes in immunosuppressive therapy be initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist. The recommended initial doses presented below are intended to act solely as a guideline. Envarsus is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The dose may vary depending upon the immunosuppressive regimen chosen. Envarsus dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring. If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered. As tacrolimus is a substance with low clearance, adjustments to the Envarsus dose regimen may take several days before steady state is achieved. Envarsus doses are usually reduced in the post-transplant period. Post-transplant changes in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments. *Prophylaxis of kidney transplant rejection:* Envarsus therapy should commence at a dose of 0.17 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery. *Prophylaxis of liver transplant rejection:* Envarsus therapy should commence at a dose of 0.11 – 0.13 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery. *Conversion of Prograf- or Advagraf-treated patients to Envarsus - allograft transplant patients:* Allograft transplant patients maintained on twice daily Prograf (immediate-release) or Advagraf (once daily) dosing requiring conversion to once daily Envarsus should be converted on a 1:0.7 (mg:mg) total daily dose basis and the Envarsus maintenance dose should, therefore, be 30% less than the Prograf or Advagraf dose. Envarsus should be administered in the morning. When converting from tacrolimus immediate-release products (e.g. Prograf capsules) or from Advagraf prolonged-release capsules to Envarsus, trough levels should be measured prior to conversion and within two weeks after conversion. Dose adjustments should be made to ensure that similar systemic exposure is maintained after the switch. In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels. In clinical studies patients converted from twice daily Prograf were converted to Envarsus using a 1:0.85 (mg:mg) conversion. *Conversion from ciclosporin to tacrolimus:* Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. The combined administration of ciclosporin and tacrolimus is not recommended. Envarsus therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, tacrolimus-based therapy has been initiated 12 to 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected. *Treatment of allograft rejection:* Increased doses of tacrolimus, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity such as severe adverse reactions are noted, the dose of Envarsus may need to be reduced. *Treatment of allograft rejection after kidney or liver transplantation:* For conversion from other immunosuppressants to once daily Envarsus, treatment should begin with the initial oral dose recommended in kidney and liver transplantation respectively for prophylaxis of transplant rejection. Therapeutic drug monitoring: Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient aided by whole blood tacrolimus trough level monitoring. As an aid to optimise dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood. Comparisons of concentrations from the published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods. The relationship between tacrolimus trough levels and systemic exposure (AUC_{0-24}) is well correlated and is similar between the immediate-release formulation and Envarsus. Blood trough levels of tacrolimus should be monitored during the post-transplantation period. Tacrolimus blood trough levels should be determined approximately 24 hours post-dosing of Envarsus, just prior to the next dose. Blood trough levels of tacrolimus should also be closely monitored following conversion from tacrolimus products, dose adjustments, changes in the immunosuppressive regimen, or co-administration of substances which may alter tacrolimus whole blood concentrations. The frequency of blood level monitoring should be based on clinical needs. As tacrolimus is a substance with low clearance, following adjustments to the Envarsus dose regimen it may take several days before the targeted steady state is achieved. Data from clinical studies suggest that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels. In clinical practice, whole blood trough levels have generally been in the range of 5-20 ng/ml in kidney transplant patients in the early post-transplant period, and 5-15 ng/ml during subsequent maintenance therapy. See SmPC for dosage adjustments in special populations. Method of administration: Envarsus should be taken once daily in the morning, swallowed whole with fluid (preferably water) immediately following removal from the blister. Envarsus should generally be taken on an empty stomach to achieve maximal absorption. **Contraindications** Hypersensitivity to active substance or excipients. Hypersensitivity to macrolides. **Warnings and precautions** Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed with tacrolimus. This has led to serious adverse reactions, including graft rejection, or other adverse reactions which could be a consequence of either under- or over-exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist. Envarsus is not recommended for use in children below 18 years of age due to the limited data on safety and/or efficacy. During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered. Gastrointestinal perforation has been reported in patients treated with tacrolimus, adequate treatments should be considered immediately after suspected symptoms or signs occur. Extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea. Cardiomyopathies have been observed in tacrolimus treated patients on rare occasions. Most cases have been reversible, occurring with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at 3 months and then at 9-12 months). If abnormalities develop, dose reduction of Envarsus or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval, caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome. Patients treated with tacrolimus have been reported to develop EBV-associated lymphoproliferative disorders. Risk factors include using a combination of immunosuppressives, such as antilymphocytic antibodies (e.g. basiliximab, daclizumab) concomitantly, or EBV-Viral Capsid Antigen (VCA)-negative patients. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with Envarsus. Careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma. As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown. Exposure to sunlight and UV light should be limited. Patients treated with immunosuppressants, including Envarsus are at increased risk for opportunistic infections (bacterial, fungal, viral, and protozoal). Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML).These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control, and immediate discontinuation of systemic tacrolimus is advised. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medicinal product associated with PRCA. Dose reduction may be necessary in patients with severe liver impairment. Envarsus contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. (Refer to SmPC for full list of interactions). **Side effects** *Very common:* tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension, insomnia, headache, diarrhoea, nausea, abnormal liver function tests *Common:* anaemia, thrombocytopenia, leukopenia, abnormal red blood cell analyses, leukocytosis, anorexia, metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, decreased appetite, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypophosphataemia, confusion and disorientation, depression, anxiety symptoms, hallucination, mental disorders, depressed mood, mood disorders and disturbances, nightmare, nervous system disorders, seizures, disturbances in consciousness, peripheral neuropathies, dizziness, paraesthesias and dyaesthesias, writing impaired, eye disorders, blurred vision, photophobia, tinnitus, ischaemic coronary artery disorders, tachycardia, thromboembolic and ischaemic events, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders, parenchymal lung disorders, dyspnoea, pleural effusion, cough, pharyngitis, nasal congestion and inflammations, gastro-intestinal (GI) signs and symptoms, vomiting, GI and abdominal pains, GI inflammatory conditions, GI haemorrhages, GI ulceration and perforation, ascites, stomatitis and ulceration, constipation, dyspeptic signs and symptoms, flatulence, bloating and distension, loose stools, bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice, rash, pruritus, alopecias, acne, increased sweating, arthralgia, back pain, muscle cramps, pain in limb, renal failure, acute renal failure, toxic nephropathy, renal tubular necrosis, urinary abnormalities, oliguria, bladder and urethral symptoms, febrile disorders, pain and discomfort, asthenic conditions, oedema, disturbed body temperature perception, increased blood alkaline phosphatase, increased weight, primary graft dysfunction. In clinical studies in kidney transplant patients receiving Envarsus, the most frequent adverse reactions (at least in 2% of patients) were tremor, diabetes mellitus, blood creatinine increased, urinary tract infection, hypertension, BK virus infection, renal impairment, diarrhoea, toxicity to various agents, and toxic nephropathy. Among the most frequent adverse reactions (at least in 2% of patients) in clinical studies in liver transplant patients receiving Envarsus were tremor, headache, fatigue, hyperkalaemia, hypertension, renal failure, blood creatinine increased, dizziness, hepatitis C, muscle spasms, tinea infection, leukopenia, sinusitis, and URTI. *Uncommon:* coagulopathies, pancytopenia, neutropenia, abnormal coagulation and bleeding analyses, dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia, psychotic disorder, encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, speech and language abnormalities, paralysis and paresis, amnesia, cataract, hypoacusis, heart failures, ventricular arrhythmias and cardiac arrest, supraventricular arrhythmias, cardiomyopathies, abnormal ECG investigations, ventricular hypertrophy, palpitations, abnormal heart rate and pulse investigations, deep limb venous thrombosis, shock, infarction, respiratory failures, respiratory tract disorders, asthma, acute and chronic pancreatitis, peritonitis, increased blood amylase, paralytic ileus, gastrooesophageal reflux disease, impaired gastric emptying, dermatitis, photosensitivity, joint disorders, haemolytic uraemic syndrome, anuria, dysmenorrhoea and uterine bleeding, decreased weight, influenza like illness, increased blood lactate dehydrogenase, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance. *Rare:* thrombotic thrombocytopenic purpura, hypoprothrombinaemia, hirsutism, hypertonia, blindness, neurosensory deafness, pericardial effusion, acute respiratory distress syndrome, pancreatic pseudocyst, subileus, veno-occlusive liver disease, hepatic artery thrombosis, toxic epidermal necrolysis (Lyell's syndrome), fall, ulcer, chest tightness, decreased mobility, thirst. *Very rare:* myasthenia, impaired hearing, abnormal echocardiogram, hepatic failure, Stevens Johnson Syndrome, nephropathy, haemorrhagic cystitis, increased fat tissue. *Not Known:* pure red cell aplasia, agranulocytosis, haemolytic anaemia, allergic and anaphylactoid reactions (Refer to SmPC for full list of adverse reactions) **Legal category** POM **Packs and prices** 0.75mg £44.33 1x30 tablets, 1mg £59.10 1x30 tablets, 4mg £236.40 1x30 tablets **Marketing authorisation numbers** EU/1/14/935/001, EU/1/14/935/004, EU/1/14/935/007. 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Understanding human leukocyte antigen typing and crossmatch techniques in renal transplantation

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The human leukocyte antigen (HLA) system, located on the short arm of chromosome 6, has a critical role in the immune response to antigens in organ transplantation; rejection rates of transplanted organs are increased when HLA mismatch is high. The risk of graft rejection is also affected by sensitisation, as highly sensitised patients who have donor-specific anti-HLA antibodies may experience a hyperacute rejection. Detection of anti-HLA antibodies that may cause rejection of the graft is, therefore, a critical step before transplantation.

The methods used to detect anti-HLA antibodies have changed dramatically in recent years. The introduction of complement-dependent cytotoxicity (CDC) assays has brought a major change in the transplantation field, and, since then, newer and better techniques have been improving clinicians' understanding of immunological risk.

HLA: a peek into history

Tremendous progress has been made in the field of kidney transplantation from the late 1950s onwards. This period was marked by the discovery of the HLA system by Jean Dausset and of anti-HLA antibodies by Rose Payne and Jon van Rood, independently, in patients who had received blood transfusions and in multiparous women, respectively.[1–3] Many other HLA antigens were subsequently discovered, including HLA-DR, by Ting and Morris.[1,3] Another milestone in this field was the development of the CDC assay in 1964 by Paul Terasaki, who later also identified that presence of donor-specific antibodies (DSAs) in patients' serum as a predictor of hyperacute rejection of the graft.[1]

Crossmatch techniques continued to evolve, improving the sensitivity and efficacy, and reducing or eliminating the drawbacks of the older techniques. CDC assay was improved as another method gained importance: the antihuman globulin-augmented (AHG-augmented) cytotoxicity assay, which enhanced the sensitivity of CDC, was developed by Johnson *et al.*[4] Later, flow cytometry crossmatching, as well as enzyme-linked immunosorbent assay (ELISA) and Luminex® single-antigen bead (SAB) assays were established, improving scientific accuracy and credibility for predicting the outcome of transplantation.[1,4–6]

HLA inheritance

The HLA system on chromosome 6 is highly gene-dense, containing more than 250 genes, which are inherited together as haplotypes. Inheritance of the haplotype from each parent is co-dominant, so that two forms of the genes (alleles) are expressed at each locus.[3,7]

The alleles from parents are inherited in a Mendelian fashion; for example (using arbitrary values), if the father has haplotypes W, X and the mother Y, Z, then the child can have haplotypes W, Y; W, Z; X, Y and X, Z.[7]

HLA system

The HLA system is divided into two classes:

- HLA class I contains the antigens HLA-A, HLA-B, HLA-C, HLA- E, HLA-F and HLA-G. These are found in all nucleated cells. Their function is to present peptide fragments of foreign proteins to cytotoxic T-lymphocytes.[3,7] HLA-E, HLA-F and HLA-G serve as ligands for receptors of natural killer cells and have been shown to be important in the defence against viruses, such as the cytomegalovirus, post transplantation. These loci may be important in bone marrow transplantation when natural killer cells are involved in rejection. Their relevance in solid-organ transplantation has not been established yet.[3]
- HLA class II contains the antigens HLA-DR, HLA-DQ, and HLA-DP. These are expressed on antigen-presenting cells (monocytes, macrophages and dendritic cells), B-lymphocytes and activated T-lymphocytes.[3,7] HLA class II antigens present peptide fragments of foreign proteins to CD4-positive T-lymphocytes.[3]

HLA nomenclature

HLA nomenclature depends on the typing method, whether serological or molecular. The serological method became available for testing first, and many HLA antigens were discovered using this method. They were named in order of their discovery – HLA-A1, HLA-A2 and so on. With refinement of serological technique, some antigens that were earlier thought to be one entity were later found to be two; for example, B40 was later discovered to in fact be two antigens, named B60 and B61.[8]

Serological methods were found to be inadequate to fully define the HLA antigens, with molecular methods proving to be far superior in classifying the HLA

antigens in detail.[8] A new nomenclature for HLA, based on molecular methods, came into existence in 1987. The complexities of nomenclature have increased with molecular methods for typing, as these methods provide high-resolution differentiation between HLA specificities.[8] With this form of nomenclature, the prefix HLA is followed by the locus, followed by an asterisk. The two digits that follow indicate the group of alleles and the next two the unique allele, while further digits may be added to indicate silent mutations and polymorphism in non-coding regions. In 2010, a colon was introduced to separate the two-digit entities; for example, HLA-A*01:01:01.[2,8] The World Health Organization Nomenclature Committee for Factors of the HLA system standardises the nomenclature of the HLA system.[7]

An antigen initially thought to have a single specificity is sometimes found to consist of two or more entities with different specificities. These called 'splits' of the original antigen; for example, HLA-A9 (broad specificity) can be divided into HLA-A23 and HLA-A24 (split specificity).[3]

Null alleles

Null alleles are those that lack in expression of corresponding proteins on the plasma membrane. Although null alleles are found in both HLA I and HLA II classes, most are located in HLA-A and HLA-B loci. Null alleles may cause significant problems in transplantation. A patient with a null allele for a particular HLA may still produce antibodies against that particular antigen. A donor with that specific antigen should, therefore, not be considered as a zero mismatch if the recipient has a null allele for that antigen.[9]

HLA typing

HLA typing of a transplant donor and recipient to assess HLA matching, and improve graft and patient survival, can be undertaken by a number of methods.[7,8,10–14]

Serological methods

Serological methods use sera from individuals who have been sensitised to foreign antigens (usually from multiparous females sensitised during pregnancy) and express anti-HLA antibodies against a number of HLA antigens. Monoclonal antibodies that bind to the tertiary HLA glycoprotein epitopes on the surface of cells can also be used.[3,7,8]

In this method, multiwell plates are used, with each well containing serum with known antibodies against a specific HLA. Lymphocytes from the person being tested are incubated in the wells and, depending on the specificity, antibodies in the serum attach to the lymphocytes (if the specific HLA is present on the lymphocytes). Complement (derived from rabbit serum) is added. In the wells in which antibodies are bound to lymphocytes, the addition of complement results in lysis of the lymphocytes and, hence, detection of HLA types.[7,8]

Advantages of serological method

- It is rapid; hence, it can be used for HLA typing in deceased donors, when saving time means reducing the cold ischaemia time and reducing the risk of delayed graft function.[8]
- It is helpful in detecting null alleles, which can be missed with other methods.[8]

> "Human leukocyte antigen matching remains one of the most important techniques for modifying risk factors in renal transplantation"

Disadvantages of serological method

- Finding sera containing anti-HLA antibodies against the large number of different HLA antigens is difficult; for example, the availability of serological test to detect HLA-Cw, DP and DQ is limited.[8]
- Very minor differences between HLA antigens (differences at amino acid level) are difficult to detect using serological assays; for these, molecular methods need to be used.[8]

Molecular methods

Molecular typing (DNA-based) methods have enabled high-resolution HLA typing. This has resulted in rapid progress in identification of HLA antigens, and also of different specificities of an HLA allele; for example, DNA-based molecular methods of HLA typing have identified more than 1,000 DR HLA-DR allele specificities to date, while the relatively crude serological methods could identify 19 only.[3]

Molecular methods of HLA typing include:

- sequence-specific oligonucleotide probes (SSOP)[8,15]
- sequence-specific primer polymerase chain reaction (SSP-PCR)[8,15]
- direct DNA sequencing.[8]

These methods have reduced errors in HLA typing.[16] Molecular techniques, especially the PCR-SSP method, are being favoured over serological testing in an increasing number of laboratories.[16–19] Molecular methods provide both high-resolution HLA typing and matching (to the level of a single amino acid difference between donor and recipient alleles) and low-resolution (generic) DNA typing, enabling identification of broad and split HLA specificity.[3]

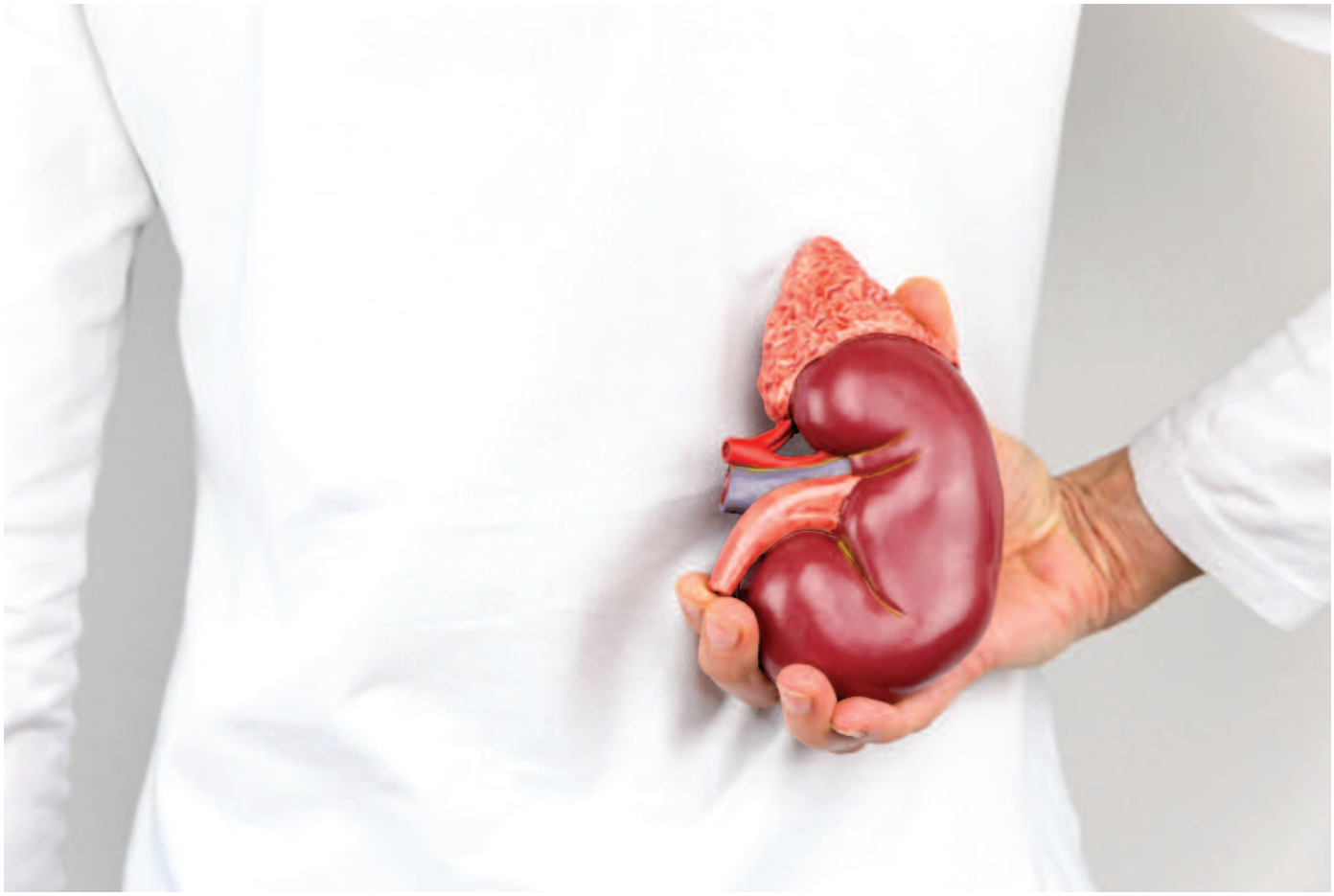
DNA typing targets specific genetic regions and may not target the nucleic acid sequence of a null allele. This means that DNA methods may actually fail in detecting a null allele and serological methods may be required to detect this.[9]

Significance of HLA matching

HLA matching remains one of the most important techniques for modifying risk factors in renal transplantation.[10–14] Even a single HLA mismatch can result in a poorer outcome,[14] with HLA-DR matching found to have a greater effect on graft survival than HLA-A and HLA-B matching.[12,14]

Other antigens that can lead to graft rejection

- Minor histocompatibility antigens (MiHA) are small endogenous peptides that occupy the antigen-presenting sites of major histocompatibility complex (MHC) and can be recognised by T-cells, causing graft rejection. The H-Y MiHA is encoded by the Y chromosome and can elicit an immunological response, leading to graft rejection when a male organ is transplanted to a female.[20]
- MHC class I-related chains A (MICA) and B (MICB) are expressed in endothelial cells. Antibodies against MICA and MICB can cause graft rejection.[20]
- Anti-angiotensin-2 receptor, anti-glutathione S-transferase T1 and anti-endothelial antibodies may cause



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antibody-mediated rejection. Anti-endothelial antibodies may be tested by using monocytes for crossmatch.[20]

Sensitisation

A person may become sensitised to HLA antigens (develop antibodies against foreign HLA antigen) in three important ways: blood transfusion, pregnancy and previous organ transplantation.[3,7] In some people, anti-HLA antibodies may be detected even when they have not been exposed to the three factors mentioned above. This may occur due to cross-reactivity with infectious agents. Such antibodies are reactive against denatured HLA antigens (not intact HLA antigens) and are generally not significant in kidney transplantation.[3]

Detection of HLA-specific antibodies: crossmatch techniques

HLA-specific antibodies may be detected by:

- antigen-non-specific tests; for example, CDC, AHG-enhanced cytotoxicity crossmatch and flow cytometry crossmatch [21,22]
- antigen-specific tests; for example, solid-phase antibody detection assays such as ELISA or Luminex SAB technology.[21,22] Over the last decade, Luminex SAB technology has become the gold standard for detecting anti-HLA antibodies.[22]

CDC crossmatch

Lymphocytes that express HLA antigens are used for the test. The CDC crossmatch provides direct evidence of the presence in patients of donor-specific anti-HLA antibodies against donor lymphocytes.[23–25] The CDC crossmatch, also called microlymphocytotoxicity assay, was developed by Terasaki *et al* in the 1960s and involves incubating the potential recipient's serum, which may contain anti-HLA antibodies, with the potential donor's lymphocytes, which express HLA antigens.[5] Rabbit serum containing complement is added to this incubated sample.[22] If anti-HLA antibodies are present, CDC becomes evident as cell lysis.[22] Cell lysis is reported as either a percentage of lysed lymphocytes relative to live lymphocytes or as the amount of dilution needed to render the result crossmatch negative (the higher the dilution needed, the higher the titre of antibodies).[5]

The CDC crossmatch detects both HLA and non-HLA complement-fixing antibodies of the immunoglobulin (Ig) G and M classes.[23] The IgG class antibodies detected, IgG1 and IgG3, are critical for graft rejection,[26] whereas the IgM class antibodies detected by CDC do not play any significant role in rejection.[22]

The target cells used to determine a crossmatch are donor lymphocytes. T-lymphocytes express HLA class I antigens, as well as non-HLA antigens. B-lymphocytes express both HLA Class I and HLA Class II antigens, as well as non-HLA antigens.[8,23] In general, if a CDC crossmatch is negative for T-lymphocytes and positive for B-lymphocytes, it means that the crossmatch is positive due to the presence of HLA class II antibodies. Similarly, if the test is positive for both T- and B-lymphocytes, this implies positivity due to class I antibodies.[8]

B-lymphocyte CDC crossmatch positivity confers a higher risk for kidney transplantation and is an independent risk factor for acute rejection and graft loss, compared with a B-lymphocyte CDC negative crossmatch.[27]

One of the problems with the CDC test is that it is dependent on the viability of donor lymphocytes – a viability of less than 90% may give rise to unpredictable results.[28]

False positive CDC crossmatch

A positive CDC crossmatch can occur in patients with lupus nephritis. A negative ELISA-based crossmatch result in these patients suggests that the CDC-based result is a false positive.[29,30] Renal transplantation may cautiously progress in such cases.[31]

Irrelevant positive CDC crossmatch

The presence of IgM antibodies may result in a positive CDC test; however, these, especially if they are autoantibodies, are not usually significant in contributing to rejection. It is desirable to eliminate the effect of these antibodies on the CDC test to obtain a more dependable result.[5,22,32] Negating the effect of IgM on the CDC test can be achieved by performing an auto-crossmatch, adding dithioerythritol (DTE) or dithiothreitol (DTT), or by heat inactivation.[5,28,33,34]

- In an auto-crossmatch, the recipient's serum is incubated with their own lymphocytes, and complement derived from rabbit serum is added (as in a regular CDC test) to look for lysis of the lymphocytes.[5] If autoantibodies have resulted in a positive CDC test, the auto-crossmatch will show a positive result, indicating that it might be safe to go ahead with transplantation.
- DTE and DTT (also called Cleland's reagent) are reducing agents. When a CDC test is repeated with the addition of DTE or DTT,[5,20,32,33,35] these agents reduce the disulphide bonds in IgM, negate the effect of IgM and generally render the crossmatch negative, if the positive CDC result was due to IgM antibodies.[5,20,32,35]
- Heat inactivation involves heating the recipient's serum by incubating it at 55 °C (131 °F). This disrupts the disulphide bonds in IgM antibodies and renders them inactive.[33,34,36]

False negative CDC crossmatch

Another major problem that can occur with a CDC crossmatch is a false negative result. When this happens, transplant recipients can experience early rejection and graft loss despite a negative crossmatch result.[4,37] This has prompted the scientific world to develop methods to augment the sensitivity of the CDC test. Some noteworthy methods are the addition of AHG, prolonged or extended incubation, or an Amos wash.

- The addition of AHG augments the sensitivity of CDC.[4] This test was developed by Johnson *et al* in 1972 and involves adding a complement-fixing AHG (for example, goat-antihuman light chain) to the recipient's incubated serum with lymphocytes from the donor, before the complement (from rabbit serum) is added and the serum is analysed for lysed lymphocytes.[4] AHG molecules bind to donor-specific HLA antibodies in the recipient's serum, thereby increasing the total number of receptors available for binding with the complement.[5,20,22,28]
- Prolonged or extended incubation can be used to make the CDC test more sensitive.[4,22]

> "Solid-phase antibody testing ... has eliminated many of the problems associated with cellular assays"

- An Amos wash (3-Wash) or Amos wash modified (1-Wash) can be performed after the serum from the recipient is mixed with donor lymphocytes. The washes remove the unbound serum, thereby removing the anticomplementary factors that interfere with the crossmatch and render the test falsely negative. Rabbit serum containing complement is added after this, as in a standard CDC test.[4]

Flow cytometry crossmatch

Flow cytometry was developed by Leonard and Leonore Herzenberg and colleagues[6] and was first described in 1983.[5] It is more sensitive (estimates suggest about 50 times more sensitive) than the standard CDC test,[23,38] and is also more sensitive than an AHG-CDC test.[20] Like the CDC crossmatch, flow cytometry detects both HLA and non-HLA antibodies. It detects all IgG subclasses, both complement-fixing and non-complement-fixing, as it is highly sensitive;[23,26] hence, it can detect some antibodies that CDC is unable to detect.[23]

In flow cytometry, the first step is the same as for the CDC test: recipient serum is incubated with donor lymphocytes. After this, fluorochrome-conjugated anti-IgG antibodies are added that bind only if IgG DSAs are bound to the donor lymphocytes. Additional antibodies conjugated with different fluorochromes identifying specific T- and B-lymphocytes may be added to identify DSAs attached to these T- or B-lymphocyes.[8] Moreover, subclasses of anti-IgG antibodies may be used; for example, antibodies that bind with IgG1, 2, 3 or 4. That way, the result can be refined further, directing the test to be more specific. This can be used to determine the likelihood of *in vivo* complement activation, as IgG4 does not activate complement.[5]

Flow cytometry can rapidly analyse a large number of cells (5,000 to 10,000 cells in less than a minute). It is much faster and more accurate than the CDC assay, which involves a tiresome, manual study of 200 cells under a microscope.[8,38]

If the CDC assay is negative and flow cytometry is positive, the patient may have an increased risk of early graft loss, and this may be a relative contraindication to transplantation.[31]

Solid-phase antibody testing

Solid-phase antibody testing has brought a major leap in the testing of DSAs,[39] having eliminated many of the problems associated with cellular assays, such as:

- dependence on the viability of lymphocytes: unlike cellular assays, solid-phase immunoassays do not depend on donor lymphocytes; hence, the problem of viability of lymphocytes is completely circumvented[37]
- the detection of HLA and non-HLA antibodies: while cellular assays are exposed to both HLA and non-HLA antigens on donor lymphocytes, solid-phase immunoassays use specific HLA targets for testing, so only HLA antibodies are detected[37]
- the effect of IgM antibodies on the test result: solid-phase immunoassays do not detect IgM antibodies.[2,40]

One of the limitations of solid-phase immunoassays is that they detect both complement-binding and non-complement-binding antibodies.[8,29] In addition, a detectable antibody can be so low in titre that it may not be clinically significant.[8]

Solid-phase antibody testing is performed by ELISA or the Luminex SAB technique.[23,29,39] Both the Luminex SAB and ELISA test are more sensitive and specific than the CDC technique.[23]

ELISA testing uses purified soluble HLAs, usually derived from Epstein–Barr virus-transformed cell lines. Lymphocytes and other cells are not used as targets for HLA antibodies.[2,22] The technique was first described in 1993 and adapted for detecting anti-HLA antibodies in 1995, when HLA antigens were directly fixed on to microtitre plates or wells used to test for DSAs.[2,22,37] The technique detects only anti-HLA antibodies and can distinguish between those targeting class I and those targeting class II HLA.[2] It utilises alkaline phosphatase-conjugated antibody that binds to human IgG, and eliminates detecting IgM antibodies; hence, it proves to be much more specific than the CDC crossmatch test. Enzyme substrate added to the testing mixture is dephosphorylated by the alkaline phosphatase, which results in a colour change that can be read by spectrophotometry.[2,22,40] One of the drawbacks of the ELISA technique is that it does not differentiate between complement-fixing and non-complement-fixing antibodies.[22]

The Luminex SAB technique has gained importance in testing for DSAs in the last few years.[41] This technique uses synthetic polystyrene microspheres (beads) coated with recombinant soluble HLAs.[23,29,37,39,41] Each bead contains an embedded fluorochrome, and a single HLA molecule is attached to it (SAB) to detect anti-HLA antibodies in the recipient's serum with high specificity.[22,37] When the recipient's serum is added to the beads, anti-HLA antibodies bind to the beads that have the corresponding antigens. Phycoerytherin-labelled anti-human IgG is then added, which binds to the anti-HLA antibodies attached to the beads. This is passed through a laser that excites the phycoerythrin and the beads, allowing analysis by flow cytometry or Luminex fluorocytometry.[2,22,37] Luminex SAB testing detects both complement-fixing, and non-complement-fixing antibodies. It does not detect IgM antibodies or non-HLA antibodies.[37] The result is presented as the mean fluorescence intensity (MFI), a readout of the degree of fluorescence, which depicts the presence of DSAs in a sample. The higher the MFI, the higher the DSA level.[2,37]

Prozone phenomenon

When performing a Luminex SAB test, a diluted serum may sometimes result in a higher MFI than the undiluted serum (contrary to expectation), due to an inhibitory effect in the undiluted serum that dissipates upon dilution. This is called the prozone phenomenon, or the hook effect.[22,42] Possible explanations of the inhibitory effect observed in the prozone phenomenon are:

> "In deceased-donor programmes, kidneys are allocated to recipients according to human leukocyte antigen matching"

- the presence of IgM antibodies against an HLA, which block the binding site for IgG antibodies with the same HLA specificity. On dilution, the effect of IgM antibodies, which are lower in titre, wanes [22,42]
- the effect of the C3 component of complement, which is a product of C1. C3 binds to the Luminex beads and, hence, inhibits the binding of IgG antibodies.[22]

The problem of the prozone phenomenon can be solved by:

- pre-heating the serum sample: this destroys the complement activity (especially that of the C1 component) and inactivates IgM [22,33,34,36,42]
- adding ethylenediaminetetraacetic acid (EDTA) to the serum sample [22,42]
- adding DTT, which reduces disulphide bonds in IgM, rendering it inactive [5,20,22,32,35,42]
- freeze–thaw cycles [43]
- adding a C1 inhibitor.[42]

Transplantation programmes

Kidney transplantation can be performed from either a deceased or a live donor. Graft and patient survival are reduced following transplantation from a deceased donor, when compared with a live-donor transplantation. In deceased-donor programmes, kidneys are allocated to recipients according to HLA matching. In addition, many transplantation programmes assess the presence of DSAs in the recipient.[23,37]

To determine how likely it is that a suitable, crossmatch-compatible donor is found for a prospective recipient, the recipient is required to undergo a panel reactive antibody (PRA) test.[44]

Panel-reactive antibody test

The PRA test has been a recognised measure of sensitisation since the 1960s. In this method, HLAs from a panel of donors that represent the local population are identified. Potential recipients are tested for antibodies against these HLAs from the panel of donors. PRAs are calculated as the percentage of these predefined antigens to which the recipient has reactive antibodies.[44] The PRA value indirectly provides an estimate of the percentage of the local population that has the HLAs against which the recipient has antibodies; for example, if a recipient's PRA level is 60%, this means they have HLA antibodies against 60% of the donors in the local population and these donors will not be crossmatch-compatible.[37,44]

Highly sensitised patients (PRA >80%) usually have to wait longer for a transplant, as it is less likely that a suitable crossmatch-compatible donor is found. A study in Australia showed that highly sensitised individuals might have to wait twice as long for a kidney from a deceased donor as those who are not sensitised.[37]

Disadvantages of the PRA test include:

- it may be calculated by different tests with different sensitivities, which means that some laboratories will report a lower PRA value (those that use a less sensitive test to detect HLA antibodies) than others (those that use a more sensitive test) [37,44]
- autoantibodies may lead to a false positive result and a spuriously high PRA value if a CDC assay is used to calculate the PRA value.[23]

Calculated PRA test

The calculated PRA (cPRA) test is now a more commonly used test than the PRA test.[23] The calculation is based on unacceptable HLAs to which the patient is sensitised; that is, HLAs in the donor that would pose an unacceptably high risk for graft survival in a sensitised patient. Anti-

HLA antibodies in the recipient are tested against the HLA frequencies from thousands of kidney donors (a large number of actual organ donors who have one or more of the unacceptable HLA antigens). The higher the cPRA level, the lower the chances finding a suitable donor for the patient.[44]

Virtual crossmatch

A standard laboratory crossmatch is time-consuming and, more recently, a method called virtual crossmatch has been developed. This is swift, reduces the cold ischaemia time considerably and reduces the chance of delayed graft function.[23,37] A virtual crossmatch is not a true crossmatch in the sense that the recipient's serum is not mixed with cells in a test tube; rather, anti-HLA antibodies in the recipient's blood are evaluated against a panel of selected HLAs in prospective donors.[8,20]

The antibody and virtual crossmatch results may change over time as a result of numerous factors, including pregnancies or blood transfusions, so a recent (less than three to six months old) virtual crossmatch result is required to make a good judgement.[8]

A negative virtual crossmatch is a reliable indicator of a negative laboratory crossmatch and may, therefore, avoid the need for a prospective laboratory crossmatch; however, a positive virtual crossmatch is not always associated with a positive laboratory crossmatch, as it may be due to antibodies directed against epitopes on the surface of denatured antigens.

Consideration of the antibody specificity, the strength of the reaction and, where known, the patient's exposure to potential sensitising events is important in the risk analysis in such cases.[23] If a virtual crossmatch shows HLA antibodies that are not against the donor but are directed against other HLA antigens (called third-party HLA antibodies), this may imply a reduced graft survival compared with cases with no third-party HLA antibodies.[5]

Cellular crossmatch

We have discussed crossmatch techniques for donor-specific anti-HLA antibodies that may cause rejection. Rejection may also occur due to sensitisation of the cellular arm of the immune system in the recipient. Experimental methods that can test for sensitisation of the cellular arm of the immune system include the enzyme-linked immunospot (ELISPOT) assay.[5,45]

ELISPOT assay

The ELISPOT assay is a cytokine assay that detects the release of cytokines such as interferon gamma when recipient T-lymphocytes encounter antigen-presenting cells from the donor. In this test, plates are coated with an antibody to capture a specific cytokine. The donor and recipient lymphocytes are mixed and incubated on the plate. Then the mixture is washed, removing the cells, and a second antibody for the specific cytokine is added. After staining for that antibody, the results are read.[5]

Studies have shown that high levels of donor-reactive T-lymphocytes are associated with graft rejection.[5] If increased levels of lymphocytes producing cytokines such as interferon gamma are detected during post-transplant monitoring, this may independently predict an adverse graft outcome.[46]

A pre-transplant ELISPOT test may be useful in individualising the dose of anti-thymocyte globulin (ATG), which is used during induction therapy to deplete preformed memory T-lymphocytes that can result in graft rejection.[45] The ELISPOT test can categorise recipients into high- and low-risk groups based on the cellular reactivity. Decreasing the dose of ATG in low-risk groups may decrease the risk of malignancies and infections due to use of ATG. This remains a matter of controversy, however, and further studies are needed to arrive at a decisive guideline.[45]

Other options for improving transplantation outcomes

Matching cross-reactive groups, epitope matching and peptide motif matching may offer additional advantages to conventional HLA matching.[12] The computer algorithm 'HLAMatchmaker' may further augment the probability of transplantation success in cases of HLA mismatchs.[12] HLAMatchmaker helps in HLA matching at epitope level and analyses amino acid triplet differences in mismatched HLAs, as well as predicting the presence of anti-HLA antibodies.[12,47] The fewer triplet differences, the better the chances of graft survival. This is particularly beneficial for patients with a high immunological risk of graft rejection.[12]

Conclusions

HLA matching has a pivotal role in deciding the success of a transplant. The fewer HLA mismatches, the better the chances of graft survival. HLA-DR mismatch has the worst outcome, when compared with mismatches at HLA-A and HLA-B loci.

Crossmatch testing for DSAs (sensitisation) is essential, and the results have a profound impact on decision-making regarding transplantation. The probability of acute rejection of a transplanted organ is very high in highly sensitised recipients. CDC crossmatch is the cornerstone of DSA testing. CDC crossmatch results should be followed by flow cytometry crossmatch

Key points

- The human leukocyte antigen system plays a critical role in the immune response to antigens in organ transplantation, and rejection rates of transplanted organs are increased when HLA mismatch is high.
- Highly sensitised patients who have donor-specific anti-HLA antibodies may experience a hyperacute rejection, and detection of anti-HLA antibodies is, therefore, a critical step before transplantation.
- Crossmatching techniques developed over the last five decades include complement-dependent cytotoxicity (CDC), antihuman globulin-enhanced CDC and flow cytometry crossmatching, enzyme-linked immunosorbent assay (ELISA), Luminex single-antigen bead technology and, most recently, virtual crossmatching.
- HLA matching, as well as evolving lymphocyte crossmatching techniques with improved sensitivity and specificity, has improved transplantation outcomes.

and/or Luminex SAB tests, to better understand the crossmatch results.

Other modalities of tests exist to further quantify the risk and outcome of transplantation, and one of the most noteworthy is the virtual crossmatch. In this test, anti-HLA antibodies in the prospective recipient are quantified through flow cytometry or Luminex SAB, while HLA testing is performed in the prospective donor. Based on the results, the physical (laboratory) crossmatch results can be estimated. This method can, therefore, obviate the need for a laboratory crossmatch just before transplantation, which can reduce the cold storage (and, hence, cold ischaemia) time, thereby reducing the risk of delayed graft function ■

Declaration of interest
The authors declare that there is no conflict of interest.

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How to join the British Renal Society

I'm regularly asked the question, 'How can I become a member of the BRS?' and so I thought I would use my column in this issue to explain. The BRS is an association of affiliated organisations and therefore it has no individual members, but that doesn't mean that you can't 'join'. The way to join the BRS is to get involved in its multiple different activities. The core aim of the BRS is promote 'effective patient-centred multi-professional care to improve quality of life for people with kidney failure, their families and carers'. To achieve this, the fifteen Affiliate organisations work together and are led by the BRS Officers, comprising of a President, Immediate Past President or President-Elect, Treasurer, four Vice Presidents (Research, Education, Clinical Practice and Clinical Development) and the Communications Secretary. The Vice Presidents are each supported in their roles by a committee and Deputy Vice Presidents. In addition to the Affiliates, there are Special Interest Groups, formed to focus on specific strategic areas, currently Vascular Access, Rehabilitation, Transitional Care and Shared Decision Making. So, how can you join the BRS?

- Sign up to receive emails about events and activities by emailing brs@britishrenal.org
- Follow the BRS on Twitter (@britrenalsoc)
- Join one of our Affiliates (see our website: www.britishrenal.org)
- Volunteer to join one of the Vice Presidents' Committees
- Join a Special Interest Group
- Apply for research grant funding through the annual grant round (in association with Kidney Care UK) – applications are closed for 2017 but start planning for 2018
- Join us at UK Kidney Week 2018, to be held in association with the Renal Association in Harrogate from 19–21 June. Submit an abstract to present your quality improvement project or research and come with your colleagues for an opportunity to network, update your knowledge of best practice and see the latest research presented (see www.ukkw.org.uk)

The BRS is a dynamic community of people who are passionate about improving the quality of the care we deliver to our patients. We would like to see many more of the thousands of staff who work in renal units across all professional groups get involved, so please join us and bring your enthusiasm! ■

Maarten Taal
BRS President

Cyanosis in the renal transplant recipient – broadening the differential

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***Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) pneumonia (PCP), an opportunistic infection with a high mortality rate, is a significant complication of immunosuppression following renal transplantation.[1] Use of first-line antimicrobials may be limited by hyperkalaemia, necessitating second-line agents. We present a case of acute cyanosis secondary to second-line treatment for PCP.**

Case report

A 59-year-old male renal transplant recipient was admitted from the outpatient clinic with a three-week history of exertional breathlessness, as well as relative hypotension and a peripheral oxygen saturation measured by pulse oximetry (SpO2) of 95% on air. He received intravenous (IV) rehydration, his antihypertensive medications (including an angiotensin-converting enzyme inhibitor) were discontinued and he was commenced on antibiotics. On admission, he required 2–5 l/min oxygen to maintain his SpO2 ≥94% and his serum creatinine level was 170 µmol/l. Of his immunosuppressant medications, mycophenolate mofetil and tacrolimus were withheld, while his prednisolone dosage was increased. Within the first 24 hours, his presentation and radiographs suggested PCP infection, and he was commenced on high-dose co-trimoxazole. An urgent bronchoscopy on Day 2 confirmed PCP. He developed a marked rise in serum creatinine levels (peak 494 µmol/l) and severe hyperkalaemia (peak 6.9 mmol/l), necessitating a change in treatment by Day 4. Co-trimoxazole was substituted with the combination

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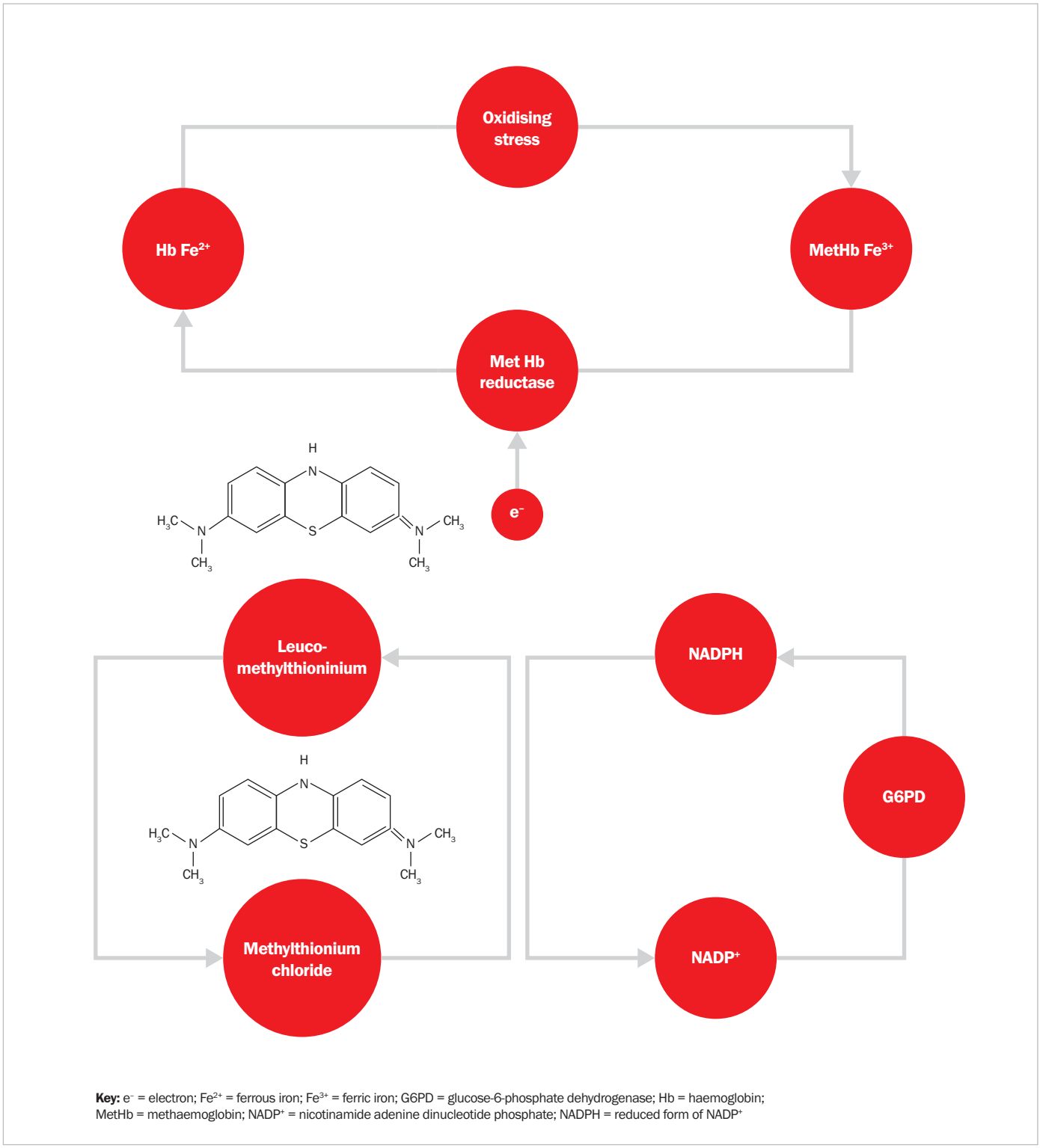

Key: e^- = electron; Fe^{2+} = ferrous iron; Fe^{3+} = ferric iron; G6PD = glucose-6-phosphate dehydrogenase; Hb = haemoglobin; MetHb = methaemoglobin; $NADP^+$ = nicotinamide adenine dinucleotide phosphate; NADPH = reduced form of $NADP^+$

■ **Figure I.** A diagram showing the mechanism by which methylthioninium chloride reduces methaemoglobin to haemoglobin. In health, oxidative stressors produce low levels (<1%) of oxidised iron (ferric iron) within haemoglobin. This is readily reduced by methaemoglobin reductase or, to a lesser extent, the NADPH pathway, which requires extrinsically administered electron carriers. Administration of intravenous methylthioninium chloride provides such a carrier, promoting reduction of ferric to ferrous iron in situations of increased oxidative stress

of primaquine and clindamycin. He continued IV hydration over the following days, before developing pulmonary oedema requiring treatment, with an IV diuretic administered to good effect. By Day 12, his renal function was recovering.

Nine days following the switch in antibiotics, he became acutely hypoxic (SpO2 85%) and was commenced on high-flow oxygen (≥10 l/min). His SpO2 improved to no more than 92% and he remained visibly cyanosed, although, remarkably, undistressed. Neither his clinical examination nor chest X-ray offered an explanation for this deterioration. Arterial blood gas sampling revealed a partial pressure of oxygen of 23.6 kPa, partial pressure of carbon dioxide of 3.4 kPa, oxygen saturation (SO2) of 99.6%, oxyhaemoglobin concentration of 78.8% and methaemoglobin concentration of 20.9%. A diagnosis of

primaquine-induced methaemoglobinaemia was made. A single dose of 100 mg IV methylthioninium chloride was administered and his oxygen requirements fell within 30 minutes. A repeat blood gas sample revealed a reduction in methaemoglobin concentration to 5.2%. Primaquine was discontinued and, following discussion with the local infectious diseases team, co-trimoxazole was re-commenced at a lower dose. He remained an inpatient for a further 12 days, during which his condition improved, with no significant deterioration in renal function. His methaemoglobin concentration was 3.5% at discharge. Methaemoglobin reductase levels and a screening test for glucose-6-phosphate dehydrogenase (G6PD) deficiency were within normal limits. Outpatient review is ongoing. His serum creatinine levels are around 200 µmol/l and he is recovering well.

Discussion

The diagnosis of PCP, historically reserved for those with HIV, is increasingly seen among those immunosuppressed after solid organ transplantation.[2] Caused by a ubiquitous airborne organism, PCP infection must be considered in all transplant recipients, particularly within the first year of transplantation, although cases have been reported as long as 15 years' post-transplantation.[3] With an increasingly prevalent transplant population, vigilance and awareness of PCP complications – including iatrogenic ones – are essential. For those who are intolerant to the first-line treatment of co-trimoxazole, alternative agents include primaquine and clindamycin combination treatment, dapsone, atovaquone or nebulised pentamidine, each of which has its own undesirable side-effect profile.

On immediate assessment, the differential diagnosis lay between worsening PCP and a further episode of pulmonary oedema, but neither diagnosis was consistent with the clinical presentation. Arterial blood gas sampling demonstrated a 'saturation-gap'[4] – the finding of an SO2 of 99.6% compared with the pulse oximeter's reading of 85% – with a methaemoglobin level of 20.9% confirming the diagnosis. Where point-of-care blood gas analysis to provide confirmatory methaemoglobin levels is unavailable, the combination of a saturation gap and absence of radiographic signs are clues to the diagnosis.

> "The diagnosis of *Pneumocystis jirovecii* pneumonia [...] is increasingly seen among those immunosuppressed after solid organ transplantation."

In healthy individuals, endogenous oxidative stressors act on haemoglobin to oxidise its ferrous iron, resulting in insignificant levels of methaemoglobin (<1%). Methaemoglobin reductase reduces ferric iron to its ferrous state, maintaining homeostasis.[5] Methaemoglobin lacks oxygen-carrying capacity, resulting in cellular hypoxia. Causes of methaemoglobinaemia are divided into inherited or acquired and we describe a case who has acquired the condition during treatment with primaquine. Of note, both prophylactic and treatment doses of drugs commonly used for PCP, such as co-trimoxazole or dapsone, are also capable of causing methaemoglobinaemia.

Once diagnosed, treatment of methaemoglobinaemia consists of removing the offending agent and use of IV methylthioninium chloride (1–2 mg/kg as a single IV dose), which reduces methaemoglobin to haemoglobin (see Figure 1). This can be repeated every 30–60 minutes, as necessary. IV methylthioninium chloride is relatively contraindicated in G6PD deficiency, where alternative treatments include hyperbaric oxygen and exchange transfusion.[6]

The case presented here highlights the importance of considering alternative causes of cyanosis in a patient with PCP in an era of increasing PCP prevalence and use of less familiar treatments. This patient suffered an unusual but recognised side effect of primaquine use, confirmed via point-of-care blood gas analysis and rapidly reversed with IV methylthioninium chloride. Nephrologists should be vigilant to this reversible complication ■

Declaration of interest
The authors declare that there is no conflict of interest.

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Key points

- *Pneumocystis jirovecii* pneumonia (PCP) is an increasingly common clinical presentation in renal transplant recipients.
- Methaemoglobinaemia is an uncommon but rapidly reversible complication of PCP treatment, presenting as hypoxia or cyanosis, which may be confused with worsening pneumonia.
- When suspected, point-of-care blood gas analysers may provide the confirmatory methaemoglobin level. Where unavailable, the combination of a saturation gap and absence of radiographic signs are clues to the diagnosis.

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Dialysis transport in Cornwall

NHS Kernow, the Clinical Commissioning Group (CCG) in Cornwall, are proposing to introduce charging for dialysis patient transport. We are completely opposed to the plan because of the danger to kidney patients who will not be able to afford to get to dialysis. The CCG issued a consultation in late 2016 that looked at non-emergency patient transport, but none of us were made aware of it. It concluded that regardless of frequency of use, all patients would pay for travel unless their income was very low or they needed an ambulance. There was no impact assessment for kidney patients and there are patients on a monthly income of £500 who would still have to pay £120 a month for their travel.

As readers will know, transport to and from dialysis treatment is a vital part of care for people with kidney failure. It is often a source of dissatisfaction for patients and has been repeatedly recognised as having a major impact on the quality of life for people who receive dialysis. The NHS is meant to be free at the point of delivery, and this goes against that principle.

Kidney Care UK have been working with patients, the Royal Cornwall Hospital Trust, the Renal Association and the British Renal Society and local MPs to resolve this. We met with the CCG in October, along with the local Healthwatch and Steve Double MP. The story even reached the national press. A pause in implementation is currently in place but, meanwhile, a similar consultation has been launched in Somerset, Gloucestershire, Wiltshire, Dorset, Swindon and Bath.

Current custom and practice elsewhere is not to charge for dialysis travel where it is needed and for local units to manage their own policies, but this challenge is only likely to grow and cannot be ignored. With others in the kidney community we, therefore, propose creating a stakeholder group to provide consensus recommendations for the provision of transport for dialysis patients. The work will start before the end of 2017. If you are interested in hearing more or contributing to this work, please let us know ■

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Peer educators pilot study

The uptake of home dialysis at Heart of England Foundation Trust (HEFT) was the lowest of seven renal centres in the West Midlands. The uptake of a home-based renal replacement therapy was particularly low in black and minority ethnic patients, who make up 40% of the catchment population.

Home-based dialysis therapy is associated with an improved quality of life and patient outcomes as well as cost-savings, so the low uptake among incident patients was of concern.

Acceptance, Choice and Empowerment (ACE) was a collaborative 17-month pilot project led by Kidney Research UK and the renal team at HEFT.

The Birmingham-based collaboration aimed to improve acceptance rates and to train accredited volunteers who have a natural empathy with a patient group through language, culture, religion and healthcare experience. In line with Kidney Research UK's strategy, the project, funded by Baxters Healthcare, aimed to address health inequalities, enabling patients on dialysis to live longer. Ten peer educators with direct renal replacement therapy experience were involved in the project, and all have vowed to continue despite the formal end of the study.

The approach of the volunteers was four-pronged: clinics, kidney information days, home visits and telephone contact. Standard operating procedures were developed to ensure consistency and to support future roll out and sustainability.

A clinical nurse specialist said, 'The support of a peer educator allowed me to get through to a lady who previously wasn't accepting her diagnosis and need for treatment.' There has also been overwhelmingly positive feedback from patients, peer educators and the renal unit staff.

All of the peer educators have been accredited and awarded their level four qualification with the Open College Network – which is the equivalent learning standard of first-year undergraduate study. The project team are committed and passionate about sustaining this work at HEFT and helping to spread it to other units who would benefit. The team's efforts were recognised at the Innovation Awards, hosted by the West Midlands Academic Health Science Network, with them winning awards in the self-care category.

To achieve sustainability and to spread a larger project across more sites, such as on a sequential basis, could provide greater evidence with independent evaluation. Kidney Research UK are now planning this next phase with key partners ■

For further information, please visit
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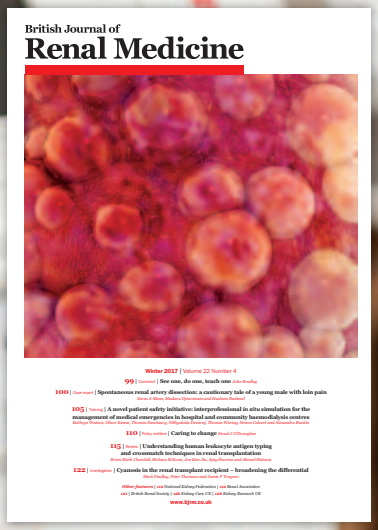

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