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Etelcalcetide is recommended as an option for treating secondary hyperparathyroidism in adults with chronic kidney disease on haemodialysis, only if:

1. Treatment with a calcimimetic is indicated but cinacalcet is not suitable **and**
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Parsabiv®▼ (etelcalcetide) Brief Prescribing Information

Please refer to the Summary of Product Characteristics (SmPC) before prescribing Parsabiv. **Pharmaceutical Form:** Parsabiv contains etelcalcetide (as hydrochloride) 5 mg/ml solution for injection in vials of 2.5 mg, 5 mg and 10 mg. **Indication:** Parsabiv is indicated for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy. **Dosage and Administration:** The recommended initial dose of etelcalcetide is 5 mg administered 3 times per week. Corrected serum calcium should be at or above the lower limit of the normal range prior to administration of first dose of Parsabiv, a dose increase, or reinitiation after a dose stop. Parsabiv should not be administered more frequently than 3 times per week. Parsabiv should be titrated so that doses are individualised between 2.5 mg and 15 mg 3 times per week to achieve the desired parathyroid hormone (PTH) target, while maintaining serum calcium at or above the lower limit of normal. The dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks. PTH should be measured after 4 weeks from initiation or dose adjustment, and approximately every 1-3 months during maintenance. Serum calcium should be measured within 1 week of initiation or dose adjustment and approximately every 4 weeks during maintenance. If clinically meaningful decreases in corrected serum calcium levels occur, steps should be taken to increase serum calcium levels. Please refer to the Parsabiv SmPC for further details on dose adjustments based on PTH and calcium levels. Parsabiv may be used in combination with phosphate binders and/or vitamin D sterols. If a regularly scheduled haemodialysis treatment is missed, do not administer any missed doses. Parsabiv should not be initiated in patients until 7 days after the last dose of cinacalcet. **Method of Administration:** Parsabiv is administered by bolus injection into the venous line of the dialysis circuit at the end of the haemodialysis treatment during rinse-back, or intravenously after rinse-back. When given during rinse-back, at least 150 mL of rinse-back volume should be administered after injection. If rinse-back is completed and Parsabiv was not administered, then it may be administered intravenously followed by at least 10 mL saline flush volume. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Parsabiv should not be initiated if corrected serum calcium is less than the lower limit of the normal range. **Special Warnings and Precautions:** Hypocalcaemia: Parsabiv treatment should not be initiated in patients if the corrected serum calcium is less than the lower limit of the normal range. Potential manifestations of hypocalcaemia include paraesthesias, myalgias, muscle spasm and seizures. Since etelcalcetide lowers serum calcium, patients should be advised to seek medical attention if they experience symptoms of hypocalcaemia and should be monitored for the occurrence of hypocalcaemia. Serum calcium levels should be closely monitored in patients with congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death and other conditions that predispose to QT prolongation and ventricular arrhythmia. Serum calcium levels should be closely monitored in patients with a history of a convulsion disorder. Worsening heart failure: Serum calcium levels should be monitored in patients with a history of congestive heart failure. Co-administration with other medicinal products: Administer Parsabiv with caution in patients receiving any other medicinal products known to lower serum calcium. Patients receiving Parsabiv should not be given cinacalcet. Concurrent administration may result in severe hypocalcaemia. Adynamic bone: Adynamic bone may develop if PTH levels are chronically suppressed below 100 pg/mL. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or Parsabiv should be reduced or therapy discontinued. Immunogenicity: No evidence of altered pharmacokinetic profile, clinical response or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. **Interactions:** No interaction studies have been performed. There is no known risk of pharmacokinetic interaction with etelcalcetide. **Fertility, Pregnancy and Lactation:** There are no or limited data from the use of etelcalcetide in pregnant women. It is preferable to avoid the use of Parsabiv during pregnancy. It is unknown whether etelcalcetide is present in human milk. A risk to breastfed newborns/infants cannot be excluded. No data are available on the effect of etelcalcetide on human fertility. **Undesirable Effects:** Adverse reactions from controlled clinical studies and post-marketing experience: very common (≥1/10) blood calcium decreased, nausea, vomiting, diarrhoea and muscle spasms; common (≥1/100 to < 1/10) hypocalcaemia, hyperkalaemia, hypophosphataemia, headache, paraesthesia, worsening heart failure, QT prolongation, hypotension and myalgia; uncommon (≥1/1,000 to < 1/100) convulsions; not known frequency hypersensitivity reactions (including anaphylaxis). Please refer to the Parsabiv SmPC for further information on undesirable effects. **Pharmaceutical Precautions:** Store in a refrigerator (2°C – 8°C). Keep the vial in the outer carton to protect from light. Clear colourless solution. For single use only. **Legal Category:** POM. **Presentations, Basic Costs and Marketing Authorisation Numbers:** Parsabiv 2.5 mg solution for injection Pack of 6 vials: £136.87; EU/1/16/1142/002. Parsabiv 5 mg solution for injection Pack of 6 vials: £163.92; EU/1/16/1142/006. Parsabiv 10 mg solution for injection Pack of 6 vials: £327.84; EU/1/16/1142/010. **Marketing Authorisation Holder:** Amgen Europe B.V. Minervum 7061, 4817 ZK Breda, The Netherlands. Further information is available from Amgen Limited, 240 Cambridge Science Park, Milton Road, Cambridge, CB4 0WD. Parsabiv is a registered trademark of Amgen Inc. **Date of PI preparation:** March 2019 (Ref: UKIE-P-416-1216-042520(2))

This medicinal product is subject to additional monitoring. Adverse events should be reported.

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COMMENT

VALUING HEALTH: SOLVING THE EQUATION IN RENAL DISEASE

Value in healthcare has been defined as health outcomes divided by cost.[1] The first step in solving this equation and delivering value in healthcare is knowing how to measure both health outcomes and the cost of achieving them. Both are challenging.

Counting the cost

The NHS has developed a national costing system for hospital-based care. Payment by Results (PbR) was first introduced in the NHS in 2003–04 to improve the fairness and transparency of hospital payments and to stimulate provider activity and efficiency. It has now been replaced by the National Tariff Payment System and relies on reporting by hospitals of the average unit cost to the NHS of providing defined services. These are reported annually as reference costs. Before it was dissolved, the Audit Commission found that while PbR improved the transparency of the payment system, it had not had a significant impact on activity and efficiency.[2] In some areas, PbR had a detrimental effect on efficiency,[3] and in renal medicine, erroneous costs have threatened to destabilise services.[4]

Made to measure

In the same way that costs have to include all aspects of a patient's care, outcome measurements need to be multidimensional and cannot be captured by a single outcome.[5] Renal disease lends itself to quantitative measures. Alongside outcomes used by many specialties, such as hospitalisation and survival, renal medicine is full of stages, modalities, co-morbidities and biomarkers that can be readily quantified. Despite this, health professionals have been at the forefront of seeking and using outcomes that matter to patients and carers across the spectrum of renal disease. Symptom burden is complex in patients with chronic kidney disease who receive multiple medications, particularly in the more advanced stages of the disease. Monitoring health-related quality of life (HRQoL) can require different approaches at different stages of a patient's journey.[6]

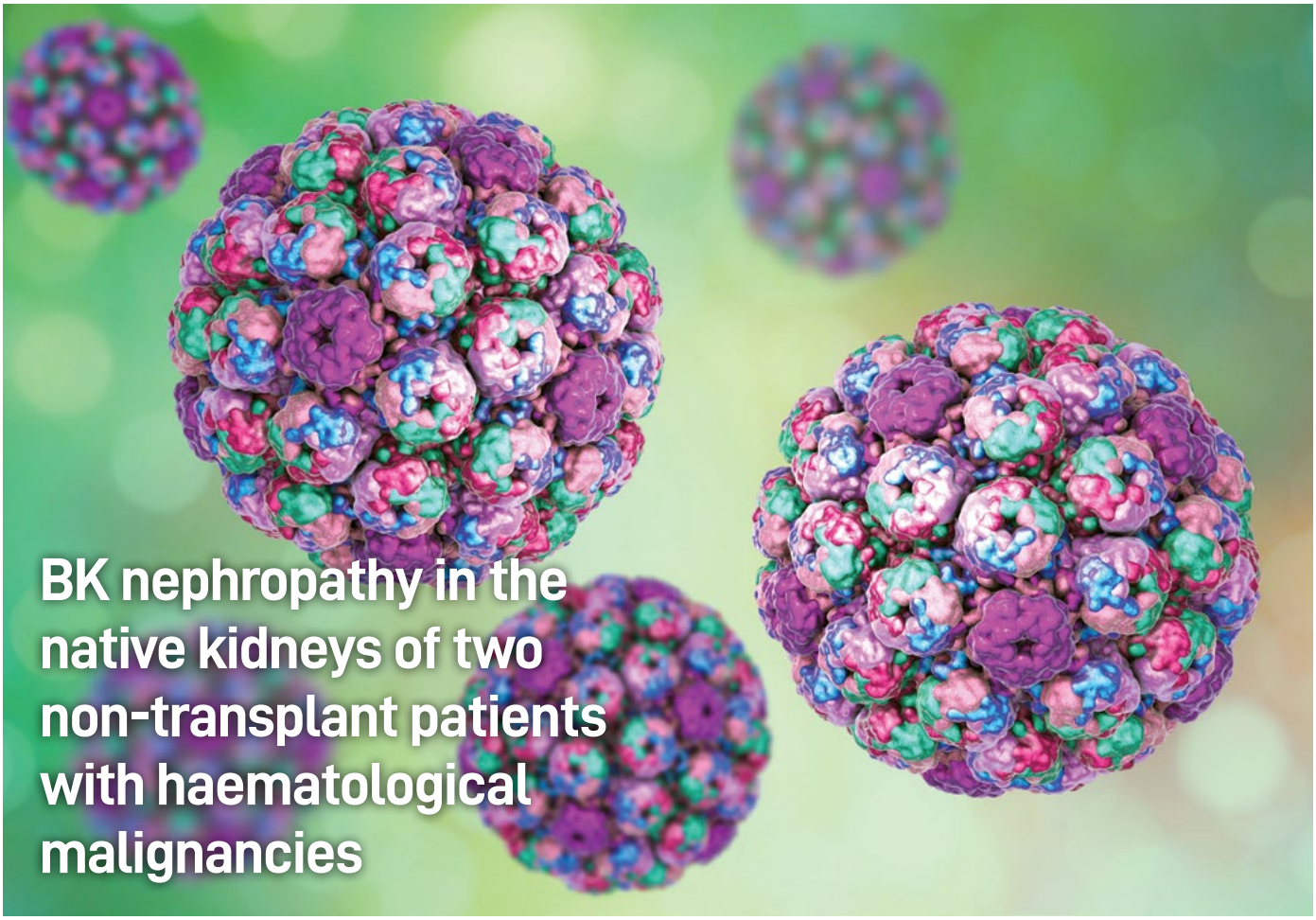
A tailored approach

The International Consortium for Health Outcomes Measurement (ICHOM) chronic kidney disease working group is an international group of health professionals and patient representatives that is developing a standardised minimum set of patient-centred outcomes for clinical use.[7] Nineteen outcome domains were defined from a total of 76 identified from the literature, registries and patient advisory groups. Of these, nine are relevant to all patients with chronic kidney disease, and ten to treatment-specific groups, reflecting further the requirement for different approaches across the complexity of renal disease. The domains across all groups could be broken down into four categories: survival, burden of disease (hospitalisation and cardiovascular events), patient-reported outcomes (HRQoL, pain, fatigue, physical function, depression and daily activity), and treatment modality-specific outcomes (kidney function, albuminuria, bacteraemia, vascular access survival, peritoneal dialysis modality survival and peritonitis, and for transplant patients, function, survival and acute rejection of kidney allografts, and malignancies). While recognising the need for continual review, the working group's consensus recommendations provide an important tool for improving the care of kidney patients.

The next challenge, recognised by the ICHOM working group, is the implementation in routine clinical practice. On page 10, Rachel Gair and colleagues describe how the collection of patient-reported measures can be achieved in patients with advanced chronic kidney disease. This can only happen if there is a structured approach and appropriate support in renal units, which are often already hard pressed by competing priorities ■

John Bradley CBE, Editor

References
1. Porter ME, Larsson S, Lee TH. Standardizing Patient Outcomes Measurement. *N Engl J Med* 2016; **374:** 504–506.
2. Audit Commission. *The right result? Payment by Results 2003-07.* Audit Commission, 2008. https://webarchive.nationalarchives.gov.uk/20101217230831/http://www.audit-commission.gov.uk/SiteCollectionDocuments/AuditCommissionReports/NationalStudies/The_right_result_PbR_2008_summary.pdf (last accessed 11/3/2019)
3. Alam SM, Brown A, Moreea S. The Payment by Results (PbR) national tariff severely penalises efficiency and early hospital discharge. *Acute Med* 2009; **8:** 123–126.
4. National Kidney Foundation. *Response from NKF (National Kidney Federation) to consultation on the '2015/16 National Tariff Payments System: Engagement on national prices': 19 December 2014.* NKF 2014. www.kidney.org.uk/assets/Uploads/201516-National-Tariff-Payments-System-Engagement-on-national-prices113.pdf (last accessed 11/3/2019)
5. Porter ME. What is value in health care? *N Engl J Med* 2010; **363:** 2477–2481.
6. Aiyegbusi OL, Kyte D, Cockwell P *et al.* Measurement properties of patient-reported outcome measures (PROMs) used in adult patients with chronic kidney disease: A systematic review. *PLoS One* 2017; **12:** e0179733.
7. Verberne WR, Das-Gupta Z, Allegretti AS *et al.* Development of an International Standard Set of Value-Based Outcome Measures for Patients With Chronic Kidney Disease: A Report of the International Consortium for Health Outcomes Measurement (ICHOM) CKD Working Group. *Am J Kidney Dis* 2019; **73:** 372–384.



BK nephropathy in the native kidneys of two non-transplant patients with haematological malignancies

KATERYNA KON/SHUTTERSTOCK.COM

The BK virus (BKV) is a human polyomavirus. It was first isolated in 1971 and the first case of BK nephropathy (BKN) was reported in 1978.[1] It is the most important virus to infect the renal allograft, with BKN a well established and frequently encountered cause of graft dysfunction and loss.[1] BKN in native kidneys is a far less common entity, although it has been increasingly described in recent years, with a number of cases reported among non-renal solid organ transplant, especially heart transplant, recipients and in those receiving bone marrow transplants for haematological malignancies.[1–4] In addition, a very small number of cases of BKN in non-transplant patients have been described.[1,4]

We present two cases of BKN in non-transplant patients with haematological malignancies, one with non-Hodgkin lymphoma (NHL) and another with chronic lymphocytic leukaemia (CLL), which, as far as the authors are aware, represent the second and fifth such cases reported in the literature, respectively.

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Case 1

Our first case is that of a 69-year-old gentleman who was referred by his GP for a nephrology opinion because he had developed progressively worsening renal function (see Figure 1) and general fatigue. He had a background of stage 4b marginal zone lymphoma diagnosed four years previously, for which he had completed six cycles of chemotherapy with bendamustine and rituximab, and had been considered in complete remission for ten months before his initial nephrology appointment. He also had a history of mild bronchiectasis and depression. Since remission had been established, the patient had been found to have hypogammaglobulinaemia and received low-dose intravenous immunoglobulin (IVIG) replacement for six months. During that time, he had suffered several lower respiratory tract and urinary tract infections. In the three months prior to his nephrology appointment, he had developed predominantly voiding lower urinary tract symptoms. One month prior to his appointment, he had been admitted in urinary retention and discharged with a long-term catheter.

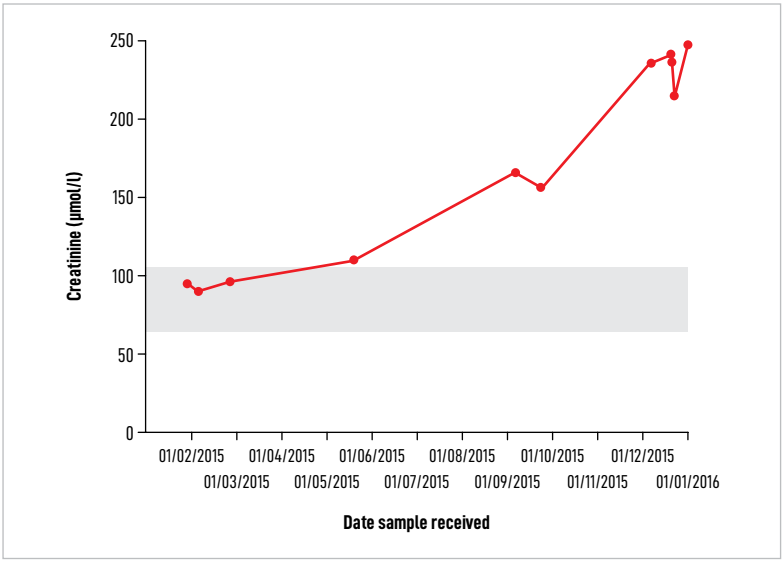
When the patient attended the nephrology clinic, his urine albumin-to-creatinine ratio was found to be 18.5 mg/mmol. A vasculitic screen was negative and an ultrasound of the kidneys, ureters and bladder showed only a simple-looking 1.3 cm cortical cyst on the left kidney. A technetium-99m mercaptoacetyltriglycine (MAG3) scan was performed and demonstrated possible partial obstruction in relation to the right renal collecting system and a complete obstruction in relation to the smaller, likely dysfunctional, left kidney. A CT scan of the neck, chest, abdomen and pelvis showed no recurrence of lymphoma. Bilateral ureteric stents were placed but renal function continued to deteriorate (see Figure 2).

Six weeks after the initial renal appointment, a renal biopsy was performed. Light microscopy revealed extensive tubular atrophy and scarring. Immunohistochemistry revealed numerous nuclei positive for simian virus 40 (SV40), in keeping with a diagnosis of BKN. A serum BK viral load was performed and returned 89,518 copies/ml. The patient received a course of cidofovir, but BK viral load rose to 191,489 copies/ml. Two weeks later, a five-day course of high-dose IVIG (dosed at 4 g/kg/day) was administered, followed by a second course of cidofovir. After this treatment, the BK viral load began to reduce and, over two months, fell to <5,000 copies/ml. During this time, the patient's renal function continued to deteriorate and he complained of severe lethargy (see Figure 3). He underwent a medical peritoneal dialysis (PD) catheter insertion and was started on continuous ambulatory PD (CAPD). He struggled to cope with PD over the following three months and was, therefore, switched to haemodialysis. The patient responded poorly to dialysis over the following months and had dehydration and hypokalaemia. He died early the following year, 14 months after his initial nephrology appointment.

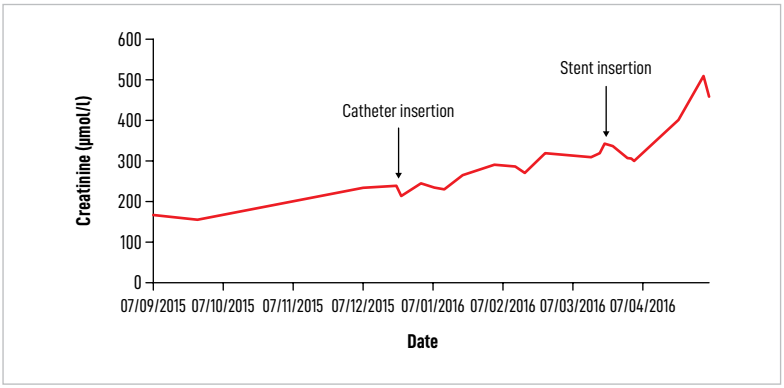
Case 2

Our second case is that of a 71-year-old gentleman who was referred by the haematologists with a history of worsening renal function (see Figure 4). He had a background of CLL, which had been in remission for the past six months, after completion of six cycles of chemotherapy with bendamustine and rituximab. Since that time, he had developed aspergillosis and *pneumocystis jirovecii* pneumonia. He had also developed urinary retention prior to the renal review and had a long-term catheter *in situ*. For this patient, BKV titres were performed at the time of initial renal review and demonstrated a viral load of 500,000 copies/ml. A prompt renal biopsy showed features of tubulointerstitial nephritis and the presence of viral inclusions within the tubular epithelial cells, suggestive of BKN, along with a mild and patchy chronic inflammatory cell infiltrate in the interstitium with scattered foci of tubulitis.

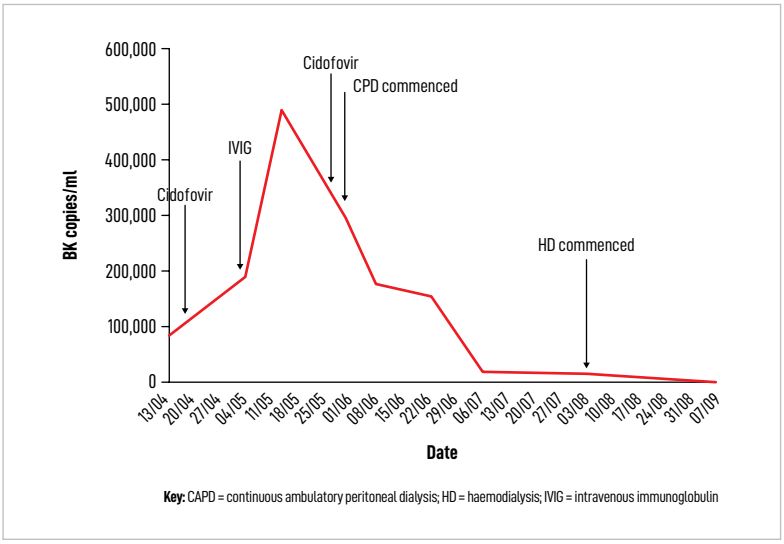
The patient was treated with a course of cidofovir, resulting in a modest improvement in BKV titres. He remained well but renal function deteriorated to an estimated glomerular filtration rate of 16 ml/minute/1.73 m^2, so he was treated one month later with IVIG, receiving the same dosing regimen (4 g/kg/day) as the first patient. Despite this treatment, BKV titres rose to >1,000,000 copies/ml and renal function continued to deteriorate, necessitating commencement of haemodialysis. At this time, the patient's white cell count rose to 35.5 x 10^9/l, with a predominant lymphocytosis, and he developed cervical lymphadenopathy. A CT scan confirmed a major relapse of CLL and the patient was started on ibrutinib. He remained well on dialysis and BKV titres gradually fell to 142,741 copies/ml over the following months.



■ FIGURE 1. Case 1: trend in creatinine levels before the initial renal appointment



■ FIGURE 2. Case 1: trend in creatinine levels over time, noting insertion of catheter and ureteric stents



■ FIGURE 3. Case 1: BK viral titres over time, with arrows showing treatment interventions

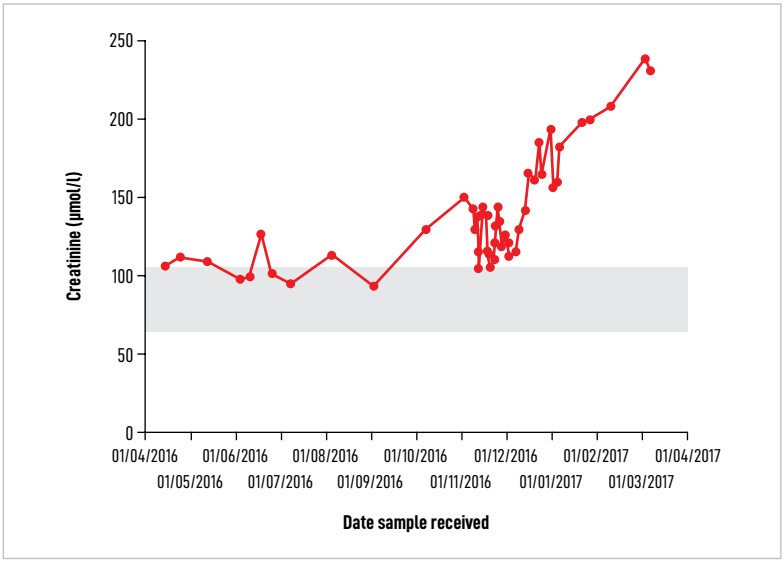
Pathophysiology and epidemiology

BKV and the JC virus are the two most clinically important polyomaviruses in humans. BKV is virtually ubiquitous among the general population, with 80–90% of the adult population infected; primary infection occurs at a median age of four to five years, most probably via the respiratory route.[4] The virus exhibits tropism for renal tubular and transitional epithelial cells, where it has lifelong latency; autopsy studies of the urinary tracts (renal pelvis, ureter and bladder)

of immunocompetent individuals have confirmed polyomavirus presence in all subjects studied.[4,5] BKV was isolated predominantly from the urinary bladder and was found in only 21% of immunocompetent kidneys.[5] In an individual who becomes immunosuppressed, the virus becomes reactivated and begins replication. In the case of renal transplant patients, this appears to be triggered by a combination of intragraft inflammation and an insufficient antiviral immune response.[6] Viral replication leads to cell lysis and spilling of virions into the extracellular space, with infection of adjacent cells.[7] Infected cells then exfoliate into the urine and may facilitate ascending infection of the kidney.[5-7] In severe infection, virions are released into the blood via the rupture of the tubular basement membrane.[7] The inflammatory response that follows can lead to urinary tract ulceration, with or without haemorrhage, ureteral stenosis and, in the kidney, tubulointerstital nephritis and inflammatory infiltration, which can be confused with rejection in a renal transplant patient.[7] The distinct diseases caused by BKV appear not to be related to its topographic distribution, but to the genomic instability of the virus and the type and severity of the patient's immune impairment altering the resultant infectiveness and replicative potential of BKV.[5] Indeed, various patterns of BKV serology have been associated with the risk of BKN in renal transplant patients.[4]

BKN is a common and important cause of deteriorating renal function in renal transplant patients. Over the past few years, BKN has become increasingly recognised as a condition that also occurs in native kidneys. The majority of these reports have been in recipients of bone marrow or non-renal solid organ transplants.[4,8] Among these, reports of BKN have been especially frequent in heart transplant recipients, which has led to the recommendation by some authors to routinely screen for the condition in these patients,[8] although cases have also been reported in the recipients of lung, liver and pancreas transplants.[4] In addition, BKN has been reported in a small number of non-transplant patients; to the best of the authors' knowledge, these include four patients with CLL, three with chronic myeloid leukaemia, three with acute myeloid leukaemia, two with acute lymphocytic anaemia, one with NHL, one with Hodgkin disease, five with AIDS, one with rheumatoid arthritis and one in an apparently immunocompetent man.[1,4,9–12] With the exception of the latter individual, all of these patients had been clearly immunosuppressed, usually for several years, and had evidence of opportunistic infections such as tuberculosis, cytomegalovirus or herpes simplex virus infection.[1]

Risk factors for BKN have been established in renal transplant patients and include male sex, older age, severity of leukocyte antigen mismatch, longer cold ischaemic time, serology of BKV, ureteric stent placement and co-infection with the Epstein–Barr virus.[4,8] Prompt recovery of BKV-specific T-cells in transplant patients on relaxation of immunosuppression with control of BKV replication appears to halt progression to overt BKN.[6] Incubation of BKV with immunoglobulin G *in vitro* leads to significant viral inhibition, suggesting that virus-specific antibodies may also provide important protection against viral reactivation.[4]



■ **FIGURE 4. Case 2: trend in creatinine levels before the initial renal review**

Diagnosis and treatment

A diagnosis of BKN can only be established definitively with a renal biopsy, although a positive serum polymerase chain reaction (PCR) viral count of >1 x 10^4 copies/ml has a positive predictive value of 50–80% for BKN. This is much more specific than urinary measures; for example, the finding of urinary decoy cells, which does not allow differentiation between BKN and asymptomatic reactivation of the virus.[1] In addition, BK viruria has been detected in a large proportion of asymptomatic, clinically well and immunocompetent patients with haematuria,[13] while measurement of BK viral load by urinary PCR does not allow differentiation between active viral replication in the lower urinary tract and that in the renal parenchyma.[1]

It is well established that the most effective treatment of BKN in renal transplant recipients involves reduction in immunosuppression, with additional specific treatments showing little efficacy and no additional survival benefit.[4,6] Such a strategy is often not possible in non-transplant patients with BKN and treatment in these patients relies on a number of antiviral medications: cidofovir, a synthetic purine analogue and viral DNA polymerase inhibitor;[14] leflunomide, a *de novo* pyrimidine synthesis inhibitor; fluoroquinolones, which have been shown to have a DNA gyrase inhibitor action *in vitro;*[14,15] and IVIG infusions, which are considered to have direct virus-neutralising activity along with immune-modulating effects.[14] The use of cidofovir can be limited by its nephrotoxic effect and that of leflunomide is often precluded by its haematological side effects.[15] Apart from the use of antiretroviral treatment in HIV

patients, which may be effective, convincing evidence for the use of any of these treatments is lacking.[6,15,16]

Prognosis and discussion

The renal outcomes in the two patients presented here are in keeping with previous case reports.[1,4,17,18] Although treatment appears to have been effective in reducing viral load, progression of renal decline was relentless. In a case report of six non-transplant BKN patients treated with either cidofovir or leflunomide, four had a reduction in their BK viral load but all six showed progressive renal decline; three of the six died and two reached end-stage renal disease (ESRD).[1] Previous studies have associated BKN with a poor prognosis in renal and other solid organ transplant recipients.[4] Although our second patient was overtly immunosuppressed, as evidenced by two opportunistic infections, our first patient displayed his immunosuppression less obviously, with several easily treated, more typical infections. The first patient received regular IVIG infusions for hypogammaglobulinaemia, a characteristic shared with other non-transplant BKN patients and in keeping with the role of virus-specific antibodies in the control of BK reactivation.[17] Interestingly, both our patients developed urinary retention shortly after the onset of renal decline, with the first showing bilateral collecting system obstruction requiring stenting. This suggests active urothelial BKV-related disease developing along with, and possibly preceding, the nephropathy. This is in keeping with the postulated role of infected, desquamated urothelial cells leading to ascending infection and BKN, particularly in an obstructed system, and is supported by the previous finding of ureteric stenting as a risk factor for BKN in renal transplant patients.[4,5] It seems reasonable that urinary obstruction should be considered as a risk factor for BKN in immunosuppressed patients and may act as a trigger for the physician to perform serum BKV PCR.

Conclusion

BK nephropathy remains a very rare condition in the native kidneys of non-transplant patients. We add to the literature on this subject by presenting two immunosuppressed patients with haematological malignancies, not on active treatment, who were found to have BKN. Treatment with IVIG and cidofovir reduced BK viral load but failed to halt progression to ESRD. In keeping with previous case reports, a falling BK PCR is not a reliable predictor of outcome.[1] Both patients presented with concomitant urinary obstruction and we use the ascending infection theory to suggest that obstruction should prompt the renal physician to perform a serum BK PCR in high-risk patients with declining renal function. Greater awareness of this condition allowed a quicker diagnosis and earlier definitive management plan in our second patient compared with the first. The outcome for patients with BKN is poor and antiviral treatment appears poorly effective.[1,4,6,16,17] It could be considered that BKN is a marker of general deterioration and an increasingly inadequate immune system. However, in keeping with treatment for BKN in transplant patients, benefit may be gleaned by relaxation of immunosuppression in patients undergoing active immune suppression as part of their cancer therapy and by immune restoration with antiretroviral treatment in patients with AIDS.[15,16] Despite the gloomy prognosis, greater awareness of BKN in the non-transplant population will lead to more effective and prompt diagnosis with the benefit of greater potential for treatment effectiveness and clearer communication and planning with patients and their families ■

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

References

1. Sharma SG, Nickeleit V, Herlitz LC *et al.* BK polyoma virus nephropathy in the native kidney. *Nephrol Dial Transplant* 2013; **28:** 620–631.
2. Viswesh V, Yost SE, Kaplan B. The prevalence and implications of BK virus replication in non-renal solid organ transplant recipients: A systematic review. *Transplant Rev (Orlando)* 2015; **29:** 175–180.
3. Harkensee C, Vasdev N, Gennery AR, Willetts IE, Taylor C. Prevention and management of BK-virus associated haemorrhagic cystitis in children following haematopoietic stem cell transplantation–a systematic review and evidence-based guidance for clinical management. *Br J Haematol* 2008; **142:** 717–731.
4. Vigil D, Konstantinov NK, Barry M *et al.* BK nephropathy in the native kidneys of patients with organ transplants: Clinical spectrum of BK infection. *World J Transplant* 2016; **6:** 472–504.
5. Boldorini R, Veggiani C, Barco D, Monga G. Kidney and urinary tract polyomavirus infection and distribution: molecular biology investigation of 10 consecutive autopsies. *Arch Pathol Lab Med* 2005; **129:** 69–73.
6. Babel N, Volk H-D, Reinke P. BK polyomavirus infection and nephropathy: the virus-immune system interplay. *Nat Rev Nephrol* 2011; **7:** 399–406.
7. Drachenberg CB, Hirsch HH, Ramos E, Papadimitriou JC. Polyomavirus disease in renal transplantation: review of pathological findings and diagnostic methods. *Hum Pathol* 2005; **36:** 1245–1255.
8. Ducharme-Smith A, Katz BZ, Bobrowski AE. Prevalence of BK polyomavirus infection and association with renal dysfunction in pediatric heart transplant recipients. *J Hear Lung Transplant* 2015; **34:** 222–226.
9. Jung SW, Sung JY, Park SJ, Jeong KH. BK virus-associated nephropathy with hydronephrosis in a patient with AIDS: a case report and literature review. *Clin Nephrol* 2016; **85:** 173–178.
10. Filler G, Licht C, Haig A. Native kidney BK virus nephropathy associated with acute lymphocytic leukemia. *Pediatr Nephrol* 2013; **28:** 979–981.
11. Go S, Conlin M, Hooper JE, Troxell ML. Polyoma virus nephropathy-related mass lesion in an apparently immunocompetent patient. *Int Urol Nephrol* 2012; **44:** 1585–1588.
12. Krystel-Whittemore M, McCarthy ET, Damjanov I, Fields TA. Polyomavirus nephropathy of the native kidney in a patient with rheumatoid arthritis and pulmonary fibrosis. *BMJ Case Rep* 2015; **2015:** bcr2015211564.
13. Lee SH, Hong SH, Lee JY *et al.* Asymptomatic hematuria associated with urinary polyomavirus infection in immunocompetent patients. *J Med Virol* 2013; **86:** 347–353.
14. Gupta N, Lawrence RM, Nguyen C, Modica RF. Review article: BK virus in systemic lupus erythematosus. *Pediatr Rheumatol Online J* 2015; **13:** 34.
15. Collett J, Fuller S, P'Ng CH, Gangadharan Komala M. A Man With Chronic Lymphocytic Leukemia and Declining Kidney Function. *Am J Kidney Dis* 2016; **67:** A18–A21.
16. Antoniolli L, Borges R, Goldani LZ. BK Virus Encephalitis in HIV-Infected Patients: Case Report and Review. *Case Rep Med* 2017; **2017:** 4307468.
17. McCrory R, Gray M, Leonard N, Smyth J, Woodman A. Native kidney BK virus nephropathy associated with chronic lymphocytic leukaemia. *Nephrol Dial Transplan*t 2012; **27:** 1269–1271.
18. Sangala N, Dewdney A, Marley N, Cranfield T, Venkat-Raman G. Progressive renal failure due to renal infiltration by BK polyomavirus and leukaemic cells: which is the culprit? *NDT Plus* 2011; **4:** 46–48.

Key points

- **BK nephropathy (BKN) is increasingly recognised in the native kidneys of non-transplant immunosuppressed individuals.**
- **Awareness of this fact is likely to lead to more effective and prompt diagnosis, with the benefit of greater potential for treatment effectiveness and clearer communication and planning with patients and their families.**
- **Immune restoration is the key in the treatment of BKN, while specific antiviral treatment currently appears poorly effective.**
- **The renal prognosis for BKN in native kidneys of non-transplant individuals is currently very poor.**

The NHS Long Term Plan

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The NHS Long Term Plan **(previously known as the ten-year plan) was published in January 2019.[1] It sets out key ambitions for the service over the next ten years.**

Since 2010, the NHS, like the rest of the UK's public services, has felt the cold hand of austerity. The NHS has experienced significant slowdown in funding growth, while the population has aged, multimorbidity and the public's expectations have increased – less money and more demand at a time when the costs to provide services have grown rapidly and, as Mr Micawber said, 'result misery'.

Cuts to local authorities, now responsible for public health, and to social care funding have added further pressure. As a result, NHS performance has declined. Key waiting-time targets are being consistently missed and the four-hour target may well be scrapped. Finances have deteriorated rapidly. In 2017–18, the overspend of hospitals was close to £1 billion.[2] Workforce shortages are everywhere; there are more than 100,000 whole-time equivalent staff vacancies in hospitals, including more than 40,000 nurse vacancies.[3] The NHS is currently in a perpetual winter.

In June 2018, Mrs May announced a new five-year funding settlement for the NHS: a 3.4% average real-term annual increase in NHS England's budget between 2019–20 and 2023–24 (a £20.5 billion increase over the period).[2]

To unlock this funding, NHS bodies were asked to develop a long-term plan for a sustainable NHS. The plan is not a major deviation from current policy. It builds on the foundations of the *NHS Five Year Forward View*,[4] which articulated the need to integrate care to meet the needs of a changing population. The settlement does not cover elements such as capital, education and training, which are in the Department of Health and Social Care's budget. Local authority public health spending and social care are also excluded. These will be addressed in the awaited social care green paper and the next comprehensive spending review due to be published later this year and may be influenced by the state of the post-Brexit economy.

Clinical priorities include cancer, cardiovascular disease, maternity and neonatal health, mental health, stroke, diabetes and respiratory care. There is also a strong focus on children and young peoples' health. Can these priorities be delivered? This will depend on increasing workforce capacity, especially in primary care, investment in diagnostic equipment and leadership at all levels. The plan is almost silent on multimorbidity and yet this is the very segment of the population with the highest increase

in demand. The change agenda needs to be focused around the needs of people living with multiple long-term conditions as much as those of people living with a single condition. In kidney care, the majority of patients have more than one condition, many people attend multiple different outpatient clinics, and a lack of coordination or integration often leads to fragmented provision of care, with resulting poor outcomes to be added to the poor experience and inefficient use of resources in this now outdated 20th-century model of care.

Although multimorbidity does not figure as a clinical priority, the focus on primary care with the move to formal primary care networks providing services for between 30,000 and 50,000 residents and the continued push for integrated care and population health does signal a mechanism for better coordination and more person-centred care. In the section on outpatient services, the excellent work by the kidney team in East London is cited as an exemplar of how modern long-term condition care can be achieved. Too often national reports focus on structural change, reconfiguration of services and mergers, rather than starting with function – what the population needs – and promoting partnerships, shared infrastructure and good governance to achieve improvement. The team at Barts Health NHS Trust

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show what can be done with a bit of ingenuity, a focus on adding value to patients, excellent multiprofessional working and great leadership at all levels. Well done to the Barts Health kidney team! This is a model that can be emulated up and down the UK. Let's do it!

Workforce shortages are the biggest challenge facing the health service. I was disappointed that *The NHS Long Term Plan* did not include the workforce, but hopefully that means that any additional monies for workforce development will be in addition to the £20.5 billion for service delivery. In the wake of the long-term plan, a cross-sector national workforce group has been established. It is chaired by the remarkable Dido Harding, while Julian Hartley, Chief Executive Officer at Leeds Teaching Hospitals, is the senior responsible officer. A workforce implementation plan will be published later this year and will figure in the spending review, following which the budget for training, education and continued professional development will be set.

There are commitments to increase medical school places from 6,000 to 7,500 per year,[1] although the Royal College of Physicians has called for at least a doubling of the number over the next four years.[5]

More accessible routes into nursing will be developed and nursing undergraduate placements are set to rise by up to 50%.[1] Not enough is said about the here and now and next few years until the numbers of all staff groups have been increased. We have a workforce crisis now.

Digital technology will play a part but most believe it will alter our work – improving it, giving service users more access and more of a say – but will not replace clinical caring and clinical jobs. The plan largely reiterates the existing direction of travel for IT set in 2016 by the 'Wachter review'.[6] Clearly healthcare needs to move from analogue to digital. Kidney services have a role to play here. We lead on patient access to data through PatientView, we lead on writing in plain English to service users and, with our Renal Registry, we can begin to use big data analytics to answer research questions and design services to improve care ■

References

1. NHS. *The NHS Long Term Plan.* NHS, 2019. www.longtermplan.nhs.uk/publication/nhs-long-term-plan/ (last accessed 6/3/2019)
2. National Audit Office. *NHS financial sustainability.* NAO, 2019. www.nao.org.uk/wp-content/uploads/2019/01/NHS-financial-sustainability_.pdf (last accessed 6/3/2019)
3. Buchan J, Charlesworth A, Gershlick B, Seccombe I. *A critical moment: NHS staffing trends, retention and attrition.* The Health Foundation, 2019. www.health.org.uk/sites/default/files/upload/publications/2019/A%20Critical%20Moment_1.pdf (last accessed 6/3/2019)
4. NHS England. *NHS Five Year Forward View.* NHS England, 2014. www.england.nhs.uk/five-year-forward-view/ (last accessed 6/3/2019)
5. Royal College of Physicians. Innovation in Medicine 2018: Government must double number of medical students. www.rcplondon.ac.uk/news/innovation-medicine-2018-government-must-double-number-medical-students (last accessed 6/3/2019)
6. National Advisory Group on Health Information Technology in England. *Making IT work: harnessing the power of health information technology to improve care in England.* Department of Health and Social Care, 2016. www.gov.uk/government/publications/using-information-technology-to-improve-the-nhs (last accessed 6/3/2019)

Transforming Participation in Chronic Kidney Disease – is it possible to embed patient-reported outcome measures to make a difference to care and the perception of care?

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Assessment of the success of treatments for renal patients has historically been based on measures considered important by the professionals delivering care; however, these measures do not capture many other outcomes, which are of real importance to patients and have a big impact on their care. These include the symptom burden, patients' experience of care and their readiness to engage in their own care. Many of the instruments assessing the patient's perspective have been available for decades, but their incorporation into routine clinical practice and pathways of care has been slow.

A patient's knowledge, skills and confidence to make effective decisions and take action to maintain or improve their own health is known as 'patient activation'. This can be measured using a validated tool, known as the Patient Activation Measure® (PAM®; Insignia Health),[1,2] and licences for the PAM tool were provided by NHS England to several organisations in 2016.[3] A growing body of research has shown that increasing activation can reduce health inequalities, deliver improved outcomes and better-quality care, as well as reducing cost. Furthermore, appropriately designed interventions can increase patient activation, often bringing about associated improvements in health and well-being.[4] Collecting patient measures from those with long-term conditions is of great potential value to both healthcare professionals and patients, providing support for shared decision-making on the choice of treatment modalities and supporting increased participation in self-management.

The Transforming Participation in Chronic Kidney Disease (TP-CKD) programme, a collaboration between the UK Renal Registry and NHS England, implemented PAM and patient-reported outcome measures (PROMs) across 14 renal units in England. The programme commenced in January 2015 and completed in December 2017.

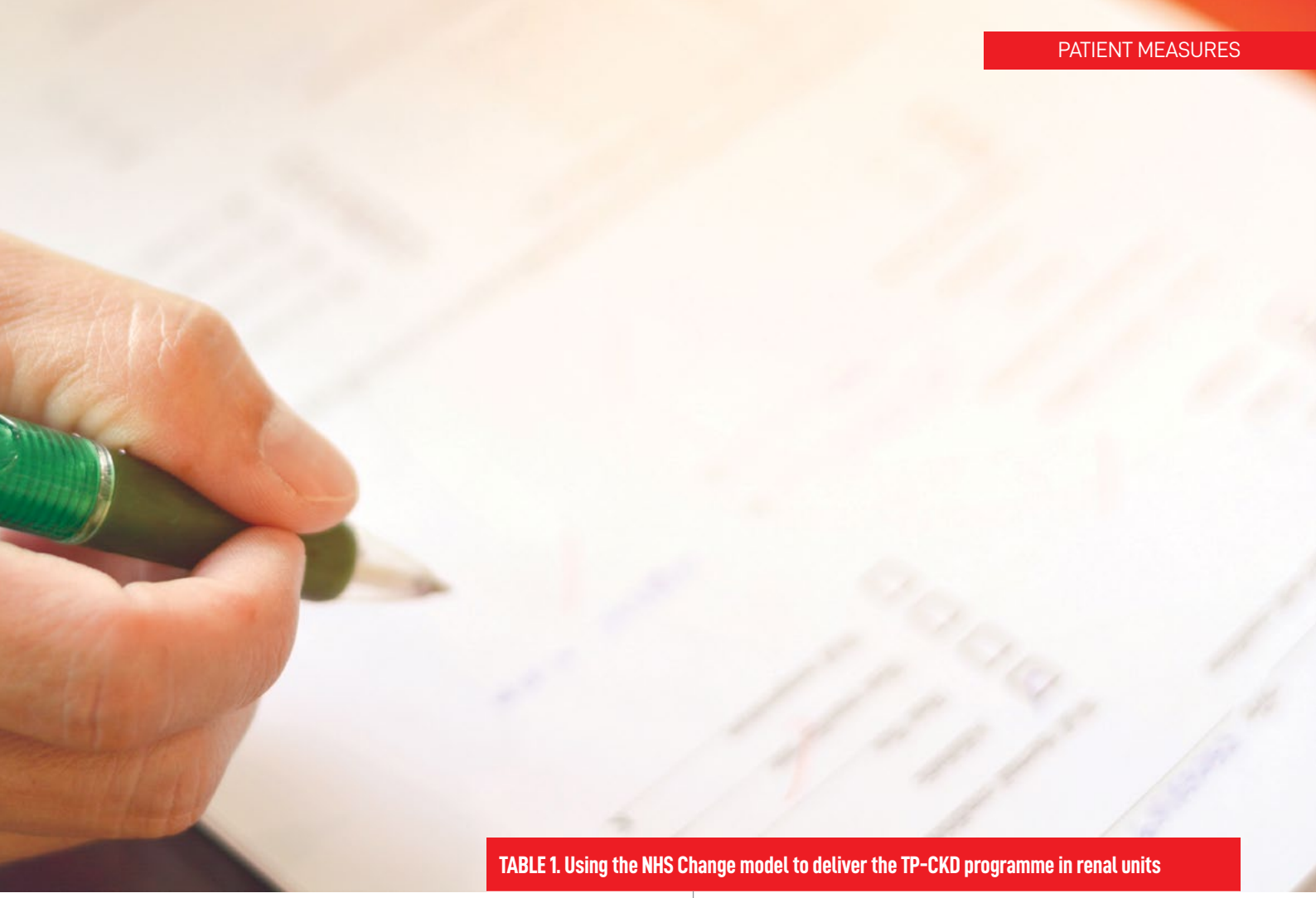
What we wanted to do

The main aim of the TP-CKD programme was to test the feasibility of routinely collecting patient-reported measures including assessment of patients' knowledge, skills and confidence in self-managing their health. We used the PAM tool to measure patients' activation,[1,2] the Palliative care Outcome Scale-Symptom list-Renal (POS-S-Renal)[5] to assess the patients' symptom burden, and the five-level EuroQol-five dimensions (EQ-5D-5L) tool[6] to assess their quality of life (QoL). These instruments were embedded into a survey tool, in the form of a questionnaire, known as 'Your Health Survey',[7] which contains 13 questions on the knowledge, skills and confidence of patients in managing their health, 17 questions on symptoms and five questions on QoL.

How we did it

The TP-CKD programme was developed between January and July 2015, commencing with a national co-design event involving patients, carers, clinicians, NHS England representatives and commissioners. This was followed by the establishment of a programme board and two workstreams. The role of the measurement workstream was to agree a set of patient-reported measures suitable for routine collection, while the role of the intervention workstream was to develop and agree targeted interventions for patients and clinical teams to support patients' active participation in their own healthcare, published in the form of an intervention toolkit.[8]

NHS England's Change Model[9] was used to frame the TP-CKD programme. The Change Model, originally developed in 2012, is a framework for any project or programme that is seeking to achieve transformational, sustainable change. The model has eight components and these were used to design the improvement structure of the TP-CKD programme (see Table 1),[10] which was then briefed to units via detailed guidance on what each stage encompassed. A person-centred care facilitator (PCCF) was recruited to support participating units with their improvement



plans, so that the knowledge gained could be used to good effect.

Programme leadership was based on the principles of co-production that underpinned the programme, with patient involvement and influence from the inception. Based on these principles, the delivery of the programme was supported by a board comprising a range of stakeholders, including patients, carers, clinicians, NHS England representation, commissioners and academics. A patient and a professional were recruited as co-chairs to the board and to each workstream, aspiring to a membership with a 50:50 ratio of patients and professionals, which was, in the main, achieved. Patient and public input and influence were represented at every level of the programme, from creating the programme plan to the end evaluation, and from its central down to local design.

The programme recognised that targeting interventions solely at patients was unlikely to achieve the necessary culture change. Achieving this would also require healthcare professionals to be sufficiently 'activated' to engage with patients in a way that improves activation. The knowledge, skills and confidence

TABLE 1. Using the NHS Change model to deliver the TP-CKD programme in renal units

NHS Change model	TP-CKD criteria
Shared purpose/vision	• Programme vision outlined in aims and objectives
Leadership for change	• Working groups • Champions and leaders • Senior buy-in
Spread of innovation	• Peer assist • Communication
Improvement methodology	• QI cycles • Peer assist • 30-60-90 day plans
Rigorous delivery	• Person-centred care facilitator • Programme delivery board • UK Renal Registry infrastructure • 30-60-90 day plans
Transparent measurement	• Data collection
System drivers	• NHS England – collection of PAM and PROMs • NHS Five Year Forward View (www.england.nhs.uk/five-year-forward-view/) • Person-centred care drivers
Engagement to mobilise	• Engagement of the whole team • Co-production

PAM = Patient Activation Measure; PROMs = patient-reported outcome measures; QI = Quality improvement; TP-CKD = Transforming Participation in Chronic Kidney Disease

cube (see Figure 1),[10] designed by the programme team, illustrates an 'activation space', defined by both the patient's and healthcare professional's levels of activation, in which the level of healthcare professional activation may play a crucial role in motivating or demotivating a patient with respect to engagement in self-management. The likelihood of achieving full involvement of patients in their own care is thus dependent on both their own level of activation and the level of activation of the people looking after them.[11]

Fourteen of the 52 renal units in England self-selected to participate in the programme and were divided into two cohorts. Units from Cohort 1 were invited to an initiation event in November

2015, with the implementation of patient measures beginning in January 2016. Units from Cohort 2 were invited to a peer assist event in November 2016 and commenced measurement in January 2017.

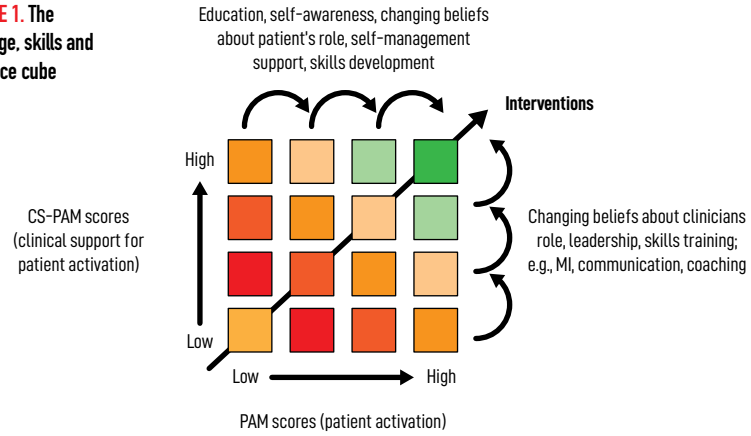
Asking the questions

Under the banner of Your Health Survey, the programme introduced the use of the PAM tool and the collection of PROMs (symptom burden using the POS-S-Renal instrument and QoL using EQ-5D-5L tool) across several populations of people with CKD. These included patients with moderate-to-severe CKD attending renal outpatient clinics, those on dialysis at home and in renal units, and those with renal transplants. On addition, as the programme recognised that healthcare professional activation could be an important factor, units also collected data on clinician support for patient activation, using the Clinical Support for Patient Activation Measure (CS-PAM) instrument.[12]

The success of implementing Your Health Survey varied across units. All 14 units managed to collect survey data at least once from a group of patients; however, only some succeeded in subsequently re-surveying patients. This was mainly due to difficulties in embedding the measure and sustaining the processes necessary to enable re-survey. In addition, incorporating discussion of patient-level survey results into care processes or clinic appointments proved challenging for a variety of reasons.

Of the 14 participating units, two dropped out after an initial data collection, six encountered challenges in the routine data collection, especially pertaining to re-surveying, and seven developed robust solutions to collect and submit data. Together these seven units submitted 2,524 of the total 3,325 surveys, with six units also managing to re-survey patients, collecting a total of 842 re-surveys.

■ **FIGURE 1. The knowledge, skills and confidence cube**



Key: CS-PAM = Clinical Support for Patient Activation Measure; MI = motivational interviewing; PAM = Patient Activation Measure

Assessment of units using a red-amber-green rating system

Red-amber-green (RAG) rating of each participating unit, according to predefined characteristics outlined in Table 1, was carried out by the PCCF at regular intervals throughout the programme. These ratings were subjective and arrived at with reference to examples of good practice and solution-finding in response to the challenges faced and were not formally shared with the units. The final RAG rating was used to help define each unit's characteristics associated with successful implementation of routine collection of patient measures and was validated by the TP-CKD board.

Table 2 shows the final RAG rating of the 14 participating units,[10] together with an overall assessment of the unit to indicate a preponderance of characteristics likely to facilitate successful engagement with the programme. Those units rated green were seen to have adopted the majority of the pre-defined characteristics, while those rated red did not adopt the majority. There was some correlation between these overall RAG ratings and the success in achieving routine collection of patient measures.

Conclusion and key findings

TP-CKD aimed to establish the feasibility of routinely collecting PAM and PROMs in kidney patients. Fourteen units participated in the programme, with a total of 3,325 patients completing at least one survey.

As the programme has shown, the routine implementation and collection of patient-reported measures is challenging; however, it has also demonstrated that with support and a structured approach – in this case, based on the Change Model and a peer assist approach – the routine collection of patient-reported measures in patients

TABLE 2. Final red-amber-green (RAG) rating for the participating renal units

	Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Unit 6	Unit 7	Unit 8	Unit 9	Unit 10	Unit 11	Unit 12	Unit 13	Unit 14
Peer assist														
30-60-90 day plans														
Working groups														
Champions and leaders														
Senior 'buy-in'														
Quality Improvement														
Co-production														
Engagement of the whole team														
Communication														
Overall														

in England with moderate-to-severe CKD and those on renal replacement therapy is feasible. More specifically, the study has shown the following:

- The UK Renal Registry has developed the infrastructure to receive and process patient-reported data on paper and to support the return of data from Your Health Survey to patients and healthcare providers via newly developed screens on PatientView.
- Renal units can collect data via Your Health Survey from patients in England who receive renal replacement therapy (dialysis and transplantation) or have CKD. Routine collection was established in the haemodialysis and transplant population but appeared to be less straightforward in those with CKD.
- There was some correlation between success in achieving routine collection of patient-reported measures and unit adoption of the pre-defined characteristics likely to facilitate successful engagement with the programme.
- The renal units that facilitated successful collection of patient-reported measures displayed a number of common characteristics. These include commitment of the unit, senior leadership, patient involvement and team engagement. On the other hand, factors such as a depleted work force, lack of staff time, as well as competing priorities hindered successful implementation of these measures within renal units.
- Including both patients and healthcare professionals in the co-production and co-design of the programme at a national and local level enhanced the delivery of the programme and provides the foundation for future service development, although the sustainability of this approach without additional resource investment is uncertain.
- A peer assist model provides a positive approach to share learning and experiences to overcome challenges.
- Up-skilling of the clinical workforce is required to support ongoing collection of patient-reported measures and their use as a clinical tool within practice.
- Further work with centres on how best to embed these tools within their own IT systems is required to address issues such as the availability of real-time data and accessibility of patient measures to those who may not have health or digital literacy.

In order to further embed patient-reported measures into mainstream practice, a number of commissioning and professional levers need to be considered. Although the role of Commissioning for Quality and Innovation (CQUIN) and other incentives remains unclear, commissioning levers such as CQUIN, as well as service specifications and dashboards need to be considered. Further work is required to understand the differing success of incentives to influence, drive and embed change.

These assessments alone, however, will not improve outcomes of patients with renal disease or those with other long-term conditions unless healthcare professionals, in partnership with patients, use these data to guide care. It is important that clinical staff and patients gain an understanding of the benefits of collecting these data and more information is required on how these may be used. Further work is necessary to up-skill the workforce to enable them to tailor support to those patients who have a low activation level and a high symptom burden. In 2018, NHS England's personalised care team and the UK Renal Registry agreed to work together on a 12-month follow-up programme, known as TP2.[13] The TP2 programme is being run in partnership with four renal units, and is exploring the feasibility of tools such as health coaching and social prescribing within a renal setting, and how such tools can support clinicians to improve patient activation and patient outcomes ■

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

References
1. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. *Health Serv Res* 2005; **40:** 1918–1930.
2. Insignia Health. Patient Activation Measure® (PAM®) www.insigniahealth.com/products/pam-survey (last accessed 24/1/2019)
3. NHS England. Patient activation. www.england.nhs.uk/ourwork/patient-participation/self-care/patient-activation/ (last accessed 24/1/2019)
4. Hibbard JH, Greene J. What the evidence shows about patient activation: better health outcomes and care experiences; fewer data on costs. *Health Aff (Millwood)* 2013; **32:** 207–214.
5. Palliative care Outcome Scale. POS-S Renal Patient Card. https://pos-pal.org/maix/pos-s-in-english.php (last accessed 24/1/2019)
6. Herdman, M, Gudex C, Lloyd A *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20:** 1727–1736.
7. Renal Registry and NHS England. Think Kidneys: Resources – Surveys: Your Health Survey (PAM / PROM Survey). www.thinkkidneys.nhs.uk/ckd/resources/surveys/ (last accessed 24/1/2019)
8. Renal Registry and NHS England. Think Kidneys: Tools for Change. www.thinkkidneys.nhs.uk/ckd/tools-for-change/ (last accessed 24/1/2019)
9. NHS England. Change Model www.england.nhs.uk/sustainableimprovement/change-model/ (last accessed 24/1/2019)
10. Gair RM, Stannard C, Wong E *et al. Transforming Participation in Chronic Kidney Disease Programme Report.* Renal Association, 2019. www.thinkkidneys.nhs.uk/ckd/wp-content/uploads/sites/4/2019/01/Transforming-Participation-in-Chronic-Kidney-Disease.pdf (last accessed 24/1/2019)
11. Hibbard J, Gilburt H. *Supporting people to manage their health: An introduction to patient activation*. The King's Fund, 2014. www.kingsfund.org.uk/sites/default/files/field/field_publication_file/supporting-people-manage-health-patient-activation-may14.pdf (last accessed 24/1/2019)
12. Hibbard JH, Collins PA, Mahoney E, Baker LH. The development and testing of a measure assessing clinician beliefs about patient self-management. *Health Expect* 2010; **13:** 65–72.
13. Renal Registry and NHS England. Think Kidneys: About TP2. www.thinkkidneys.nhs.uk/ckd/about-us/about-tp2/ (last accessed 24/1/2019)

Key points

- **The Transforming Participation in Chronic Kidney Disease (TP-CKD) programme implemented the Patient Activation Measure and patient-reported outcome measures in 14 renal units in England. NHS England's Change Model was used to frame the programme.**
- **Although the routine implementation and collection of patient-reported measures is challenging, the programme has demonstrated that, with support and a structured approach, this is feasible in patients with moderate-to-severe CKD and those on renal replacement therapy.**
- **There was some correlation between success in achieving routine collection of patient-reported measures and unit adoption of pre-defined characteristics likely to facilitate successful engagement with the programme.**
- **Common characteristics displayed by renal units that facilitated successful collection of patient-reported measures included commitment of the unit, senior leadership, patient involvement and team engagement, whereas factors such as competing priorities, a depleted work force or lack of staff time hindered successful implementation of these measures.**
- **The collection of patient-reported measures alone will not improve patient outcomes unless healthcare professionals, in partnership with patients, use these data to guide care. It is important that clinical staff and patients gain an understanding of the benefits of collecting these data.**

UK Kidney Week 2019

The Renal Association (RA) and British Renal Society (BRS) will again host UK Kidney Week (UKKW) together, from 3rd to 5th June 2019 at the Hilton Metropole in Brighton. Many of you have contributed to shaping UKKW 2019 and the planning for the meeting is almost complete.

The programme committee has worked hard and consulted widely with many of you to produce a programme that covers the full breadth of kidney care and caters for all members of the multiprofessional team. UKKW 2019 will address your education needs, provide a platform for your work, energise your intellect, and bring you together with friends and colleagues from the UK and beyond.

We want to share with you some of the highlights of what promises to be the best UKKW ever. For full details, please see **www.ukkw.org.uk**

VENUE

We are using a hotel venue this year. The Hilton Metropole is situated on the seafront and a short walk from the railway station in this vibrant city. Many delegates will be able to stay at the venue, offering good value for money and convenience. Accommodation is also available at multiple other hotels nearby. A creche will be provided to enable delegates with young children to attend.

PLENARY PROGRAMME

We have an outstanding plenary programme, comprising the following:

- An opening plenary on genetics and big data, focused on the patient perspective, will be delivered by two world-class speakers: Nine Knoers, who is a leading international investigator into genetic causes of kidney disease, and Andrew Hattersley, who is a major figure in the genetics of diabetes.
- Steve Powis, Medical Director of the NHS (and a professor of nephrology!), will speak on Tuesday morning; Steve will be followed by Myles Wolf, who is an international expert in mineral and bone disease and who will provide us with a state of the art overview of this field.
- On Wednesday morning, we are joined by Baroness Ilora Finlay, who is a consultant in palliative care and a major international figure in end-of-life care. Baroness Finlay will be followed by the prestigious professional society lectures, the Mallick (Karen Jenkins) and the Raine (Alexander Hamilton).
- The conference will end with a plenary session featuring the 2019 Osman Lecturer, Charles Pusey, who, over 30 years, has been at the forefront of vasculitis research.
- Monday and Tuesday will finish with a succinct highlights session, which will signpost the key messages from some of the sessions and include interactive discussions between faculty and audience. The final plenary session will finish with an overview of the highlights of the meeting.

CONFERENCE SYMPOSIA

We invited all members of the renal community to submit suggestions for symposia and were overwhelmed by the response. The programme committee has worked with the proposers of the symposia to shape a diverse programme that will cover the needs of all members of the UK kidney community.

The key features of the symposia include:

- seven parallel symposia throughout the conference, to ensure that all areas of the specialty are covered
- outstanding speakers, many with an international reputation in their field
- the Donna Lamping, Jane MacDonald, Chandos and de Wardener lectures
- continuing professional development sessions organised by the education committees of the RA and BRS.
- a strong focus on supporting the development of your clinical practice
- an emphasis throughout the programme on addressing inequality and variance, including on quality improvement, patient-reported outcomes and patient involvement
- strong renal science symposia, including on fibrosis and regeneration, aging and the kidney, polycystic kidney disease, vascular disease, diabetic nephropathy, tubulointerstitial disease and epigenetics.
- the popular '3-minute heroes' session, showcasing the best of the posters
- the best clinical and basic science abstracts presented as oral communications
- late-breaking abstract session.

POSTERS

We have received a record number of abstract submissions; those accepted for poster presentation will be on display throughout the conference. Moderated poster sessions featuring a short presentation of each poster and opportunity for discussion will remain a popular feature of UKKW.

POP-UP SESSIONS

These are short small-group sessions that provide opportunity for practical training and group discussions that have become increasingly popular in recent years. We are currently inviting all members of the renal community to submit ideas for pop-up sessions; this is a further opportunity for you to shape the meeting.

INDUSTRY SYMPOSIA AND EXHIBITION

Our industry partners play an integral role in UKKW and this year will be presenting several symposia with excellent speakers on specialist topics. This is a further opportunity to hear the latest updates in important therapeutic areas. Industry partners will also participate in the exhibition to present attendees with information on novel therapies, equipment and services.

CONFERENCE DINNER

The conference dinner is a meeting highlight and is an opportunity for your teams to celebrate their achievements together and share social time with friends in the UK kidney community. There were shortfalls in some aspects of the 2018 dinner, and we are putting in extra effort to make the dinner enjoyable and memorable in 2019.

AND FINALLY

We are aware that it is becoming increasingly difficult for all categories of staff to attend conferences, but we hope that we have convinced you that if you can attend only one meeting in 2019, it should be UKKW. Start planning now and register early to take advantage of the 'early bird' rates. We would encourage units to think carefully about making it possible for staff who have never experienced UKKW to attend for the first time.

We look forward to welcoming you in Brighton ■

PAUL COCKWELL
Clinical Vice President
The Renal Association

MAARTEN TAAL
President
British Renal Society

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Envarsus® 0.75mg, 1mg, 4mg prolonged-release tablet tacrolimus (as monohydrate) Prescribing Information Please refer to Summary of Product Characteristics (SPC) before prescribing.

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 20 ng/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 SPC 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 have 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. The risk of secondary cancer is unknown. Exposure to sunlight and UV light should be limited. Patients treated with 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). 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. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product (refer to SPC for further information). **Interaction with other medicinal products and other forms of interaction:** Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is strongly recommended to closely monitor tacrolimus blood levels, as well as renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly, and to interrupt or adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (refer to SPC for full list of interactions). **Fertility, pregnancy and lactation:** *Pregnancy:* Human data show that tacrolimus crosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse events on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. Tacrolimus treatment can be considered in pregnant women when there is no safer alternative, and when the perceived benefit justifies the potential risk to the foetus (refer to SPC for further information). *Breast-feeding:* Human data demonstrate that tacrolimus is excreted in breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving Envarsus. *Fertility:* A negative effect of tacrolimus on male fertility in the form of reduced sperm count and motility was observed in rats. **Effects on ability to drive and use machines:** Envarsus may have a minor influence on the ability to drive and use machines. Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if Envarsus is administered in association with alcohol. No studies on the effects of tacrolimus (Envarsus) on the ability to drive and use machines have been performed. **Side effects:** *Very common:* tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension, insomnia, headache, diarrhoea, nausea, liver function tests abnormal *Common:* anaemia, thrombocytopenia, leukopenia, red blood cell analyses abnormal, leukocytosis, anorexia, metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, 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, sweating increased, arthralgia, back pain, muscle cramps, pain in limb, renal failure, renal failure acute, nephropathy toxic, renal tubular necrosis, urinary abnormalities, oliguria, bladder and urethral symptoms, febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed, blood alkaline phosphatase increased, weight increased, primary graft dysfunction. *Uncommon:* coagulopathies, pancytopenia, neutropenia, abnormal coagulation and bleeding analyses, hypoglycaemia, psychotic disorder, encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, paralysis and paresis, cataract, 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, paralytic ileus, dermatitis, haemolytic uraemic syndrome, influenza like illness, increased blood lactate dehydrogenase, multi-organ failure, *Rare:* thrombotic thrombocytopenic purpura, hypoprothrombinaemia, blindness, deafness neurosensory, pericardial effusion, acute respiratory distress syndrome, pancreatic pseudocyst, subileus, veno-occlusive liver disease, hepatic artery thrombosis, toxic epidermal necrolysis (Lyell's syndrome), ulcer. *Very rare:* myasthenia, hearing impaired, echocardiogram abnormal, hepatic failure, Stevens Johnson Syndrome, nephropathy, cystitis haemorrhagic. *Not Known Frequency:* pure red cell aplasia, agranulocytosis, haemolytic anaemia, allergic and anaphylactoid reactions (refer to SPC for full list of adverse reactions). **Legal category:** POM **Prices and Packs:** 0.75mg £44.33 1x30 tablets, 1mg £59.10 1x30 tablets, 4mg £236.40 1x30 tablets **Marketing authorisation (MA) numbers:** EU/1/14/935/001, EU/1/14/935/004, EU/1/14/935/007. Full prescribing information is available on request from the **UK Distributor:** Chiesi Limited, 333 Styal Road, Manchester, M22 5LG **Date of Preparation:** June 2018.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellowcard in the Google Play or Apple App Store.

Adverse events should also be reported to Chiesi Limited on 0800 0092329 (UK) or 1800 817459 (IE) PV.UK@Chiesi.com

References

1. Envarsus Summary of Product Characteristics. Chiesi Limited.
2. Nigro V, Glicklich A, Weinberg J. American Transplant Congress (ATC), Seattle, Washington, May 2013. Abstract B1034.
3. Tremblay S, Nigro V, Weinberg J, Woodle ES, Alloway RR. Am J Transplant 2017;17:432-442.
4. Gaber AO, Alloway RR, Bodziak K, et al. Transplantation 2013;96:191-197.
5. Alloway RR, Eckhoff DE, Washburn WK, et al. Liver Transpl 2014;20:564–575.
6. Trofe-Clark J, Brennan DC, West-Thielke P, et al. Am J Kidney Dis 2018;71:315-326.
7. Langone A, Steinberg S, Gedaly R, et al. Clin Transplant 2015;29:796-805.
8. Bunnapradist S, Ciechanowski K, West-Thielke P, et al. Am J Transplant 2013;13:760-769.
9. Hung R, Basu S, Goldet G, et al. Recipient Age is a Significant Factor in Immunological and Infective Complications Following Kidney Transplantation. Poster PO64 BTS Brighton 2017.
10. Richards KR, HagerD, Muth B, et al. Transplantation 2014;97(10):986-991.

Help and support for all kidney patients

The National Kidney Federation (NKF) continues to offer help and support to all kidney patients throughout the UK. Our dedicated helpline is manned by fully trained advisers who are there to speak to patients about their renal concerns, which can be backed up by patient information leaflets that have been written especially for the NKF by medical professionals.

By dialling the free-to-call NKF Helpline on 0800 169 0936, patients can put their questions directly to a qualified member of staff. Renal patients have found that being able to speak in confidence about their worries and concerns with people who understand this emotive diagnosis helps enormously. Lines are open Monday to Friday, 9 am – 5 pm.

The helpline could not run without the assistance of our medical specialists who write the renal information for the NKF. Established in 2001, the helpline started out with just six titles in its 'Kidney Matters' patient information library, which has steadily grown to over 200 titles, ranging from early chronic kidney disease to rare diseases, such as Fabry disease, Lupus and Alport's syndrome. The NKF can also help renal patients find suitable travel insurance, holiday dialysis, benefits and dietary advice. New titles are always welcome to be added to our library of information. Any topic that would be of benefit to kidney patients can be printed in-house for distribution to patients and renal units.

The NKF is currently working very hard to bring about a much improved website for the benefit of all kidney patients, carers and medical professionals, and it is anticipated that this will be available within the coming months.

The NKF has its heart firmly in the right place, as this charity is run by kidney patients for the benefit of all UK kidney patients. Representatives from the 54 local kidney patient associations from all around the UK make up the executive committee of the charity. As such, they are well placed to identify the trials and tribulations associated with kidney disease and they maintain good relations with their own nephrologists and dialysis/transplant nurses. They can also help identify the problems which can arise within the hospitals and renal units and use their experiences, both good and bad, to help the NKF with its campaigning. The NKF chairman is the secretariat for the All-Party Parliamentary Kidney Group representing the voice of kidney patients from all around the UK to ensure that problems are brought to the attention of the government and quality renal services are maintained.

All the latest renal news, patient stories and information can be found in the NKF magazine, *Kidney Life*. This goes out free of charge to all patients and renal units and anyone who wishes to receive it. If you are not receiving *Kidney Life* but wish to receive a copy, please ring the helpline's free-to-call number and we will add you to our database to receive the magazine four times per year ■

NATIONAL KIDNEY FEDERATION
HELPLINE 0800 169 09 36

PAULINE PINKOS **NKF Helpline**

IRON TRIAL RESULTS PAVE THE WAY FOR IMPROVED HAEMODIALYSIS TREATMENT

An update of the results of the Kidney Research UK-facilitated Proactive IV irOn Therapy in haemodiALysis patients (PIVOTAL)trial, designed to determine the optimum dose of intravenous (IV) iron for a kidney patient on haemodialysis, has been published in the *New England Journal of Medicine*.[1]

The updated PIVOTAL trial results show that a higher dose of IV iron reduces the risk of death, hospitalisation for heart failure and other major cardiovascular events, as well as reducing both erythropoietin (EPO) dose requirements and the need for blood transfusions, in comparison with lower doses of iron. In addition, no increased infection risk was observed in those receiving a higher dose of iron, which is important, given that previous research has suggested that iron might increase bacterial growth and infection.

Steering Committee member for the trial, Professor David Wheeler, said, 'Intravenous iron is a routine part of anaemia management in haemodialysis patients worldwide. However, there has been little evidence to guide optimum dosing, and no consistency in approach across the UK or globally. The PIVOTAL trial was designed to address this shortfall in the evidence base, comparing proactive, high-dose and reactive low-dose intravenous iron treatment.'

'PIVOTAL shows that patients treated with higher iron doses (who also received less EPO) experienced fewer cardiovascular events and no increase in serious adverse events when compared to those receiving lower doses.'

Another outcome of the PIVOTAL trial is a reduction in the number of blood transfusions needed in those receiving high-dose iron. This is potentially positive news, as blood transfusions can lead to the production of antibodies, which could increase the likelihood of kidney transplant rejection further down the line.

Taking place exclusively in the UK, PIVOTAL was a four-and-a-half year randomised controlled trial, which involved the collaboration of doctors and nurses based at 50 of the UK's 80 renal units, along with 2,141 kidney patients. It was led by Professor Iain Macdougall at King's College Hospital in London, in partnership with Glasgow University Clinical Trials Unit.

It is anticipated that the results of PIVOTAL will lead to a review of national and international clinical practice guidelines.

Kidney Research UK Chief Executive, Sandra Currie, said, 'This is the first trial of its kind and one of the largest to have taken place in the UK dialysis population and we are immensely proud of everyone who took part and helped to make it happen. It brought together patients and clinical staff from right across the country to understand how we can improve the clinical care of patients on dialysis.'

'This has been a huge project for the charity to facilitate and we are delighted to see it has yielded positive results. There was a gap in the understanding of intravenous iron therapy which needed to be addressed and we now believe that the results will lead to improved treatments and better outcomes for patients.'

The charity was supported by an unrestricted grant of just under £3.5 million from Vifor Fresenius Medical Care Renal Pharma Ltd. The company also provided all the iron for the study, free of charge.

The results of the trial are available in the *New England Journal of Medicine*[1] and a video with one of the research nurses involved in the trial explaining the results is available to view at **www.youtube.com/watch?v=7v9pm-UpiC0** ■

Reference
1. Macdougall IC, White C, Anker SD *et al.* Intravenous Iron in Patients Undergoing Maintenance Hemodialysis. *N Engl J Med* 2019; **380:** 447–458.

Kidney Research UK
Funding research to save lives

Balloon-assisted maturation: a valid option for arteriovenous fistulas that fail to mature?

RACHA PHUANGPOO/SHUTTERSTOCK.COM

An arteriovenous fistula (AVF) is the access of choice for haemodialysis (HD).[1,2] Unfortunately, its success is limited by a high rate (28–53%) of maturation failure,[3] which represents the most significant shortcoming of this type of vascular access.[4] Complications associated with vascular access account for elevated morbidity and mortality levels among HD patients, as well as increasing the financial cost of managing these patients.[5]

Fistula maturation is the process by which a fistula becomes suitable for cannulation. In general, this is the case when it has a diameter of at least 6 mm, is less than 6 mm below the surface of the skin and has a blood flow of at least 600 ml/minute. If it does not meet these criteria six weeks after its surgical creation, the cause of non-maturation should be investigated.[6]

The mechanisms underlying AVF maturation failure are not fully understood; however, after the creation of an AVF, both outward vascular remodelling and potential luminal narrowing by intimal hyperplasia take place, the latter an adaptive mechanism in response to the increased shear stress.[3,7] The net balance between these two responses is ultimately considered to determine luminal diameter, flow and long-term AVF patency.[7,8] Impaired outward remodelling and increased intimal hyperplasia are, therefore, important contributors to AVF stenosis and maturation failure.[7]

The majority of AVFs with early failure demonstrate stenotic lesions,[3] mainly in the juxta-anastomotic region.[9,10] This is caused by the dramatic increase of shear stress in this segment, along with the surgical trauma due to the creation of the anastomosis.[5]

Early AVF failure is considered to occur when the access either never develops adequately to support dialysis (with adequate blood flow and size to allow successful repetitive cannulation) or fails within the first three months of use.[11]

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Balloon-assisted maturation

Balloon-assisted maturation (BAM) is a technique that has recently been employed to improve fistula maturation. It attempts to promptly mature an AVF by dilating a significant stenosis and performing serial graduated dilatations of the entire fistula length in repeated percutaneous transluminal angioplasties (PTAs) with progressively increasing balloon diameters until the desired diameter and flow rate are achieved in the AVF.[1,12]

BAM is a relatively new, controversial and aggressive approach to managing the important clinical problem of AVF maturation failure. Data from studies with robust evidence on the outcomes of BAM are lacking and our understanding of the long-term effects and complications of the procedure is scarce; however, it should be emphasised that no effective alternative therapies are currently available to manage this problem.[13]

The success rates reported so far vary, with maturation achieved in 47.6% to 96.7% of cases.[1,14,15] A retrospective analysis of 336 office-based BAM procedures evaluated the complications occurring after the procedure. This analysis found that wall haematoma

was the most common injury (40.5%), followed by extravasation or rupture (9.5%), spasm (7.7%), puncture-site haematoma (3.9%) and thrombosis (1.5%).[16]

Review of our experience with BAM

Before patients receive an AVF at our hospital, they are assessed in a vascular access clinic, where they undergo a physical examination and duplex ultrasound scan. After AVF creation, a physical examination of access maturation is performed eight days and six weeks post-surgery. If non-maturation occurs, the AVF is re-evaluated in the vascular access clinic with a duplex ultrasound scan, and a decision is made on whether it is suitable for BAM.

We reviewed all cases of BAM performed at our hospital between 2015 and 2017.

Methods

We conducted a retrospective review of all cases of BAM performed at our centre between 2015 and 2017. Variables assessed were access type, aetiology of non-maturation, outcomes and complications of the technique.

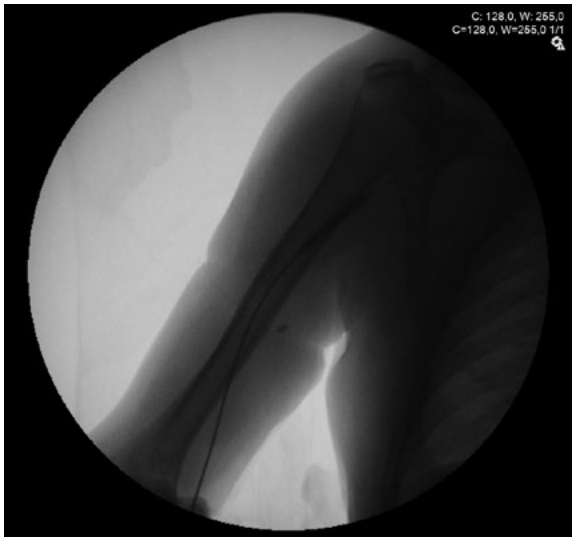
Informed consent for BAM was obtained from all patients undergoing the procedure. Endovascular procedures were performed in an operating room under local anaesthesia. To avoid multiple punctures of an immature vein, all punctures were done under ultrasound guidance. Balloon dilatation was performed under fluoroscopic, ultrasound or CO2 guidance. Ultrasound or CO2 guidance was used in pre-dialysis patients to avoid the use of iodinated contrast. Depending on the location and cause of AVF maturation failure, one of three approaches was used: if the initial venous segment was mature, anterograde venous puncture was performed 2 cm after anastomosis; if an entire immature venous segment and focal stenosis were found, we performed retrograde venous puncture as distal as possible; if an entire immature venous segment and multiple stenoses were found, anterograde arterial puncture was performed. After placement of the introducer sheath, angioplasty of the entire venous segment was performed with a 4 mm angioplasty balloon (see Figures 1 and 2). Over the following weeks, and according to two-weekly clinical and Doppler ultrasound evaluations, progressive angioplasty with a 5 mm and 6 mm balloon was performed. For all procedures, heparin 2,500 IU was administered.

Technical success was defined by the usability of the AVF for haemodialysis.

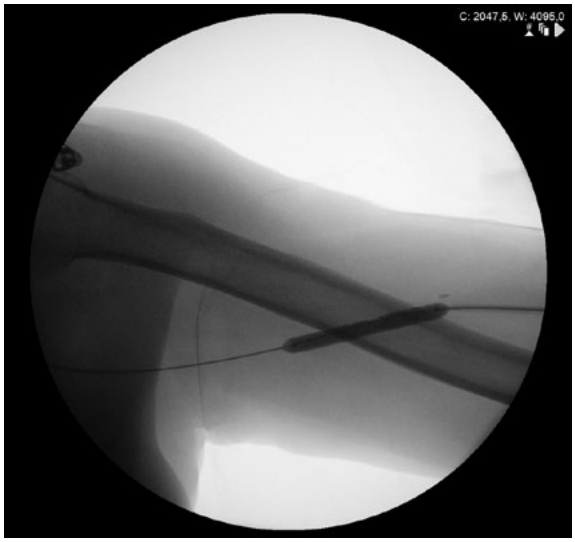
Results

Between 2015 and 2017, twelve patients underwent BAM. The mean age among these patients was 67.4±16 years (range 35–85 years) and most (66.7%) were male. One-third of the patients were diabetic.

Almost all of the fistulas were brachiocephalic, with only one being radiocephalic, and in 83% of the cases the fistula was the patient's first vascular access.



■ FIGURE 1. Placement of the introducer sheath and guidewire



■ FIGURE 2. Angioplasty of the venous segment with a 4 mm balloon

The first evaluation of the vascular access was performed eight days after surgery in all patients, while the second evaluation was performed a median of 6.5 weeks after surgery.

After duplex ultrasound imaging in the vascular access clinic, the presence of a juxta-anastomotic stenosis was diagnosed in nine patients (75%), whereas a proximal cephalic vein stenosis was detected in the remaining three cases (25%).

Before BAM, the diameter of the arterialised vein was, on average, 4.9 ± 0.6 mm (range 4.0–6.0 mm) and the mean access flow rate was 586 ± 230 ml/minute (range 260–850 ml/minute). The first PTA was performed a median of nine weeks after the access creation. The number of procedures necessary until AVF maturation was 1.75 ± 1 per access (range 1–3). Interventions were performed under ultrasound guidance in three patients and CO2 guidance in one patient, with all four of these patients being at the pre-dialysis stage, while fluoroscopic guidance was used for eight patients.

In eight patients (66.7%), BAM was successful, making the AVF suitable for dialysis. After BAM, the diameter of the arterialised vein was, on average, 6.5 ± 0.5 mm (range 6.0–7.5 mm) and the mean access flow rate was 1,078 ± 406 ml/minute (range 650–1,700 ml/minute).

The remaining four cases had resistant stenosis and of these four, one thrombosed after the first angioplasty, two showed no response to PTA and presented a *de novo* stenosis at the introducer site with subsequent partial thrombosis, and one underwent surgical revision. No other complications were registered.

Discussion

Although BAM is an invasive and controversial treatment, the results obtained in this small series of patients were favourable, with success achieved in most of the cases. The observational and retrospective design, together with the small sample size, are the major limitations of our study.

Some authors associate angioplasty with significant deleterious effects on AVFs, mainly because of significant endothelial and smooth muscle cell injury, promoting cytokine activation, neo-intimal hyperplasia and medial hypertrophy.[8,17] Others, however, believe that the success of BAM is due to the difference in physiology of arterial and venous angioplasty. Venous angioplasty for the purpose of fistula maturation involves rupture of the entire vessel wall.[4,15] The arterial pressure subsequently exerted on the injured walls of the veins precipitates fistula dilatation, rather than injury-mediated sclerosis and stenosis.[4]

BAM focuses on dilating the usable segment of the AVF to a sufficiently large diameter, thereby facilitating cannulation,[18] and allows simultaneous resolution of significant stenosis.

The success rate we achieved with BAM was 66.7%, with success defined as the ability to use the AVF for HD, although definitive criteria have not yet been established. The success rates reported in the literature, using the same definition, are variable, ranging from 46% to over 80%.[1,14,15,19,20]

In the four cases without success, resistant proximal cephalic vein stenosis (n=2) and juxta-anastomotic stenosis (n=2) were found to be the cause.

When compared with the retrospective analysis of 336 BAM procedures by DerDerian *et al,*[16] we had a higher rate of access thrombosis (17% versus 1.5%), although the small sample size of our analysis limits comparison. We also report *de novo* stenosis at the introducer puncture site, an otherwise rarely described complication.

By allowing access rescue, BAM can contribute to vascular territory preservation, as it can greatly expand the pool of patients suitable for an AVF (using veins and arteries of marginal diameter) and with a usable AVF. This is associated with subsequent reductions in the placement and duration of dialysis catheters, morbidity, mortality and global costs.

Another point of note from this analysis is the use of CO2- and ultrasound-guided PTA to avoid iodinated contrast administration. In our hospital, these techniques have been evaluated over the past few years, demonstrating their efficacy and safety, and they are now routinely used for patients with a previous history of iodinated contrast allergy and those who are not yet on dialysis.[12]

Conclusion

The experience with BAM in our centre demonstrated that it can be a valid and successful option to overcome the problem of AVF non-maturation, since there are currently few alternatives for its resolution ■

Declaration of interest
The authors declare that there are no conflicts of interest.

References

1. Park SC, Ko SY, Kim J Il, Moon IS, Kim SD. Balloon-assisted maturation for arteriovenous fistula maturation failure : an early period experience. *Ann Surg Treat Res* 2016; **90:** 272–278
2. Santoro D, Benedetto F, Mondello P *et al.* Vascular access for hemodialysis: Current perspectives. *Int J Nephrol Renovasc Dis* 2014; **7:** 281–294.
3. Asif A, Roy-Chaudhury P, Beathard GA. Early arteriovenous fistula failure: a logical proposal for when and how to intervene. *Clin J Am Soc Nephrol* 2006; **1:** 332–339.
4. Miller G, Friedman A. Balloon-Assisted Maturation of Arteriovenous Fistulas. *Endovascular Today* 2010; 46–54.
5. Pirozzi N, Garcia-Medina J, Hanoy M. Stenosis complicating vascular access for hemodialysis: indications for treatment. *J Vasc Access* 2014; **15:** 76–82.
6. Vascular Access 2006 Work Group. Clinical practice guidelines for vascular access. *Am J Kidney Dis* 2006; **48**(Suppl 1): S177–S247.
7. Rothuizen TC, Wong C, Quax PH *et al.* Arteriovenous access failure: More than just intimal hyperplasia? *Nephrol Dial Transplant* 2013; **28:** 1085–1092.
8. Roy-Chaudhury P, Spergel LM, Besarab A, Asif A, Ravani P. Biology of arteriovenous fistula failure. *J Nephrol* 2007; **20:**150–163.
9. Nassar GM, Nguyen B, Rhee E, Achkar K. Endovascular treatment of the "failing to mature" arteriovenous fistula. *Clin J Am Soc Nephrol* 2006; **1:** 275–280.
10. Sivanesan S, How TV, Bakran A. Sites of stenosis in AV fistulae for haemodialysis access. *Nephrol Dial Transplant* 1999; **14:** 118–120.
11. Beathard GA, Arnold P, Jackson J, Litchfield T. Aggressive treatment of early fistula failure. *Kidney Int* 2003; **64:** 1487–1494.
12. Rizvi SA, Usoh F, Hingorani A *et al.* The Clinical Efficacy of Balloon-Assisted Maturation of Autogenous Arteriovenous Fistulae. *Ann Vasc Surg* 2017; **41:** 41–45.
13. Roy-chaudhury P, Lee T, Woodle B *et al.* Balloon-assisted maturation (BAM) of the arteriovenous fistula: the good, the bad, and the ugly. *Semin Nephrol* 2012; **32:** 558–563.
14. Miller GA, Goel N, Khariton A *et al.* Aggressive approach to salvage non-maturing arteriovenous fistulae: a retrospective study with follow-up. *J Vasc Access*. 2009; **10:** 183–191.
15. De Marco Garcia LP, Davila-Santini LR, Feng Q *et al.* Primary balloon angioplasty plus balloon angioplasty maturation to upgrade small-caliber veins (<3mm) for arteriovenous fistulas. *J Vasc Surg* 2010; **52:** 139–144.
16. DerDerian T, Hingorani A, Boniviscage P, Carollo A, Ascher E. Acute complications after balloon-assisted maturation. *Ann Vasc Surg* 2014; **28:** 1275–1279.
17. Van Belle E, Bauters C, Asahara T, Isner JM. Endothelial regrowth after arterial injury: from vascular repair to therapeutics. *Cardiovasc Res* 1998; **38:** 54–68.
18. Chawla A, DiRaimo R, Panetta TF. Balloon angioplasty to facilitate autogenous arteriovenous access maturation: a new paradigm for upgrading small-caliber veins, improved function, and surveillance. *Semin Vasc Surg* 2011; **24:** 82–88.
19. Voormolen EH, Jahrome AK, Bartels LW *et al.* Nonmaturation of arm arteriovenous fistulas for hemodialysis access: A systematic review of risk factors and results of early treatment. *J Vasc Surg* 2009; **49:** 1325–1336.
20. Nikolic B. Hemodialysis fistula interventions: diagnostic and treatment challenges and technical considerations. *Tech Vasc Interv Radiol* 2008; **11:** 167–174.

Key points

- **Arteriovenous fistulas (AVFs) are the vascular access of choice for haemodialysis (HD); however, their success is limited by high rates of maturation failure.**
- **To overcome this problem, balloon-assisted maturation (BAM) has emerged as an innovative and controversial technique, during which the AVF is exposed to serial graduated dilatation of the entire length, with repeated percutaneous transluminal angioplasties until the desired diameter and flow are achieved.**
- **We conducted an observational retrospective review of patients undergoing BAM at our centre between 2015 and 2017, assessing the access type, aetiology of non-maturation, outcomes and complications of the technique.**
- **The results were favourable and success, defined as the ability to use the AVF for HD, was achieved in most cases. In those without success, resistant proximal cephalic vein stenosis and juxta-anastomotic stenosis were found to be the cause.**
- **By allowing access rescue, BAM can contribute to vascular territory preservation and can greatly expand the pool of patients suitable for an AVF and with a usable access.**

Vaccines for kidney transplant recipients: efficacy considerations and recommendations

Infection remains a major cause of morbidity and mortality among kidney transplant recipients (KTRs); hence, protection against vaccine-preventable diseases is desirable. Guidelines recommend that every effort should be taken to complete the vaccination schedule prior to transplantation, as the immune response is better during this period compared with the immunosuppressed post-transplant period.[1]

Vaccination in KTRs is fraught with numerous challenges. Inadequate immune response and live vaccine-induced disease in the immunocompromised host are potential hazards.[1–4] Inactivated vaccines are safe for KTRs, as they are incapable of replicating in the host. Live vaccines, such as the mumps, measles, rubella, varicella-zoster virus (VZV) and Bacillus Calmette–Guérin (BCG) vaccines, are contraindicated after kidney transplantation (see Box 1), as patients are immunosuppressed and, thus, face the theoretical risk of unchecked replication of the viruses/bacteria that can result in vaccine-related disease.[3]

The optimal time to start vaccination in KTRs is not known. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend starting vaccinations once the patient is on a minimal maintenance dose of immunosuppressive medications (generally three to six months post-transplant). An exception is the influenza vaccine, which can be given one month post-transplantation, before the start of the influenza season, regardless of the state of immunosuppression, because the disease is more aggressive and severe if contracted early post-transplantation.[3,5–8]

A major factor that helps in protecting immunocompromised patients is full vaccination of household contacts as per recommendations.[5,6]

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Vaccine response in CKD patients and KTRs

A uremic milieu and protein energy wasting may both contribute to the immunosuppressed state of patients with chronic kidney disease (CKD). This increases their susceptibility to infections and weakens response to vaccination. Dysfunction of both innate and adaptive immunity is seen in CKD. CKD results in impaired phagocytic function of granulocytes, monocytes and macrophages, decreased proliferation of T-lymphocytes, dysfunction of antigen-presenting cells (APCs) and B-cell lymphopenia. Dysfunction of APCs is the result of faulty expression and/or reduced activity of Toll-like receptors leading to alteration of the co-stimulatory molecules CD80 and CD86. This may account for a poorer than normal response to most vaccines in this group of patients.[9]

For kidney transplantation, an immunosuppressed state is therapeutically achieved to reduce the risk of graft rejection. Immunosuppression can cause poorer response to most vaccines. Induction therapy may involve T-cell-depleting agents, such as polyclonal antibodies (for example, thymoglobulin or lymphoglobulin), or non-depleting agents like humanised monoclonal antibodies directed against interleukin-2 receptors (such as basiliximab) that inhibit T-cell proliferation. Lifelong immunosuppression is required post-transplantation; agents used to achieve this include calcineurin inhibitors (such as tacrolimus or ciclosporin), antimetabolites (such as mycophenolate mofetil or azathioprine), mammalian target of rapamycin (mTOR) inhibitors (such as sirolimus or everolimus) and steroids (such as prednisolone).[10,11]

Not all immunosuppressive medications affect immune response to vaccines in the same manner; for example, Smith *et al* showed in their study that mycophenolate mofetil and ciclosporin may result in a poorer response to influenza vaccination, when compared with azathioprine.[12] Similarly, a study by Versluis *et al* demonstrated that ciclosporin-treated individuals showed a significantly lower antibody titre after influenza vaccination, compared with azathioprine-treated individuals and healthy controls.[13] Ciclosporin blocks the synthesis and release of lymphokines. This inhibits T-cell dependent B-cell activation, leading to a diminished response to influenza vaccination, as the immune response to the influenza vaccine is T-cell dependent.

BOX 1. Vaccines not recommended in kidney transplant recipients[3]

- Live influenza vaccine
- Live attenuated hepatitis A vaccine
- Live oral typhoid vaccine
- Live oral cholera vaccine
- Oral polio vaccine
- Measles vaccine
- Mumps vaccine
- Rubella vaccine
- Bacillus Calmette–Guérin (BCG) vaccine
- Rotavirus vaccine
- Zoster vaccine
- Varicella vaccine
- Live attenuated yellow fever vaccine
- Live Japanese B encephalitis vaccine
- Small pox vaccine

In contrast, azathioprine diminishes the primary antibody response to T-cell dependent antigens, but the peripheral lymphocytes retain their ability to respond. This may be the reason why azathioprine-treated patients build a better antibody response to the influenza vaccine.[13]

Given the poorer response to the standard vaccination doses, a different strategy for vaccination in KTRs and CKD patients may be required. Mujtaba *et al* investigated the antibody response to a standard influenza vaccine in 47 KTRs four to eight weeks after vaccination. They found that only three patients seroconverted after vaccination, out of a total of 17 whose test was negative before vaccination (response rate 17.6%). The investigators, therefore, suggested that a high-dose or two-stage standard-dose vaccine may offer a more robust immune response in KTRs.[14] Intradermal vaccines may also be helpful in this regard.[15] All these proposed solutions require further investigation.

Recommended vaccines

National recommendations may vary by geographical area, according to the prevalence of diseases. Specialists involved in the care of transplant recipients must refer to the guidelines practised in their country before prescribing vaccines to their kidney transplant patients. Table 1 summarises guidelines from various international societies.[3,4,6,16]

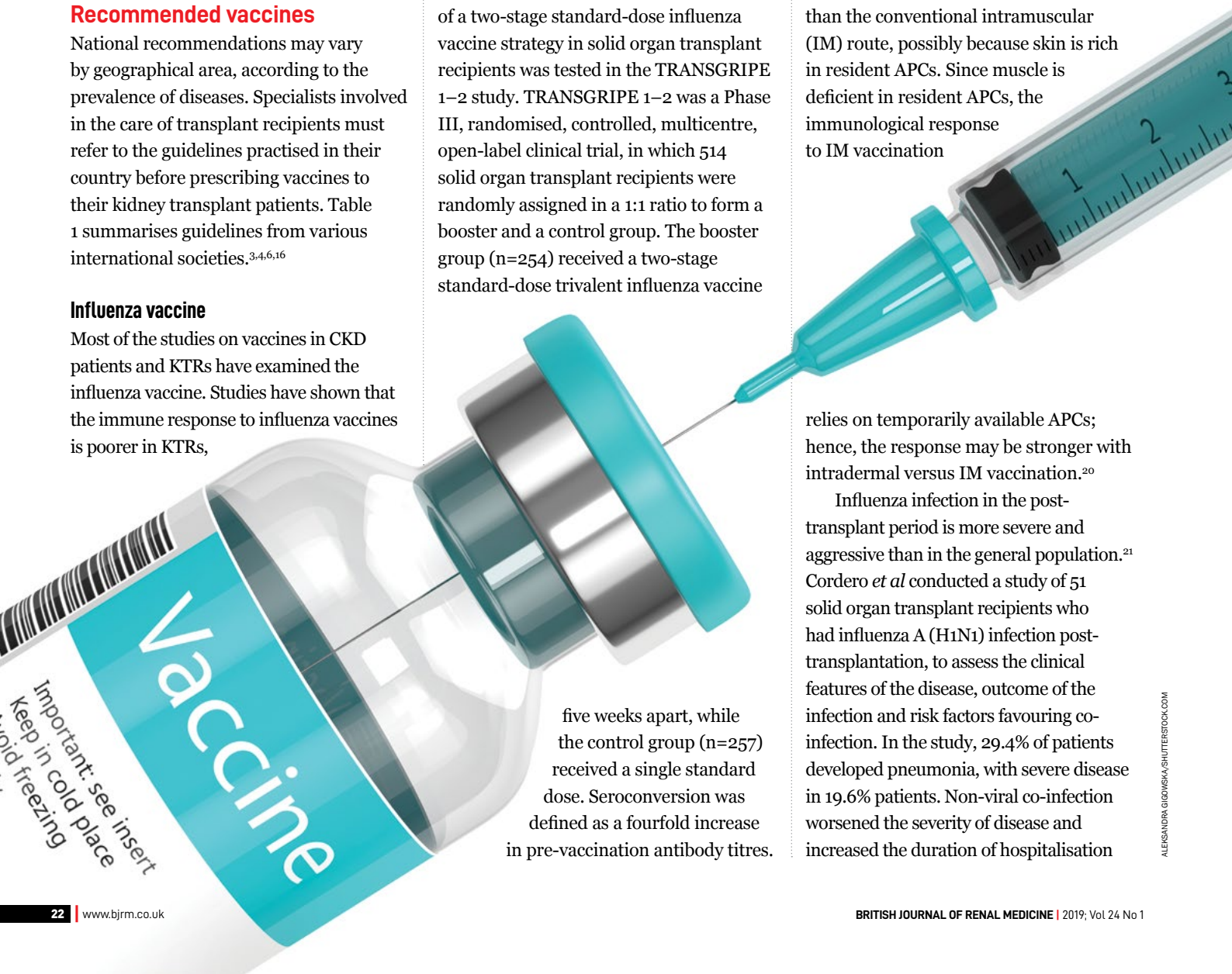
Influenza vaccine

Most of the studies on vaccines in CKD patients and KTRs have examined the influenza vaccine. Studies have shown that the immune response to influenza vaccines is poorer in KTRs, compared with the normal population and, to a lesser extent, haemodialysis patients. Broeders *et al* enrolled 21 healthy members of hospital staff as controls, alongside 53 haemodialysis patients and 111 KTRs. The study evaluated the immune response to a split-virion, inactivated, adjuvanted pandemic influenza vaccine (H1N1) one month after vaccination. The KTRs were on a calcineurin inhibitor (tacrolimus 52% of patients; ciclosporin 33%), proliferation inhibitor (mycophenolic acid 59%; azathioprine 32%) or mTOR inhibitor (10%), and most were on methylprednisolone (82%). Seroconversion was defined as fourfold or greater increase in an individual's antibody titre compared with their pre-vaccination level. This study showed that, compared with healthy controls, seroconversion rates were lower in haemodialysis patients and, in particular, in KTRs (90% seroconversion in the control population, compared with 57% in haemodialysis patients and 44% in KTRs).[17]

The concept of better immunogenicity of a two-stage standard-dose influenza vaccine strategy in solid organ transplant recipients was tested in the TRANSGRIPE 1–2 study. TRANSGRIPE 1–2 was a Phase III, randomised, controlled, multicentre, open-label clinical trial, in which 514 solid organ transplant recipients were randomly assigned in a 1:1 ratio to form a booster and a control group. The booster group (n=254) received a two-stage standard-dose trivalent influenza vaccine five weeks apart, while the control group (n=257) received a single standard dose. Seroconversion was defined as a fourfold increase in pre-vaccination antibody titres. The antibody titres were tested ten weeks and one year after the first dose. The trial demonstrated good safety outcomes with a booster dose given five weeks after the first dose and showed that the booster resulted in a better short-term immunological response (seroconversion rate >40%) for all three strains of the influenza virus in the trivalent influenza vaccine, compared with the standard one-dose regimen, which achieved adequate response only for one strain (influenza B). Response rates in the booster group compared with the control group were 53.8% versus 37.6% for influenza A (H1N1), 48.1% versus 32.3% for influenza A (H3N2) and 90.7% versus 75% for influenza B.[18,19]

A Phase II study involving 62 adult KTRs suggested that intradermal influenza vaccination may be beneficial in providing protection in KTRs who failed to respond to the trivalent influenza vaccine.[15] Similar results have been observed in other studies as well.[20] The intradermal route provides a better immunological response than the conventional intramuscular (IM) route, possibly because skin is rich in resident APCs. Since muscle is deficient in resident APCs, the immunological response to IM vaccination relies on temporarily available APCs; hence, the response may be stronger with intradermal versus IM vaccination.[20]

Influenza infection in the post-transplant period is more severe and aggressive than in the general population.[21] Cordero *et al* conducted a study of 51 solid organ transplant recipients who had influenza A (H1N1) infection post-transplantation, to assess the clinical features of the disease, outcome of the infection and risk factors favouring co-infection. In the study, 29.4% of patients developed pneumonia, with severe disease in 19.6% patients. Non-viral co-infection worsened the severity of disease and increased the duration of hospitalisation



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and mortality. Patients who were infected early post-transplantation (<90 days) had more severe influenza than those who were infected later.[7]

Given that influenza disease severity is greater if patients are infected early post-transplantation, transplant recipients may benefit from vaccination at the earliest opportunity. Concerns remain whether the immune response to the vaccine will be adequate. Pérez-Romero *et al* compared the safety and efficacy of influenza vaccination in patients who received the vaccine within six months of transplantation (n=130) and those who received it later (n=668) in a prospective, multicentre cohort study of 798 adult solid organ transplant recipients. The investigators found that the seroprotection rate was similar in both groups: 73.1% versus 76.5% for influenza A (H1N1), 67.5% versus 74.1% for influenza A (H3N2) and 84.2% versus 85.2% for influenza B. Time since transplantation did not affect the response to vaccination. The authors concluded that it was safe and effective to administer the influenza vaccine as early as one month post-transplantation.[8]

The Group for the Study of Infection in Transplant Recipients of the Spanish Society of Infectious Diseases and Clinical Microbiology and the Spanish Network for Research in Infectious Diseases recommend that severely immunosuppressed patients who are at high risk of developing influenza-related complications may need regular pre- and post-exposure chemoprophylaxis with drugs like oseltamivir and zanamivir. Patients who are not severely immunosuppressed and not at high risk of complications do not require such chemoprophylaxis routinely; however, they will need antiviral therapy if they have confirmed exposure and develop symptoms of influenza. Administration of post-exposure chemoprophylaxis is recommended for ten days. Pre-exposure chemoprophylaxis should be administered for the entire flu season; however, data supporting the safety and tolerability of such prophylaxis for more than six weeks are lacking.[22] Guidelines and recommendations vary between different countries.

Data on whether influenza vaccination results in an increase in anti-human leukocyte antigen (anti-HLA) antibody production in KTRs are conflicting. Katerinis *et al* evaluated 20 patients who developed anti-HLA antibodies after influenza vaccination. Thirteen of these had donor-specific anti-HLA antibodies, while the remainder had non-donor-specific anti-HLA antibodies. In most cases, these antibodies disappeared or levels decreased at six months after vaccination. The study included two independent cohorts of KTRs, whose yearly rates of anti-HLA antibody development (sensitisation) were 17.3% and 11.9%, which were higher than that observed in the historical cohort that was used for comparison (6%). Although the exact cause of sensitisation after influenza vaccination is not known, the investigators proposed that it could be due to: (a) shared epitopes between HLA proteins and influenza vaccine haemagglutinin and neuraminidase; (b) HLA triggering a B-cell response against antigens in the influenza vaccine that cross-reacts with some HLA proteins; (c) a reaction between antibodies against influenza antigens and HLA antigen on the microbeads used during Luminex® testing; and (d) squalene- and α-tocopherol-based adjuvant (AS03) in the vaccine triggering a non-specific immune response leading to the development of anti-HLA antibodies.[23] In contrast, Candon *et al* found that the influenza vaccine does not cause sensitisation. They investigated 63 KTRs for the development of anti-HLA antibodies and allograft rejection. Inactivated trivalent influenza vaccine was administered and both class I and class II anti-HLA antibodies were tested on Days 0 and 30 after vaccination, with a mean fluorescence intensity of >300 considered positive. The donor-specific antibody (DSA) titres observed on Day 30 were not significantly different to those observed on Day 0. No rejection episodes were observed in KTRs in the three months following vaccination. The authors concluded that influenza vaccination does not impact DSA and allograft rejection.[24]

TABLE 1. Recommended vaccines[a] for kidney transplant recipients[3,4,6,16]

Vaccine	KDIGO[b]	ACIP (incorporates IDSA guideline)[c]	AST	Australian Immunisation Handbook
Inactivated influenza vaccine (IM); trivalent and quadrivalent	Yes, annually	Yes	Yes	Yes: 1st year post-transplant 2 doses 4 weeks apart, then annually
Pneumococcal vaccine (IM)	Yes, if risk is high	Yes	Yes	Yes
Recombinant hepatitis B vaccine (IM)	Yes[d]	Yes	Yes	Yes
Inactivated hepatitis A vaccine	Yes[e]	Yes	Yes	Yes
Human papilloma virus vaccine	Yes[e]	Yes	Yes	Yes
Inactivated polio vaccine (IM or SC)	Yes[e]	Yes	Yes	Yes[f]
Diphtheria toxoid (IM)	Yes[e]	Yes	Yes	Yes[g]
Pertussis acellular (IM)	Yes[e]	Yes	Yes	Yes[g]
Inactivated tetanus toxoid	Yes[e]	Yes	Yes	Yes[g]

ACIP = Advisory Committee on Immunization Practices; AST = American Society of transplantation; IDSA = Infectious Diseases Society of America; IM = intramuscular; KDIGO = Kidney Disease: Improving Global Outcomes; SC = subcutaneous
[a] Guidelines differ by country; please prefer to national guidelines before prescribing; [b] Except hepatitis B, vaccination schedule for all inactivated vaccines as for general population; [c] Recommendations for altered immunocompetence (immunocompromise, immunosuppression and immunodeficiency), including haemopoietic stem cell transplantation. No specific solid organ transplant recommendations; [d] 4-dose vaccination schedule at 0, 1, 2 and 6 months; antibody titres 6–12 weeks after completing the vaccination schedule, then annually; revaccinate if titre falls <10 mIU/ml; [e] Mentioned as a general statement; no details for solid organ transplant recipients; [f] Adults who completed the polio vaccination schedule in childhood, should receive a booster every 10 years if at high risk of exposure; [g] Diphtheria-tetanus-acellular pertussis vaccine (children's formulation DTPa if aged <10 years; adolescent/adult formulation dTpa if ≥10 years). Previously unvaccinated individuals: <10 years: 3-dose DTPa; ≥10 years, 1st dose as dTpa, followed by 2 doses of diphtheria-tetanus (dT) vaccine. If dT unavailable, complete course with dTpa

Hepatitis B vaccine

As with influenza vaccination, the response to hepatitis B vaccination post-transplantation is poorer than that in the general population. The hepatitis B vaccine is administered as a three-dose series of 20 µg at Months 0, 1 and 6, resulting in protective antibody titres in 90–95% of cases in the general population; however, CKD patients and transplant recipients seem to need higher doses.[25]

An observational study of 17 KTRs was conducted to test a three-dose schedule of double-strength (40 µg) hepatitis B vaccination administered post-transplantation. This schedule was found to be safe and did not cause any rejection episodes, but it resulted in a weak immune response. Only three out of 17 KTRs showed

a positive response by mounting a hepatitis B surface antibody (anti-HBsAb) response. The cumulative antibody response rate was only 17.6% one year after vaccination.[26]

A four-dose series of the double-strength vaccine seems to provide a better immune response. Fakhrmousavi *et al* studied the development of a protective immune response within six months post-transplantation in 49 KTRs aged >18 years. Patients received double doses (40 µg) of the hepatitis B recombinant vaccine in a four-dose series at Months 0, 1, 2 and 6. The immunosuppressive medications used were prednisolone, mycophenolate mofetil, azathioprine and ciclosporin. HBsAb titres were measured eight weeks after the third and fourth dose. Patients with HBsAb titres of <10 mIU/ml were considered non-responders, while titres ≥10 mIU/ml were considered protective. The response rate was 44.89% after the third and 57.14% after the fourth dose.[25] The same four-dose schedule can be used in pre-dialysis CKD patients. Studies comparing the immunological response and effectiveness in pre-dialysis CKD patients versus KTRs are currently lacking.

As with the influenza vaccine, studies on the hepatitis B vaccine also suggest that the intradermal route may provide a better immunological response than the conventional IM vaccine. Choy *et al* enrolled 24 KTRs who failed to respond to double doses of the IM hepatitis B vaccine administered 44.7 ± 7.4 months post-transplantation. Anti-HBs titres checked within four weeks after vaccination showed no response to the vaccine. These patients were on either a two- (ten patients) or three-drug (14 patients) immunosuppressive regimen. They received eight 5 µg doses of the intradermal hepatitis B vaccine, administered at two-week intervals. The investigators observed that, after eight doses, 37.5% (nine patients) developed protective anti-HBs titres (≥10 mIU/ml) and concluded that the intradermal vaccination may be more efficacious than that administered by the IM route and may be used in those who do not mount an adequate response to the IM vaccine.[27]

Saw *et al* studied 68 haemodialysis patients awaiting transplantation (including 19 patients waiting for re-transplantation). A rise in panel reactive antibody (PRA) titre (of at least 20% in class I and 20% in class II antibodies) was observed in three out of 32 patients after hepatitis B vaccination. Development of anti-HLA antibodies was more frequent in patients who were waiting for re-transplantation than those who had never had a transplant. Blood transfusion as a cause for a rise in PRA titres was ruled out in all but one patient. The investigators suggested that HLA sensitisation might occur after hepatitis B vaccination.[28]

> *The intradermal route may provide a better immunological response than the conventional IM vaccine*

Pneumococcal vaccine

In keeping with responses to other vaccines, pneumococcal vaccine seroconversion rates are lower in KTRs than in CKD patients. When Linnemann *et al* compared the immunological response to the pneumococcal vaccine in haemodialysis patients and KTRs, the response was significantly lower in patients who had recently received a transplant compared with those on haemodialysis. The antibody levels achieved were lower than those reported in studies conducted in the general population; however, they were still in a range considered protective against most pneumococcal strains.[29]

A study by Lindemann *et al* evaluated the immunogenicity of the pneumococcal vaccine in KTRs. Forty-three KTRs received the pneumococcal vaccine, and antibody response to 14 serotypes was measured before and four weeks after vaccination. The investigators observed a good immunological response to the vaccine, as shown by a rise in median antibody titres from 12.1 mg/l in the pre-vaccination period to 51.9 mg/l four weeks after vaccination. These antibody levels were only slightly lower than those seen in vaccinated healthy controls in another study (61.5 mg/l).[30,31] The same group of investigators also noted that in 49 KTRs who had received the pneumococcal vaccine, the immune response to the vaccine at 15 months post-vaccination was 77% of the response at one month post-vaccination. The decrease in immune response from Month 1 to Month 15 post-vaccination was lesser in younger patients, women and those with better kidney function, as well as being lesser in patients on ciclosporin than those on tacrolimus. This study suggests that even at Month 15, the pneumococcal vaccine provides at least partial protection.[32]

In another study by Lindemann *et al,* the possibility of sensitisation in KTRs after pneumococcal vaccination was evaluated.[33] Forty-nine KTRs were enrolled in the study. Median time between transplantation and vaccination was 6.5 years. In three years of follow-up post-vaccination, none of the patients developed biopsy-proven acute rejection. Immunosuppressive medications included different combinations of mycophenolate mofetil, tacrolimus, prednisolone, ciclosporin and azathioprine. The investigators observed no change in anti-HLA and major-histocompatibility-complex class I-related chain A (MICA) antibody status after pneumococcal vaccination.[33]

Human papilloma virus vaccine

The human papillomavirus (HPV) vaccine is recommended in KTRs by KDIGO and American Society of Transplantation guidelines. Kumar *et al* conducted a study of 48 patients aged between 18 and 35 years who were given the quadrivalent HPV vaccine. Patients were either KTRs (64%) or lung transplant recipients (23%) and were at least three months post-transplantation. Most of the patients were on calcineurin inhibitors and mycophenolate mofetil. Vaccination followed a three-dose schedule, with injections at Months 0, 2 and 6. The vaccine was found to have a good safety and efficacy profile in this group of patients, although the immunogenicity was lower than in the general population. A positive response to the vaccine was seen in 52.6% of patients for HPV-18 to 68.4% for HPV-11.[34] The study did not have a control group with healthy individuals for comparison, but the published literature suggests much higher response rates (97–99%) to the vaccine in the general population.[34] Dosage or schedule variations to augment seroconversion rates in the transplant population have not been studied with HPV vaccines.

Tetanus vaccine

Young children are advised to complete the tetanus vaccination schedule and a booster dose is advised for older children and adults.[35] The response to a booster dose after solid organ transplantation is good, as shown in a study conducted by Enke *et al*. In that study, 42 KTR children with completed primary immunisation received a standard diphtheria and tetanus booster. A complete response to the tetanus booster dose was observed and an adequate response was sustained until the end of the one-year observation period.[36]

In people who had received previous vaccination with tetanus toxoid but not had the full three-dose primary immunisation, the previous vaccination may have primed the immune system but not provide immunity; hence, wound management may require the administration of tetanus immune globulin along with tetanus toxoid.[37]

Post-exposure prophylaxis

Post-exposure prophylaxis, or post-exposure prevention, is defined as any preventive medical treatment initiated after exposure to a pathogen with an intent to prevent occurrence of a disease.

Please refer to Table 2 for a summary of recommendations on vaccines that may be used in special circumstances, including for post-exposure prophylaxis and travel to endemic areas.[3,4,6,16]

Rabies

Limited data are available to guide management in KTRs after suspected contraction of rabies. Rabies vaccination is used mostly as post-exposure prophylaxis in KTRs. The WHO recommends that immunocompromised individuals receive adequate wound management (thorough washing of the wound with soap and water, detergent and povidone iodine), followed by rabies immune globulin and full vaccination.[38]

Rodríguez-Romo *et al* reported the case of a KTR who was bitten by a rabid dog. The patient's immunosuppressive medications consisted of ciclosporin 60 mg twice daily, mycophenolate mofetil 250 mg three times per day and prednisolone 5 mg once daily. He received the rabies vaccine according to the standard schedule, along with human rabies immunoglobulin. He showed an adequate antibody response after Day 7, which declined by Day 28; hence, immunosuppression was reduced by withholding mycophenolate mofetil and decreasing the dose of ciclosporin, and he received multiple booster doses of the vaccine over a period of one month (on Days 38, 41, 45, 52 and 66) to achieve an adequate antibody response. The patient had an adequate antibody titre over the following year and maintained good graft function, with no symptoms of rabies at the end of 19 months. Although the investigators could not discern whether the adequate immune response was due to a reduction of immunosuppression or multiple booster doses of the vaccine, they felt the combined approach was necessary to achieve the desired outcome.[39]

Transmission of rabies through solid organ transplantation has been reported.[40–42] In 2017, Chen *et al* reported transmission of rabies in solid organ transplants in Changsha, China. They reported that the kidneys and liver were harvested from a brain-dead donor who had died of viral encephalitis. Rabies was suspected in this donor before organ harvesting, but serum rabies antibody testing was negative. Two patients received kidneys and an infant received the liver from this donor. Both KTRs were readmitted with signs and symptoms of rabies around six weeks post-transplantation (the typical incubation period of rabies is one to three months) and died within a week of presentation. The liver transplant recipient presented with pneumonia on the 34th day after transplantation and died of asphyxia and multi-organ failure within five days. She did not show any sign of rabies.[40] In 2004, Srinivasan *et al* reported the deaths of four transplant recipients (two kidneys, one liver and one arterial segment) who contracted the disease through transplantation from an infected donor. All four recipients had encephalitis within 30 days of transplantation and died within an average of 13 days after the onset of neurological symptoms.[42]

Necessary precautions should, therefore, be taken to avoid transplanting organs from infected donors. In the event of transplantation from a donor infected with rabies, inactivated rabies vaccine and rabies immune globulin must be given as per recommended schedule for the general population.[5]

Other vaccines for post-exposure prophylaxis

Prophylactic administration of the tick-borne encephalitis, meningococcal, killed

TABLE 2. Recommended vaccines[a] for kidney transplant recipients in special circumstances[b] [3,4,6,16]

Vaccine	KDIGO	ACIP (incorporates IDSA guideline)[c]	AST	Australian Immunisation Handbook
Inactivated rabies vaccine (IM)	Yes[d]	Yes	Yes	Yes[e]
Inactivated tick-borne encephalitis vaccine (IM)	Yes[d]	Yes	No details for SOT recipients	No details for SOT recipients
Quadrivalent meningococcal vaccine	Yes[d]	Yes	Yes	Yes
Inactivated meningococcal C conjugate vaccine (IM)	No details for SOT recipients	No details for SOT recipients	No details for SOT recipients	Yes, in children <18 years, but not recommended in adults
Recombinant meningococcal B vaccine (IM)	Yes[d]	Yes	No details for SOT recipients	Yes
Killed Vi polysaccharide *Salmonella typhi* vaccine (IM)	Yes[d]	No details for SOT recipients	Yes	No details for SOT recipients
Killed cholera vaccine (oral)	Yes[d]	No details for SOT recipients	Yes	No details for SOT recipients
Inactivated Japanese encephalitis vaccine (IM)	Yes[d]	Yes	Yes	No details for SOT recipients

ACIP = Advisory Committee on Immunization Practices; AST = American Society of Transplantation; IDSA = Infectious Diseases Society of America; IM = intramuscular; KDIGO = Kidney Disease: Improving Global Outcomes; SC = subcutaneous; SOT = solid organ transplant
[a] Guidelines differ by country; please prefer to national guidelines before prescribing; [b] Travel/post-exposure prophylaxis – only if risk of exposure is high; [c] Recommendations for altered immunocompetence (immunocompromise, immunosuppression and immunodeficiency), including haemopoietic stem cell transplantation. No specific solid organ transplant recommendations; [d] Vaccination schedule advised as in general population; [e] Post-transplant patients not specifically mentioned, but recommended in HIV patients; as both are immunodeficient, this supports use in post-transplant patients

salmonella typhi, killed cholera and Japanese encephalitis vaccines is also recommended after exposure (see Table 2).

Under investigation

Inactivated VZV vaccine

Live VZV vaccine is currently available for the general population. As live vaccines are generally avoided in KTRs, varicella zoster immunoglobulin (VZIG), acyclovir, interferon and vidarabine are usually given to these patients in case of exposure.[43] Kaul *et al* retrospectively evaluated the records of 1,546 KTRs, 23 of whom were diagnosed as being infected with VZV. These 23 patients had no history of VZV vaccination, infection or exposure before transplantation and were negative for VZV IgG and IgM antibodies pre-transplantation. Seven of the 23 patients (60.08%) were infected during the first six months after transplantation when immunosuppression is greatest. Prior to infection, 22 of the 23 patients had stable graft function. Graft dysfunction occurred in five patients after infection and two became dialysis-dependent.[43] Administration of VZIG within 96 hours of exposure is recommended in VZV-naive KTRs becoming infected. If VZIG is not available or the KTR presents more than 96 hours after exposure, acyclovir should be given. In primary VZV infection, treatment with acyclovir is recommended for a period of 15 days.[44] Kaul *et al* had, however, previously noted an aggressive disease course in their transplant recipients. One patient who had received acyclovir therapy for two weeks had developed fulminant disease with haemorrhagic eruptions and pancreatitis and required intravenous ganciclovir followed by oral therapy for three months, along with modification of immunosuppression. The investigators, therefore, gave acyclovir therapy for three months to all patients and found that none of them relapsed.[43] This therapeutic area requires further investigation.

There is a paucity of data pertaining to the use of the VZV vaccine in solid organ transplant patients. Inferences can be made from studies in the stem cell transplant population. An investigational inactivated vaccine reduced the incidence of confirmed herpes zoster cases by an estimated 64% and the incidence of moderate-to-severe herpes zoster pain by an estimated 69.5% compared with placebo in autologous haemopoietic stem cell transplant patients.[45]

McNeil *et al* conducted an open-label, single-arm, multicentre Phase I study to evaluate the safety and efficacy of another inactivated VZV vaccine in adults with haematological malignancies receiving anti-CD 20 monoclonal antibodies. The vaccine was found to be well tolerated and elicited a good immunological response 28 days after the fourth dose.[46] Long-term safety and efficacy data are not available. The vaccine seems promising and may prove to be helpful in other immunocompromised populations including KTRs.

CMV vaccine

CMV-related deaths are estimated to occur in 1–3% of KTRs. CMV can be transmitted through a transplant; hence, CMV-seronegative recipients receiving a kidney from CMV-seropositive donors are especially at risk. CMV disease is three to four times more common in KTRs treated with T-cell-depleting agents.[47]

Key points

- **Kidney transplant recipients (KTRs) are at increased risk of infections because of their immunosuppressed state.**
- **Immunisation can be protective, although it is not as effective as in the general population, as immunosuppression diminishes the immune response of vaccines. Despite this, efforts should be made to vaccinate transplant recipients for vaccine-preventable diseases.**
- **Recommended immunisations for KTRs include the influenza, hepatitis B, human papilloma virus, tetanus and pneumococcal vaccines.**
- **KTRs may require different regimens than the general population and may benefit from increased dosage and different scheduling and routes of administration.**

Metselaar *et al* studied the use of prophylactic anti-CMV immunoglobulin (anti-CMV-Ig) in preventing CMV-related death in a double-blind placebo-controlled study. Forty KTRs who had received rabbit antithymocyte globulin for the treatment of acute rejection were evaluated. Anti-CMV-Ig at 100 mg/kg was given to 20 patients and placebo (20% albumin) to the other 20. The injections were given the same day as rabbit anti-thymocyte globulin and subsequently on Days 7, 14, 35, 56 and 77. Among patients treated with anti-CMV-Ig, no deaths occurred, while CMV viraemia occurred in 11, seven of whom developed CMV disease. This difference was not statistically significant when compared with patients receiving albumin (placebo). Seropositive recipients showed no benefit from passive immunisation. Anti-CMV-Ig prophylaxis may be beneficial for CMV-seronegative recipients of a kidney from CMV-seropositive donors.[48]

In a randomised, double-blind, placebo-controlled, parallel-group Phase II trial, Kharfan-Dabaja *et al* observed that the CMV DNA vaccine TransVax (later named ASP0113), consisting of plasmids encoding CMV glycoprotein B and phosphoprotein 65, was well tolerated and reduced the occurrence, recurrence and duration of episodes of CMV viraemia and improved time-to-event at one year of follow-up. However, a Phase II clinical trial with this vaccine in KTRs, as well as a Phase III clinical trial with the same vaccine in haemopoietic stem cell transplant recipients, did not show promising results.[49]

Summary

KTRs are at a higher risk of acquiring infections than the general population, due to the need for immunosuppressive medication to prevent organ rejection. Immunisation against vaccine-preventable diseases should, therefore, be strongly considered for these patients. Specific vaccination guidelines have been constructed according to the prevalence of diseases in different geographical areas.

Some caveats should be kept in mind with respect to immunisation in the transplant population. The available data on the risk of sensitisation and organ rejection following vaccination are conflicting. Live vaccines carry the theoretical risk of vaccine-induced disease and are not recommended

for KTRs. Inactivated vaccines may be given post-transplantation; however, the response in these immunosuppressed patients is poor compared with that in CKD patients and the general population. Stronger vaccine dosage, an increased number of doses or an alternative route of administration may result in higher and more sustained antibody titres.

Further research is required to refine the dosage, scheduling and best route of administration for the different vaccines available. In addition, research on new vaccines is ongoing and vaccines to protect KTRs against CMV and VZV are in development. While an inactivated VZV vaccine has shown promising results, an inactivated CMV vaccine has not been effective in Phase II clinical trials in KTRs ■

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

References

1. Kim YJ, Kim SI. Vaccination strategies in patients with solid organ transplant: evidences and future perspectives. *Clin Exp Vaccine Res* 2016; **5:** 125–131.
2. Fischer ASL, Møller BK, Krag S, Jespersen B. Influenza virus vaccination and kidney graft rejection: causality or coincidence. *Clin Kidney J* 2015; **8:** 325–328.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9**(Suppl 3): S1–S155.
4. Danziger-Isakov L, Kumar D; AST Infectious Diseases Community of Practice. Vaccination in solid organ transplantation. *Am J Transplant* 2013; **13**(Suppl 4): 311–317.
5. Guidelines for vaccination in kidney transplant recipients. *Indian J Nephrol* 2016; **26**(Suppl S1): 19–25.
6. Australian Technical Advisory Group on Immunisation. *The Australian Immunisation Handbook,* 10th edn. Canberra, Australia: Australian Government Department of Health, 2015.
7. Cordero E, Pérez-Romero P, Moreno A *et al.* Pandemic influenza A (H1N1) virus infection in solid organ transplant recipients: impact of viral and non-viral co-infection. *Clin Microbiol Infect* 2012; **18:** 67–73.
8. Pérez-Romero P, Bulnes-Ramos A, Torre-Cisneros J *et al.* Influenza vaccination during the first 6 months after solid organ transplantation is efficacious and safe. *Clin Microbiol Infect* 2015; **21:** 1040.e11–1040.e18.
9. Kato S, Chmielewski M, Honda H *et al.* Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008; **3:** 1526–1533.
10. Muntean A, Lucan M. Immunosuppression in kidney transplantation. *Clujul Med* 2013; **86:** 177–180.
11. Wiseman AC. Induction Therapy in Renal Transplantation: Why? What Agent? What Dose? We May Never Know. *Clin J Am Soc Nephrol* 2015; **10:** 923–925.
12. Smith KG, Isbel NM, Catton MG *et al.* Suppression of the humoral immune response by mycophenolate mofetil. *Nephrol Dial Transplant* 1998; **13:** 160–164.
13. Versluis DJ, Beyer WE, Masurel N, Wenting GJ, Weimar W. Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporine, but not azathioprine. *Transplantation* 1986; **42:** 376–379.
14. Mujtaba M, Book B, Sharfuddin A *et al.* Antibody Response Following Influenza Vaccination in Renal Transplant Recipients. 2015 American Transplant Congress. Philadelphia, Pennsylvania, USA, 2015 (abstract 448).
15. Morelon E, Pouteil Noble C, Daoud S *et al.* Immunogenicity and safety of intradermal influenza vaccination in renal transplant patients who were non-responders to conventional influenza vaccination. *Vaccine* 2010; **28:** 6885–6890.
16. Centers for Disease Control and Prevention. ACIP Vaccine Recommendations and Guidelines. www.cdc.gov/vaccines/hcp/acip-recs/index.html (last accessed 20/2/2019)
17. Broeders NE, Hombrouck A, Lemy A *et al.* Influenza A/H1N1 vaccine in patients treated by kidney transplant or dialysis: a cohort study. *Clin J Am Soc Nephrol* 2011; **6:** 2573–2578.
18. Cordero E, Roca-Oporto C, Bulnes-Ramos A *et al.* Two Doses of Inactivated Influenza Vaccine Improve Immune Response in Solid Organ Transplant Recipients: Results of TRANSGRIPE 1-2, a Randomized Controlled Clinical Trial. *Clin Infect Dis* 2017; **64:** 829–838.
19. ClinicalTrials.gov. Clinical Trial Evaluating Efficacy and Safety of One Dose Versus Two Doses of Influenza Vaccination (TraNsgripe). NCT01761435. https://clinicaltrials.gov/ct2/show/NCT01761435 (last accessed 3/1/2019)
20. Icardi G, Orsi A, Ceravolo A, Ansaldi F. Current evidence on intradermal influenza vaccines administered by Soluvia™ licensed micro injection system. *Hum Vaccin Immunother* 2012; **8:** 67–75.
21. Viasus D, Paño-Pardo JR, Pachón J *et al.* Factors associated with severe disease in hospitalized adults with pandemic (H1N1) 2009 in Spain. *Clin Microbiol Infect* 2011; **17:** 738–746.
22. López-Medrano F, Cordero E, Gavaldá J *et al.* Management of influenza infection in solid-organ transplant recipients: consensus statement of the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Network for Research in Infectious Diseases (REIPI). *Enferm Infecc Microbiol Clin* 2013; **31:** 526.e1–526.e20.
23. Katerinis I, Hadaya K, Duquesnoy R *et al.* De novo anti-HLA antibody after pandemic H1N1 and seasonal influenza immunization in kidney transplant recipients. *Am J Transplant* 2011; **11:** 1727–1733.
24. Candon S, Thervet E, Lebon P *et al.* Humoral and cellular immune responses after influenza vaccination in kidney transplant recipients. *Am J Transplant* 2009; **9:** 2346–2354.
25. Fakhrmousavi SA, Hadadi A, Hosseini SH *et al.* Immunogenicity of Four Doses of Double-Strength Intramuscular Hepatitis B. *Iran J Pathol* 2016; **11:** 127–132.
26. Jacobson IM, Jaffers G, Dienstag JL *et al.* Immunogenicity of hepatitis B vaccine in renal transplant recipients. *Transplantation* 1985; **39:** 393–395.
27. Choy BY, Peiris JS, Chan TM *et al.* Immunogenicity of intradermal hepatitis B vaccination in renal transplant recipients. *Am J Transplant* 2002; **2:** 965–969.
28. Saw CL, Ross V, Cybulsky A *et al.* 64-P: Hepatitis B vaccination may cause HLA sensitization. *Human Immunology* 2013; **74**(Suppl): 96.
29. Linnemann CC Jr, First MR, Schiffman G. Response to pneumococcal vaccine in renal transplant and hemodialysis patients. *Arch Intern Med* 1981; **141:** 1637–1640.
30. Lindemann M, Heinemann FM, Horn PA, Witzke O. Immunity to pneumococcal antigens in kidney transplant recipients. *Transplantation* 2010; **90:** 1463–1467.
31. Borgers H, Moens L, Picard C *et al.* Laboratory diagnosis of specific antibody deficiency to pneumococcal capsular polysaccharide antigens by multiplexed bead assay. *Clin Immunol* 2010; **134:** 198–205.
32. Lindemann M, Heinemann FM, Horn PA, Witzke O. Long-term response to vaccination against pneumococcal antigens in kidney transplant recipients. *Transplantation* 2012; **94:** 50–56.
33. Lindemann M, Heinemann FM, Horn PA, Witzke O. Vaccination against Streptococcus pneumoniae does not induce antibodies against HLA or MICA in clinically stable kidney transplant recipients. *Hum Immunol* 2013; **74:** 1267–1270.
34. Kumar D, Unger ER, Panicker G *et al.* Immunogenicity of quadrivalent human papillomavirus vaccine in organ transplant recipients. *Am J Transplant* 2013; **13:** 2411–2417.
35. Ljungman P. Vaccination of immunocompromised patients. *Clin Microbiol Infect* 2012; **18**(Suppl 5): 93–99.
36. Enke BU, Bökenkamp A, Offner G, Bartmann P, Brodehl J. Response to diphtheria and tetanus booster vaccination in pediatric renal transplant recipients. *Transplantation* 1997; **64:** 237–241.
37. Centers for Disease Control and Prevention. Chapter 21: Tetanus. In: Hamborsky J, Kroger A, Wolfe S (eds). *Epidemiology and Prevention of Vaccine-Preventable Diseases*, 13th edn. Washington DC, USA: Public Health Foundation, 2015.
38. World Health Organization. Rabies vaccines WHO position paper. *Weekly Epidemiological Record* 2007; **82:** 425–436.
39. Rodríguez-Romo R, Morales-Buenrostro LE, Lecuona L *et al.* Immune response after rabies vaccine in a kidney transplant recipient. *Transpl Infect Dis* 2011; **13:** 492–495.
40. Chen S, Zhang H, Luo M *et al.* Rabies Virus Transmission in Solid Organ Transplantation, China, 2015–2016. *Emerg Infect Dis* 2017; **23:** 1600–1602.
41. Centers for Disease Control and Prevention. Media Statement: CDC confirms rabies death in organ transplant recipient. www.cdc.gov/media/releases/2013/s0315_rabies_organs.html (last accessed 3/1/2019)
42. Srinivasan A, Burton EC, Kuehnert MJ *et al.* Transmission of rabies virus from an organ donor to four transplant recipients. *N Engl J Med* 2005; **352:** 1103–1111.
43. Kaul A, Sharma RK, Bhadhuria D, Gupta A, Prasad N. Chickenpox infection after renal transplantation. *Clin Kidney J* 2012; **5:** 203–206.
44. Pergam S, Limaye A; AST Infectious Diseases Community of Practice. Varicella zoster virus (VZV) in solid organ transplant recipients. *Am J Transplant* 2009; **9**(Suppl 4): S108–S115.
45. Merck. In First Phase 3 Trial, Merck's Investigational Inactivated Varicella Zoster Virus Vaccine (V212) Reduced the Incidence of Confirmed Herpes Zoster Cases by an Estimated 64 Percent in Immunocompromised Subjects [Press release February 24, 2017]. https://investors.merck.com/news/press-release-details/2017/In-First-Phase-3-Trial-Mercks-Investigational-Inactivated-Varicella-Zoster-Virus-Vaccine-V212-Reduced-the-Incidence-of-Confirmed-Herpes-Zoster-Cases-by-an-Estimated-64-Percent-in-Immunocompromised-Subjects/default.aspx (last accessed 3/1/2019)
46. McNeil S, Betts R, Lawrence S *et al.* Safety and Immunogenicity Of Inactivated Varicella-Zoster Virus Vaccine In Adults With Hematologic Malignancies Receiving Treatment With Anti-CD20 Monoclonal Antibodies. *Blood* 2013; **122:** 2290.
47. Metselaar HJ, Weimar W. Cytomegalovirus infection and renal transplantation. *J Antimicrob Chemother* 1989; **23**(Suppl E): 37–47.
48. Metselaar HJ, Rothbarth PH, Brouwer RM *et al.* Prevention of cytomegalovirus-related death by passive immunization. A double-blind placebo-controlled study in kidney transplant recipients treated for rejection. *Transplantation* 1989; **48:** 264–266.
49. Angus Liu. Vical's Astellas-partnered CMV vaccine falls short again, this time in stem cell transplant recipients. www.fiercepharma.com/vaccines/vical-s-astellas-partnered-cmv-vaccine-failed-phase-3 (last accessed 3/1/2019)

IT'S TIME TO LISTEN TO PATIENTS. THE THIRD PATIENT-REPORTED EXPERIENCE MEASURES (PREM) SURVEY

The results of the third patient-reported experience measures (PREM) survey have just been released. This joint piece of work with the Renal Association tells us what nearly 14,000 kidney patients across the whole UK thought of their care in 2018. The questions were originally produced with patients and the survey is now validated by the University of Hertfordshire. The survey is also available in Welsh, Urdu and Gujurati. This year, for the first time and because patients had asked, there were free text boxes for people to add their comments. In addition to adding feedback on the questions, the comments attested to the value patients put on PatientView. Comments also emphasised the importance of continuity of care and reflected a negative experience where this was not possible. There was much praise for caring and supportive teams.

While it is very good to see that patients express many positives about the quality of their care, rating it overall as 6.3 out of 7, the results are drawing attention to areas for improvement, which remain unchanged from last year. The greatest differences between the highest and lowest performing centres continue to be in scores awarded for Sharing Decisions About Your Care, with a range of 3.1 points between the lowest (3.6) and highest (6.6) scores, Transport (2.6-point difference) and Needling (1.9-point difference).

One of the most important findings is the way in which patients perceive sharing care decisions; deciding whether to be listed for transplant (if a suitable candidate), where to have dialysis, which type of dialysis or whether not to have dialysis at all are all life-changing issues. It is perhaps less surprising that dialysis transport experience is also perceived as less good and I look forward to sharing our recommendations on improving this in a future column, following a community investigation throughout 2018. As in 2017, dialysis needling is the third area in which experience showed wider variation. These findings should act as a call to action and closer working with kidney patients to address shared decision-making, transport and needling, highlighted by patients as key to their experience.

While the overall numbers for completion of the PREM survey are improving, the proportion of patients per unit taking part ranges from less than 1% to 60%. There is work to be done by all of us, including Kidney Care UK and the Renal Association, in encouraging patients to take part, sharing the local results with patients and staff and inviting greater representation from minority groups.

Finally, although there are undoubtedly challenges, some of the basic fundamentals of patient care continue to be highly rated, including Information, Privacy and Dignity, Access to the Team, and Scheduling and Planning. Thank you for supporting this work.

To read the full PREMs report, please see **www.kidneycareuk.org/news-and-campaigns/news/2018-prem-survey-findings-released/**

Join the discussion on twitter under #KidneyPREM

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When add-on, consider lower dose of insulin or insulin secretagogue to reduce risk of hypoglycaemia. **Children:** no data available. **Elderly:** consider renal function and risk of volume depletion. **Renal impairment:** not to be initiated with eGFR < 60 mL/min/1.73 m2. If eGFR falls below this value during treatment, adjust or maintain dose at 100 mg once daily. Discontinue if eGFR persistently < 45 mL/min/1.73 m2. Not for use in end stage renal disease or patients on dialysis. **Hepatic impairment:** mild or moderate; no dose adjustment. 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Monitor volume status and serum electrolytes. **Elevated haematocrit:** careful monitoring if already elevated. **Genital mycotic infections:** risk in male and female patients, particularly in those with a history of GMI. **Lower limb amputation:** consider risk factors before initiating. Monitor patients with a higher risk of amputation events. counsel on routine preventative foot care and adequate hydration. Consider discontinuing ***Invokana*** when events preceding amputation occur (e.g., lower-extremity skin ulcer, infection, osteomyelitis or gangrene). Urine laboratory assessment: glucose in urine due to mechanism of action. Lactose intolerance: do not use in patients with galactose intolerance, total lactase deficiency or glucose-galactose malabsorption. Diabetic ketoacidosis (DKA): rare DKA cases reported, including life-threatening and atypical presentation cases. Where DKA is suspected or diagnosed, discontinue ***Invokana*** treatment immediately. Interrupt treatment in patients who are undergoing major surgical procedures or have acute serious medical illnesses. Consider risk factors for development of DKA before initiating Invokana treatment. **Necrotising fasciitis of the perineum (Fournier's gangrene):** post-marketing cases reported with SGLT2 inhibitors. Rare but serious, patients should seek medical attention if experiencing symptoms including pain, tenderness, erythema, genital/perineal swelling, fever, malaise. If Fournier's gangrene suspected, ***Invokana*** should be discontinued, and prompt treatment instituted. **INTERACTIONS: Diuretics:** may increase risk of dehydration and hypotension. **Insulin and insulin secretagogues:** risk of hypoglycaemia; consider lower dose of insulin or insulin secretagogue. **Effects of other medicines on *Invokana:*** enzyme inducers (e.g., St. John's wort, rifampicin, barbiturates, phenytoin, carbamazepine, ritonavir, efavirenz) may decrease exposure of canagliflozin; monitor glycaemic control. Consider dose increase to 300 mg if administered with UGT enzyme inducer. Cholestyramine may reduce canagliflozin exposure; take canagliflozin at least 1 hour before or 4-6 hours after a bile acid sequestrant. **Effects of Invokana on other medicines:** monitor patients on digoxin, other cardiac glycosides, dabigatran. Inhibition of Breast Cancer Resistance Protein cannot be excluded; possible increased exposure of drugs transported by BCRP (eg, rosuvastatin and some anti-cancer agents). **PREGNANCY:** No human data. Not recommended. **LACTATION:** Unknown if excreted in human milk. Should not be used during breast-feeding. **SIDE EFFECTS: Very common (≥1/10):** hypoglycaemia in combination with insulin or sulphonylurea, vulvovaginal candidiasis. **Common (≥1/100 to<1/10):** constipation, thirst, nausea, polyuria or pollakiuria, urinary tract infection (including pyelonephritis and urosepsis), balanitis or balanoposthitis, dyslipidemia, haematocrit increased. **Uncommon (<1/100) but potentially serious:** anaphylactic reaction, diabetic ketoacidosis, syncope, hypotension, orthostatic hypotension, urticaria, angioedema, necrotising fasciitis of the perineum (Fournier's gangrene) (frequency not known), bone fracture, renal failure (mainly in the context of volume depletion), lower limb amputations (mainly of the toe and midfoot, incidence rate of 0.63 per 100 subject-years, vs 0.34 for placebo). **Refer to SmPC for details and other side effects. LEGAL CATEGORY:** POM. **PACK SIZES, MARKETING AUTHORISATION NUMBER(S) & BASIC NHS COSTS *Invokana* 100 mg film coated tablets:** 30 tablets; EU/1/13/884/002; £39.20. ***Invokana* 300 mg film coated tablets:** 30 tablets; EU/1/13/884/006; £39.20. **MARKETING AUTHORISATION HOLDER:** Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgium. ® INVOKANA is a registered trade mark of Janssen-Cilag International NV and is used under licence.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Janssen-Cilag Ltd on 01494567447 or at dsafety@its.jnj.com.

FURTHER INFORMATION IS AVAILABLE FROM: Napp Pharmaceuticals Ltd. Cambridge Science Park Milton Road, Cambridge, CB4 0AB, UK. For medical information enquiries, please contact medicalinformationuk@napp.co.uk © 2017 Napp Pharmaceuticals Limited. **UK/INV-18164(1) Date of Preparation** January 2019. **References: 1.** Invokana® Summary of Product Characteristics. Napp Pharmaceuticals. 2018. **2.** Neal B, et al. N Engl J Med 2017;377:644-57.

UK/INV-18107a(3) | February 2019