Renal problems
Disclaimer

The information set out in this publication is current at the date of first publication and is intended for use as a guide of a general nature only and may or may not be relevant to particular patients or circumstances. Nor is this publication exhaustive of the subject matter. Persons implementing any recommendations contained in this publication must exercise their own independent skill or judgement or seek appropriate professional advice relevant to their own particular circumstances when so doing. Compliance with any recommendations cannot of itself guarantee discharge of the duty of care owed to patients and others coming into contact with the health professional and the premises from which the health professional operates.

Whilst the text is directed to health professionals possessing appropriate qualifications and skills in ascertaining and discharging their professional (including legal) duties, it is not to be regarded as clinical advice and, in particular, is no substitute for a full examination and consideration of medical history in reaching a diagnosis and treatment based on accepted clinical practices.

Accordingly, The Royal Australian College of General Practitioners and its employees and agents shall have no liability (including without limitation liability by reason of negligence) to any users of the information contained in this publication for any loss or damage (consequential or otherwise), cost or expense incurred or arising by reason of any person using or relying on the information contained in this publication and whether caused by reason of any error, negligent act, omission or misrepresentation in the information.

Subscriptions

For subscriptions and enquiries please call 1800 331 626 or email check@racgp.org.au

Published by

The Royal Australian College of General Practitioners
100 Wellington Parade
East Melbourne, Victoria 3002, Australia
Telephone 03 8699 0414
Facsimile 03 8699 0400
www.racgp.org.au

ABN 34 000 223 807
ISSN 0812-9630

© The Royal Australian College of General Practitioners 2014.
Renal problems
Unit 507 July 2014

About this activity 2
Abbreviations and acronyms 3

Case 1  Jeff is worried as his mother died on dialysis 4
Case 2  George has painful toes 9
Case 3  Graham has swollen ankles 14
Case 4  Ruby refuses dialysis 18
Case 5  Irene’s blood pressure is difficult to control 22
Case 6  Anna has nausea and increased urinary frequency 28

Category 2 QI&CPD activity 32

The five domains of general practice

- Communication skills and the patient-doctor relationship
- Applied professional knowledge and skills
- Population health and the context of general practice
- Professional and ethical role
- Organisational and legal dimensions
ABOUT THIS ACTIVITY

About 500,000 Australians present with kidney disease and urinary tract infections each year. Kidney problems arise from acute illnesses (eg severe infections) or progressive damage due to conditions such as untreated diabetes or hypertension. Chronic kidney disease (CKD) is the progressive loss of renal function over time. Symptoms of worsening kidney function are non-specific and up to 90% of kidney function may be lost before symptoms appear. CKD is highlighted as one of several chronic conditions that increase the burden of disease in Australia. Early detection and management of CKD reduces deterioration of kidney function. GPs have an important role in screening people at high risk of kidney disease. This edition of check will consider renal scenarios of relevance to general practice in Australia.

AUTHORS

Frank Brennan MBBS, FRACP, FACHPM, LLB is a palliative care physician and lawyer with an interest in many aspects of palliative care, including its interface with the humanities and law. He currently runs the renal supportive care service at St George Renal & Hypertension Unit, St George Hospital, NSW.

Magid Fahim MBChB, FRACP is a staff specialist nephrologist at Princess Alexandra Hospital, a senior lecturer in medicine at the University of Queensland and an advisory board member of the Cochrane Renal Group. Dr Fahim is in the final year of his PhD and is a recipient of a National Health and Medical Research Council postgraduate scholarship and project grant.

David Johnson PSM MBBS (Hons), PhD (Syd), FRACP, D Med (Res), FASN is currently director of the Metro South and Ipswich Nephrology and Transplant Service (MINTS) and medical director of the Queensland Renal Transplant Service at Princess Alexandra Hospital, Brisbane; professor of medicine and professor of population health at University of Queensland; chair of the CARI Guidelines Working Parties on Peritoneal Dialysis Adequacy, Evaluation of Renal Function and Management of Early Chronic Kidney Disease; chair of the Kidney Check Australia Taskforce; co-chair of the Australasian Creatinine and eGFR Consensus Working Party; and co-chair of the Australasian Proteinuria Consensus Working Party.

Ivor Katz MBChB, BSc (Hons) Sports Medicine, FCP (SA) Nephrology, FRACP, PhD is a senior staff specialist at St George Hospital, Renal Department in Sydney and a conjoint associate professor at the University of New South Wales. He is on the Kidney Check Australia Taskforce committee. His research interests remain in public health and chronic kidney disease and he has a particular interest in linking specialists with primary care clinicians for the management of chronic diseases.

Carol Lawson MBBS, Dip Obst, MFM (Monash), FRACGP, is currently a general practitioner in Brunswick, Melbourne, and a QA examiner with the RACGP. She spent 10 years as an academic general practitioner with the Department of General Practice at Monash University, and has special interests in medical education and women's health.

Kelly Li MBBS is an advanced trainee in nephrology St George Renal & Hypertension Unit, St George Hospital, NSW. Dr Li has a special interest in renal supportive care.

David Mudge MBBS, FRACP, MD, FASN is a nephrologist at the Princess Alexandra Hospital and Redland Hospital, a member of the International Society of Nephrology Young Nephrologists Committee, editor for the Cochrane Renal Group, chair of the KHA-CARI guidelines peritoneal dialysis guideline implementation project and recently elected member of the Australia and New Zealand Society of Nephrology (ANZSN) Council.

Nyasha Mukandi MBChB, BAO is an advanced trainee in general and acute medicine at Princess Alexandra Hospital, Brisbane. Dr Mukandi has a keen interest in preventive medicine and medical education.

Dharmenaan Palamuthusingam MBBS is an advanced trainee in nephrology at the Princess Alexandra Hospital. He has a keen interest in medical education.

Gillian Rothwell MBBS, FRACP, FACHPM, Grad Dip Pall Med, MSpMed has worked in both rural and suburban general practice, and now practices as a palliative care specialist at Sydney Adventist and Neringah Hospitals.

PEER REVIEWERS

Tim Mathew AM, MBBS, FRACP is the medical director of Kidney Health Australia. His current interests include reduction of chronic kidney disease burden and the issues around implementing national programs to achieve this. He has been a member of many advisory committees to the government and was appointed chair of the Australian Institute of Health and Welfare CKD Monitoring Advisory Committee in 2007.

John Parikh MBBS, MD, DCO, DFP, MPM, MFM is a full-time general practitioner, a reviewer for the Healthcare Complaints Commission, conjoint lecturer in the Faculty of Medicine, University of New South Wales, and a surgical assistant at the Sydney Adventist Hospital. He is also an RACGP faculty board member (NSW ACT) and an AMA council member. Dr Parikh has interests in point-of-care-testing, family medicine and medical education.
LEARNING OUTCOMES

At the end of this activity, participants will be able to:

• outline current management options for pregnant women with a urinary tract infection
• describe problems that may arise during end-stage renal failure in palliative care settings and how these can be managed
• outline appropriate screening options for people with suspected kidney disease
• describe the differential diagnosis of nephrotic syndrome, including possible secondary causes
• define resistant hypertension and outline its management.

REFERENCES

CASE 1

JEFF IS WORRIED AS HIS MOTHER DIED ON DIALYSIS

Jeff, a Caucasian man aged 65 years, presents to your practice after the death of his mother. His mother had end-stage kidney disease (ESKD) and recently died of a complication while on dialysis. Her chronic kidney disease (CKD) was a result of her diabetes and she had diabetic kidney disease (DKD). Jeff tells you that he has had type 2 diabetes for 11 years. He explains that he has been so busy caring for his mother and ageing father that he has not had time to care for himself. His last National Glycohemoglobin Standardization Program (NGSP) HbA1c was 10.3% (International Federation of Clinical Chemistry [IFCC] HbA1c is 89 mmol/mol). He has gained weight recently and has a body mass index (BMI) of 33 kg/m². He is concerned that he now has DKD.

QUESTION 1 🧐

What is concerning about Jeff’s history? Do you think that his concerns about having DKD are appropriate?

QUESTION 2 🧐

What basic investigations (clinical and biochemical) would you consider for Jeff in order to best manage him at this stage?

QUESTION 3 🧐

What are your concerns following these findings? What would you do now?

QUESTION 4 🧐

Why does his diabetes seem to be better controlled? What are the risks with treatment now?

QUESTION 5 🧐

Should Jeff be referred to a nephrologist? If so, why?
In general, a doctor seeing a patient such as Jeff should be concerned about the likelihood of DKD, as there is a high association between diabetes and kidney disease. According to the Nefron Study,1 every second patient with type 2 diabetes whom a doctor sees is likely to have CKD (47%). In the AusDiab study (2001)2 and follow-on study (2005)3 16% of the 11,247 adults (>25 years) chosen by a census district Australian nation-representative sample had kidney damage, as evidenced by micro or macroalbuminuria (6.6%), an eGFR <60 mL/min/1.73 m² (5.8%) or haematuria (2.5%). Since 1998–2008, in most age groups, the rate of new patients with DKD per million people has been increasing. This is especially the case for people with Jeff’s duration of diabetes (>10 years) and his age group (65–74 years).4 His age group is most likely to be presenting with ESKD and requiring dialysis. Indeed, diabetes is the underlying cause of kidney failure that is largely driving up the increase in the number of dialysis patients in Australia.4

Apart from his diabetes, Jeff has a number of risks factors for CKD. He has a high likelihood of having CKD as he has a strong family history of CKD and, in particular, a first-degree relative, his mother, had CKD.5 Among race and sex groups, 14.1% of Caucasian men, 14.6% of Caucasian women, 22.9% of African-American men and 23.9% of African-American women reported a first- or second-degree relative with ESKD (P = 0.001).5 Another concern is his weight gain, which further increases his risk of CKD. Obesity (BMI ≥30 kg/m²) increases his relative risk to 1.78, compared with normal non-overweight (BMI <25 kg/m²) or overweight (BMI 25–29 kg/m²) individuals.6 Those who are overweight or obese (BMI >30 kg/m²) are 40% and 80%, respectively, more likely to develop CKD, compared with those whose weight is in the normal range. Although not as powerful as diabetes or hypertension as a risk factor, obesity increases the risk of albuminuria and proteinuria. Obesity results in greater difficulty in achieving glycaemic and blood pressure control. Lastly, two-thirds of individuals in Jeff’s age group are likely to have CKD. This means these individual have higher cardiovascular morbidity and mortality rate, compared with those without CKD, rather than a likelihood of requiring dialysis.7

As Jeff is at increased risk of DKD you need to investigate whether he has CKD and determine his stage and cardiovascular risk, as well as his likelihood of deterioration to ESKD or dialysis. He has at least five of eight established risk factors for CKD (diabetes, hypertension, age >60 years, obesity and a family history of kidney failure). He does not smoke and is not an Aboriginal or Torres Strait Islander and you are not yet sure if he has established cardiovascular disease (CVD) or controlled hypertension. As per the Kidney Check Australia Taskforce (KCAT)
Case 1

6

check

Renal problems

progression of his CKD. According to the KCAT guidelines\(^8\) he fits into the ‘Red Clinical Action Plan’.

What is further concerning is that he has uncontrolled hypertension, which is extremely common among those with type 2 diabetes and particularly in people with DKD. However, achieving blood pressure control is one of the most effective ways to delay the progression of kidney disease. In Jeff’s case, therefore, particular effort should be made to control his blood pressure to a target consistently less than 130/85 mmHg. If Jeff’s blood pressure is consistently below this target, the eGFR loss per year could be reduced by 80%\(^{12}\) (Figure 1). Antihypertensive agents preferred for use by patients with diabetes are angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs).\(^{13}\) These agents may also slow the progression of CKD.\(^{14,15}\) Other antihypertensive agents that lower blood pressure to target will also improve the patients’ future CKD and CVD outlook.

Unfortunately, Jeff’s absolute CVD risk is at the highest level. Absolute CVD risk assessment is not required for adults with any of the following conditions because they are already known to be at high risk of CVD:\(^{16}\)

- diabetes and age >60 years
- diabetes with microalbuminuria
- moderate or severe CKD (eGFR <45 mL/min/1.73 m\(^2\))
- previous diagnosis of familial hypercholesterolaemia
- systolic BP ≥180 mmHg or diastolic BP ≥110 mmHg
- serum total cholesterol >7.5 mmol/L
- Aboriginal and Torres Strait Islander adults >74 years.\(^{16}\)

In light of these findings, Jeff’s risk factors should be aggressively controlled. Treating Jeff’s diabetes aggressively will also slow progression of renal failure.\(^{17}\) The most common recommended target in ordinary adult patients with diabetes is an HbA1c <6.5–7% (48–53 mmol/mol). For some patients, tighter control is the goal and is possible. One needs, therefore, to consider lifestyle modification, pharmacotherapy to treat his hypertension and monitoring every 6–12 weeks until sufficient improvements are achieved.\(^{18}\)

---

**Table 1. The new Australian CKD staging schema\(^8\)**

<table>
<thead>
<tr>
<th>GFR stage</th>
<th>GFR (mL/min/1.73 m(^2))</th>
<th>Albuminuria stage</th>
<th>Normal (urine ACR mg/mmol) Male: &lt;2.5; Female: &lt;3.5</th>
<th>Microalbuminuria (UACR mg/mmol) Male: 2.5–25; Female: 3.5–35</th>
<th>Macroalbuminuria (UACR mg/mmol) Male: &gt;25; Female: &gt;35</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>Not CKD unless haematuria, structural or pathological abnormalities present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>45–59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>30–44</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or on dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Green = low; yellow = moderate; orange = high; red = very high.

---

**Table 2. Approximate equivalents between UACR and other measure of albuminuria and proteinuria\(^11\)**

<table>
<thead>
<tr>
<th>Microalbuminuria</th>
<th>UACR (mg/mmol)</th>
<th>24-hour urine albumin (mg/day)</th>
<th>24-hour urine protein (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: 2.5–25</td>
<td>30–300</td>
<td>Male: 4–40</td>
<td>50–500</td>
</tr>
<tr>
<td>Female: 3.5–35</td>
<td></td>
<td>Female: 6–60</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Macroalbuminuria</th>
<th>UACR (mg/mmol)</th>
<th>24-hour urine albumin (mg/day)</th>
<th>24-hour urine protein (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: &gt;25</td>
<td>&gt;300</td>
<td>Male: &gt;40</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Female: &gt;35</td>
<td></td>
<td>Female: &gt;60</td>
<td></td>
</tr>
</tbody>
</table>

From the new Australian CKD staging schema (Table 1) he is at the highest risk for developing cardiovascular complications and progression of his CKD. According to the KCAT guidelines\(^8\) he fits into the ‘Red Clinical Action Plan’.

**ANSWER 3**

According to the KCAT guidelines Jeff has stage 3b CKD (eGFR 36 mL/min/1.73 m\(^2\)) and macroalbuminuria, which is likely to be due to DKD (Table 1). The preferred measure of albuminuria should be done using UACR. Table 1 shows that he has significant proteinuria or macroalbuminuria. The approximate equivalents between UACR and other measures of albuminuria and proteinuria are shown in Table 2.\(^11\)

---

**Table 2. Approximate equivalents between UACR and other measure of albuminuria and proteinuria\(^11\)**

From the new Australian CKD staging schema (Table 1) he is at the highest risk for developing cardiovascular complications and progression of his CKD. According to the KCAT guidelines\(^8\) he fits into the ‘Red Clinical Action Plan’.

What is further concerning is that he has uncontrolled hypertension, which is extremely common among those with type 2 diabetes and particularly in people with DKD. However, achieving blood pressure control is one of the most effective ways to delay the progression of kidney disease. In Jeff’s case, therefore, particular effort should be made to control his blood pressure to a target consistently less than 130/85 mmHg. If Jeff’s blood pressure is consistently below this target, the eGFR loss per year could be reduced by 80%\(^{12}\) (Figure 1). Antihypertensive agents preferred for use by patients with diabetes are angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs).\(^{13}\) These agents may also slow the progression of CKD.\(^{14,15}\) Other antihypertensive agents that lower blood pressure to target will also improve the patients’ future CKD and CVD outlook.

Unfortunately, Jeff’s absolute CVD risk is at the highest level. Absolute CVD risk assessment is not required for adults with any of the following conditions because they are already known to be at high risk of CVD:\(^{16}\)

- diabetes and age >60 years
- diabetes with microalbuminuria
- moderate or severe CKD (eGFR <45 mL/min/1.73 m\(^2\))
- previous diagnosis of familial hypercholesterolaemia
- systolic BP ≥180 mmHg or diastolic BP ≥110 mmHg
- serum total cholesterol >7.5 mmol/L
- Aboriginal and Torres Strait Islander adults >74 years.\(^{16}\)

In light of these findings, Jeff’s risk factors should be aggressively controlled. Treating Jeff’s diabetes aggressively will also slow progression of renal failure.\(^{17}\) The most common recommended target in ordinary adult patients with diabetes is an HbA1c <6.5–7% (48–53 mmol/mol). For some patients, tighter control is the goal and is possible. One needs, therefore, to consider lifestyle modification, pharmacotherapy to treat his hypertension and monitoring every 6–12 weeks until sufficient improvements are achieved.\(^{18}\)
ANSWER 1

Case 1

Renal problems

Permanent dialysis access created prior to dialysis onset, increased likelihood of kidney transplantation and reduced initial costs of care following the commencement of dialysis.20

ANSWER 6

Jeff’s ongoing decline is probably related to the inability to control some of his risk factors. However, it may also be related to his still significant proteinuria and probable diabetic nephropathy. It is always important to consider an ultrasound to exclude obstruction as a cause for decline in renal function and to assess kidney morphology and size. Additional control is required to improve Jeff’s blood pressure, which is still high. The use of a calcium channel blocker or low-dose thiazide diuretic would be appropriate for his now isolated systolic hypertension.21

For Jeff, the risk of death due to CVD is 20 times greater than the likelihood of surviving to the stage of needing dialysis or renal transplant. CKD is one of the most potent known independent risk factors for cardiovascular disease. Individuals with CKD have a 2–3-fold greater risk of cardiac death than individuals without CKD.22 Therefore, ongoing aggressive measures to reduce morbidity and mortality due to cardiovascular disease are important. For this reason, Jeff’s dyslipidaemia needs to be managed. There is some evidence that a combination of anti-lipid medication, such as simvastatin plus ezetimibe, has an advantage, especially for the reduction in cardiovascular risk. The results of the Study of Heart And Renal Protection (SHARP) showed a 17% reduction in major atherosclerotic events when comparing a placebo versus combination anti-lipid medication. Major atherosclerotic events included coronary death, myocardial infarction, non-haemorrhagic stroke or any revascularisation.23 However, it is important to be aware that statins decrease mortality and cardiovascular events in people with early-stage CKD, have little or no effect in people receiving dialysis and have uncertain effects in kidney transplant recipients.24

REFERENCES


Jeff’s diabetes now seems better controlled as he has established renal failure. One has to now be careful not to cause hypoglycaemia with treatment. He may not require intensive control, especially if there is declining renal function. CKD increases the risk of hypoglycaemia for the following reasons:

• decreased renal glucose production
• reduced gluconeogenesis from alanine, pyruvate, glycerol, and decreased mitochondrial adenosine triphosphate/diphosphate (ATP/ADP) ratio in the liver
• decreased glycogen reserve
• reduced systemic response to adrenaline and glucagon
• decreased insulin degradation (normal kidney extracts 40% insulin), which intensifies and prolongs insulin actions
• reduced renal clearance of oral hypoglycaemic agents and their active metabolites.19

ANSWER 5

Referral to a nephrologist is recommended if any of the following are present:

• eGFR <30 mL/min/1.73 m²
• persistent significant albuminuria (UACR ≥30 mg/mmol)
• rapidly declining eGFR from a baseline of <60 mL/min/1.73 m² (a decline of >5mL/min/1.73 m² over a 6-month period, which is confirmed on at least three separate readings)
• CKD and hypertension that is difficult to get to target despite at least three anti-hypertensive agents
• haematuria with macroalbuminuria.8

Jeff’s UACR result was 70 mg/mmol and if this is persists on at least two repeat urine specimens, a referral is recommended.

Appropriate referral is associated with reduced rates of progression to ESKD, decreased rates of morbidity and mortality, decreased need for and duration of hospitalisation, increased likelihood of permanent dialysis access created prior to dialysis onset, increased likelihood of kidney transplantation and reduced initial costs of care following the commencement of dialysis.20

Figure 1. Adequate blood pressure management delays the progression of CKD12
CASE 2
GEORGE HAS PAINFUL TOES

George, a retired mechanic aged 78 years, has come to see you about his painful toes. His past history includes hypertension for over 30 years, dyslipidaemia and coronary artery disease. He is an ex-smoker with a smoking history of 60 packs per year. He quit smoking at the age of 52 years when he was referred for coronary artery bypass grafts.

He was in hospital recently for management of heart failure and tells you he was discharged last week on ‘fluid tablets’ and that his kidneys are ‘bad’.

You diagnose an acute attack of gout involving George’s first metatarsal-phalangeal joints on both feet and his left ankle. His recent hospital discharge summary is shown in Table 1.

Table 1. George’s hospital discharge summary

<table>
<thead>
<tr>
<th>Parameter</th>
<th>George</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>132 mmol/L</td>
<td>135–145 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.4 mmol/L</td>
<td>3.5–5.0 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>100 mmol/L</td>
<td>95–110 mmol/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>28 mmol/L</td>
<td>22–32 mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>12.0 mmol/L</td>
<td>3–8 mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>239 µmol/L</td>
<td>60–120 µmol/L</td>
</tr>
<tr>
<td>Urate</td>
<td>0.58 mmol/L</td>
<td>0.2–0.45 mmol/L</td>
</tr>
<tr>
<td>eGFR</td>
<td>26 mL/min/1.73 m²</td>
<td>&gt;90 mL/min/1.73 m²</td>
</tr>
</tbody>
</table>

While in hospital, George was told that he cannot have analgesia because of his ‘bad’ kidneys. He says his pain is debilitating.

QUESTION 1
What can be done for George’s pain?

FURTHER INFORMATION

George returns to see you 2 years later to discuss his insomnia. On further questioning, he tells you he is unable to lie still at night and spends most nights walking around his bedroom. He describes discomfort in his legs and an urge to move his legs, which is relieved by getting up and walking around; however, he finds it difficult to describe the exact nature of the discomfort.

QUESTION 2
How should this problem be managed?

Several months later, George presents for a routine check-up. He is now 81 years old. His cardiologist told him that his heart failure is worse and that he has concurrent chronic obstructive pulmonary disease from his previous cigarette exposure. He has been in hospital four times in the last 6 months, twice for heart failure, once for exacerbation of airways disease and once for a fall. His daily activities are severely limited by shortness of breath and he uses home oxygen at night. He is unable to care for himself and has moved in with his daughter and her family.

On his recent visit to his nephrologist, he was told that he has kidney failure but that he is not a suitable candidate for dialysis. He agreed that he does not want to be kept alive ‘hooked up to a machine’ but his family members tell him that he is ‘giving up’.

QUESTION 3
What would you say to George?
QUESTION 4
What other symptoms are common in patients with ESKD who are managed on a conservative pathway?

FURTHER INFORMATION
George’s daughter tells you that George is now in a high-level care nursing home. The nephrologist told them that George has end-stage cardiac and renal failure and does not have long to live.

QUESTION 5
What are some of the end-of-life issues for George?

ANSWER 1
Pain is a common symptom in patients with chronic kidney disease (CKD). The principles of pain management are to treat the cause and/or use analgesics (non-opioid as first-line and opioid as second-line analgesia) as described in the World Health Organization analgesic ladder (Table 2).

Treat the cause
Gout is a common clinical problem in patients with CKD. Serum urate increases as glomerular filtration rate (GFR) falls. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided in people with CKD if creatinine clearance (CrCl) is <25 mL/minute; the selective COX-2 inhibitors celecoxib and etoricoxib are contraindicated if CrCl is <30 mL/min. NSAID use is restricted in CKD because adverse effects include worsening of GFR (which is sometimes irreversible) and sodium retention, leading to oedema and hypertension. Colchicine should be used with caution, as its elimination is reduced in renal failure. Guidelines suggest avoiding colchicine or using a reduced dose. A short course of prednisone can be used safely in this setting. Allopurinol should be considered after acute attacks settle, to reduce serum urate, as patients may have recurrent attacks due to hyperuricaemia.

Analgesics
Paracetamol can be used safely at normal doses of 1 g four times daily in patients with CKD. Opioids are rarely used for acute attacks of gout, which often resolves quickly. Opioids must be used with caution in patients with CKD, as many of these agents can accumulate as GFR declines; ideally, opioids should be avoided or used at reduced doses. The preferred short-acting opioid is hydromorphone. The preferred long-acting opioids are fentanyl, oxycontin and buprenorphine. With all opioids, it is important to commence at lower doses and titrate to effect. If pain is difficult to control, it is best to consult the local pain or palliative care service.

ANSWER 2
George is describing symptoms of restless legs syndrome, which is common in end-stage kidney disease (ESKD). It is experienced by patients who continue dialysis and also those who cease dialysis, and reduces quality of life through sleep disturbance. The mainstays of pharmacological therapy include dopamine agonists, such as ropinirole, and gabapentin. Gabapentin dosing should be adjusted for renal impairment. In patients with stage 5 CKD (eGFR <15 mL/min/1.73 m²) being managed without dialysis, starting doses are 100 mg nocte on alternate days and this dose can be titrated up to effect. In stage 4 CKD (eGFR <15–29 mL/min/1.73 m²), the
dose can start from 100 mg nocte. Symptoms and response to treatment should be reassessed within 1–2 weeks. Ropinirole can be commenced at 0.5 mg nocte and increased to 1 mg nocte. Pramipexole is another dopamine agonist that can be used.

**ANSWER 3**

Patients and their carers should be making informed choices regarding ESKD management and this is best done in a multidisciplinary setting. The options of renal replacement therapy and conservative management should be discussed. Evidence from observational and retrospective studies suggest that dialysis extends life in elderly patients, but this survival advantage is negated by comorbidities, such as ischaemic heart disease, and the fact that most patients tend to lose their independence. Similarly, those with poorer functional status do not have any survival advantage with dialysis. Outcomes are poor in nursing home patients initiated on dialysis and one US study showed a mortality rate of 56% in the first year. In this study only 13% of patients maintained their pre-dialysis functional status.

According to the Renal Physicians Association Clinical Practice Guidelines, it is reasonable to consider forgoing dialysis for patients with a very poor prognosis or for whom dialysis cannot be provided safely. Such patients include:

- those with a medical condition where dialysis cannot be tolerated, such as those with dementia (unable to cooperate), or profound hypotension
- those with a terminal illness from a non-renal cause (such as metastatic cancer with poor prognosis and short life expectancy)
- those aged >75 years with stage 5 CKD who meet two or more of the following statistically significant very poor prognosis criteria:
  - clinicians’ response of ‘no, I would not be surprised’ to the surprise question (ie ‘would I be surprised if this patient died in the next year?’)
  - high comorbidity score
  - significantly impaired functional status
  - severe malnutrition.

Good communication is essential and it is important to encourage the family and the patient to meet with the nephrologist, so that all concerns can be canvassed within a shared decision-making framework.
ANSWER 4
Several symptoms are prevalent in patients with ESKD. Some of these symptoms and their recommended treatments are discussed below:13–16

- **Fatigue:** the causes of fatigue in ESKD are multifactorial. The principal reversible issue is anaemia secondary to reduced erythropoietin (EPO) synthesised by the kidney. This can be treated with synthetic EPO-analogues.
- **Pruritus:** uraemic pruritus is common in ESKD, with or without dialysis. After excluding other causes of itch (such as allergies or skin infections), pharmacotherapy may include:
  - topical moisturisers: treat dry skin
  - gabapentin: needs to be used at a reduced dose in renal impairment. In patients with eGFR <15mL/min/1.73 m², starting doses of 100 mg on alternate days (or after dialysis for patients on dialysis) would be appropriate. Titrate the dose up as needed
  - evening primrose oil: start at doses of 1 tablet twice daily and consider titrating up to 2 tablets twice daily, depending on symptoms.

There is no evidence for the efficacy of antihistamines in uraemic pruritus.

- **Nausea:** common in ESKD and reduces quality of life and nutritional intake. Constipation should be excluded, especially if opioids are used. Pharmacotherapy includes:
  - metoclopramide: may be used in ESKD and has prokinetic effects (especially preferred in patients with early satiety and/or constipation)
  - haloperidol: may be used in ESKD, starting at 50% of normal dose
  - levomepromazine: may be used if symptoms persist despite above.

Note, metoclopramide and haloperidol have extrapyramidal side-effects.

Cyclizine may induce hypotension and tachyarrhythmias and is usually reserved for refractory cases, after discussion with a specialist palliative care team.

- **Dyspnoea** is often multifactorial in nature and be due to a combination of anaemia, pulmonary oedema and co-existing cardiac and pulmonary disease. General measures to alleviate symptoms include:
  - provision of education and support for the patient and family on how to cope and respond to breathlessness.
  - sitting upright and use of oxygen therapy if the patient is hypoxic. A fan could be used for cool air.
  - gentle physiotherapy, which may improve function.
  - as disease progresses and non-pharmacological measures fail, low-dose opioids can be used to relieve breathlessness (see above, principles of use of opioids), combined with low-dose benzodiazepines (such as lorazepam 0.5–1 mg orally or sublingually), especially if there are co-existing symptoms of anxiety.

ANSWER 5
End-of-life care aims to provide the best possible quality of life for the patient and the family. The core elements for George and other patients dying from ESKD include:

- **anticipated symptoms:** these include lethargy, daytime drowsiness and shortness of breath. It is important to have meticulous communication with the family regarding these issues and to address them pre-emptively
- **location of care:** this will depend on individual circumstances and may be done in the home, a hospice or, in George's case, a high-level residential care facility, where he is expected to remain until death
- **meticulous communication and support, including bereavement support, should be provided to the family**
- **management of terminal symptoms:**14,15
  - pain: maintain adequate analgesia if the patient is in pain (refer to section on pain management above)
  - terminal agitation: midazolam, used subcutaneously, is recommended to relieve agitation in the dying phase. In CKD, dose reduction and increased dosing interval are recommended.
  - terminal secretions: hyoscine is not recommended as it crosses the blood-brain-barrier more avidly in the uraemic state and may cause heightened agitation. Agents such as glycopyrolate or atropine or will be more appropriate
  - fluid input control and judicious use of frusemide.

REFERENCES


CASE 3

Graham has swollen ankles

Graham, aged 54 years, is a financial advisor who is concerned by swelling of his ankles over the past 2 months. During this time, he has gained 5 kg and has been recently aware of having frothy urine on voiding. Three years ago, he was diagnosed with hypertension and his blood pressure has been well controlled on amlodipine 10 mg daily. Graham quit smoking 3 years ago and drinks a glass of red wine with dinner each night. On examination, Graham has bilateral pitting ankle oedema to the level of the knees. His clinic blood pressure is 155/95 mmHg, his weight is 95 kg (BMI 31.0 kg/m²) and his waist circumference is 102 cm. His physical examination is otherwise normal.

QUESTION 1

What are the possible causes of Graham’s ankle swelling?

QUESTION 2

How should Graham be screened for the presence of kidney disease?

QUESTION 3

What is the recommended test for initial evaluation of albuminuria/proteinuria?

QUESTION 4

What is your working diagnosis?

FURTHER INFORMATION

Graham’s fasting serum biochemical testing reveals the following:

- urea 9.1 mmol/L (normal 3–8 mmol/L*)
- creatinine 145 mmol/L (normal 60–120 mmol/L*)
- eGFR 47 mL/min/1.73 m², glucose 5.1 mmol/L (normal 3–5.4 mmol/L*)
- albumin 28 g/L (normal 32–45 g/L; varies with age*)
- total cholesterol 7.8 mmol/L (normal <5.5 mmol/L*)
- UACR 247 mg/mmol.

(*normal ranges for Queensland Health Pathology Services; ranges from other laboratories may vary slightly)
Bilateral ankle swelling can be caused by a number of conditions, including congestive cardiac failure (CCF), chronic kidney disease (CKD), chronic liver disease, medications (particularly dihydropyridine calcium channel blockers such as amlodipine) and bilateral lower limb venous obstruction (e.g., deep venous thrombosis). Graham’s leg swelling may be related to his amlodipine therapy, although the presence of frothy urine raises the possibility of proteinuria (protein reduces the surface tension of urine). Graham has hypertension and obesity, which are two of the seven recognised risk factors for CKD (the other risk factors are diabetes mellitus, smoking, family history of CKD, established cardiovascular disease (CVD) and Aboriginal or Torres Strait Islander origin). The presence of any CKD risk factor warrants screening for the presence of CKD.

According to the Kidney Health Australia-Caring for Australasians with Renal Insufficiency (KHA-CARI) guidelines, Graham should be screened for CKD by testing for albuminuria/proteinuria and requesting an estimated glomerular filtration rate (eGFR), which is automatically reported by all Australian pathology laboratories with every serum creatinine request in adults over the age of 18 years. Optimal detection and subsequent risk stratification of CKD requires simultaneous consideration of both eGFR and albuminuria/proteinuria.

According to the Chronic Kidney Disease and Measurement of Albuminuria or Proteinuria Position Statement, the preferred method for assessment of albuminuria in both diabetic and non-diabetic patients is urinary albumin-to-creatinine ratio (UACR) measurement in a first-void spot urine specimen. Where a first-void specimen is not possible or practical, a random spot urine specimen for UACR is acceptable.

Graham has an abnormally low eGFR (<60 mL/min/1.73 m²) and very heavy albuminuria that is in the nephrotic range (approximately >220 mg/mmol). Strictly speaking, a diagnosis of CKD requires the documented presence of a low eGFR and/or albuminuria (UACR >2.5 mg/mol in men or >3.5 mg/mol in women) on at least two occasions 3 months apart, but Graham’s clinical presentation and laboratory findings are likely to represent stage 3a CKD with macroalbuminuria (Table 1).

The constellation of ankle oedema, heavy proteinuria, hypoalbuminaemia and hypercholesterolaemia indicate that Graham has nephrotic syndrome. The most common causes of this presentation in the community are diabetes mellitus and chronic glomerulonephritis. The absence of clinical or biochemical features...
of diabetes mellitus suggest that Graham most probably has a form of chronic glomerulonephritis. The likely diagnoses in descending order of probability would be membranous nephropathy, IgA nephropathy and focal segmental glomerulosclerosis. Occasionally, nephrotic syndrome can be caused by secondary glomerulonephritis rather than primary glomerulonephritis. Possible secondary causes of nephrotic syndrome are listed in Table 2.

### Table 2. Secondary causes of nephrotic syndrome

<table>
<thead>
<tr>
<th>Other diseases</th>
<th>Diabetes mellitus, systemic lupus erythematosus, amyloidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers</td>
<td>Myeloma</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Drugs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td></td>
<td>Captopril</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
</tr>
<tr>
<td></td>
<td>Lithium</td>
</tr>
<tr>
<td>Infections</td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B and C</td>
</tr>
<tr>
<td></td>
<td>Mycoplasma</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td>Malaria</td>
</tr>
<tr>
<td>Congenital causes</td>
<td>Alport's syndrome</td>
</tr>
<tr>
<td></td>
<td>Denys-Drash syndrome</td>
</tr>
<tr>
<td></td>
<td>Congenital nephrotic syndrome of the Finnish type</td>
</tr>
</tbody>
</table>

**ANSWER 5**

Graham has a very high likelihood of having progressive kidney failure, given the combination of nephrotic-range proteinuria, low eGFR, male gender, hypertension and obesity. His nephrotic-range proteinuria, low eGFR and hypercholesterolaemia also place him at a significantly increased risk of atherosclerotic cardiovascular disease. Indeed, Graham is more than 20 times more likely to die from cardiovascular disease than survive to the point of needing kidney replacement therapy (dialysis or kidney transplantation). Other recognised complications of nephrotic syndrome include deep venous thrombosis, including renal vein thrombosis (due to intravascular volume depletion, compensatory increase in coagulation factor synthesis in response to hypoalbuminaemia and urinary loss of anticoagulants such as antithrombin III, protein C and protein S), infection (due to low serum IgG concentrations, decreased complement activity and depressed T cell function) and volume depletion (particularly in the context of diuretic therapy). 8

**ANSWER 6**

The KHA-CARI Guidelines recommend that it is important to consider the underlying cause of Graham’s proteinuria and to pursue the diagnosis sufficiently to exclude treatable pathology, such as obstruction, vasculitis and rapidly progressive glomerulonephritis.3 In the first instance, it is important to repeat the eGFR measurement to ensure that Graham is not experiencing an acute deterioration in kidney function. It would also be useful to confirm the nephrotic-range proteinuria by performing a timed urine collection to quantify 24-hour proteinuria. Other investigations that should be performed include a full blood count, urine microscopy and culture, renal ultrasound scan, urine and serum electrophoresis, serum free light chains, antinuclear antibodies (ANA), anti-double stranded DNA antibody (dsDNA), anti-neutrophil cytoplasmic antibodies (ANCA), extractable nuclear antigens (ENA), complement studies, hepatitis B and C serology, HIV serology and a serum parathyroid hormone level.3

**ANSWER 7**

Graham should receive advice about lifestyle modification, including a low salt (<100 mmol salt or 6 g salt or 2.3 g sodium per day), normal protein (0.75–1.0 g/kg/day) diet high in vegetables and fruit, and low in saturated fats.3 A low-protein diet is not recommended as patients are at risk of malnutrition and muscle wasting. Graham should also aim for a healthier weight and exercise regularly. An angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) should be started, aiming for a blood pressure <130/80 mmHg. Combination therapy with ACEIs and ARBs is not advised due to the risk of hyperkalemia or acute kidney injury.10 A repeat eGFR should be ordered within 1–4 weeks after commencing an ACEI or ARB to ensure
these agents do not cause acute kidney injury (serum creatinine rise >30% or eGFR fall >25%) or clinically important hyperkalaemia (serum potassium >6 mmol/L) necessitating a change of therapy. Controlling hypercholesterolemia through dietary modification and use of a statin has been shown to reduce the risk of CKD progression and cardiovascular disease. Loop diuretics should be used sparingly to control Graham’s salt and water retention. In the opinion of the authors, a starting dose of 40–80 mg daily would be appropriate. In refractory cases, adding a thiazide diuretic or potassium-sparing diuretic can work synergistically to inhibit distal sodium absorption and promote further diuresis. This is best undertaken under the guidance of a nephrologist, as Graham should be monitored closely for clinical evidence of intravascular volume depletion (postural light-headedness and hypotension, low jugular venous pressure, deterioration of kidney function). Graham’s amlodipine should be ceased in case this agent is aggravating his ankle oedema. Some clinicians recommend commencing aspirin to mitigate the risk of deep venous thrombosis, but this should be postponed if a kidney biopsy is imminent (as would apply in Graham’s case).

ANSWER 8
Graham’s heavy proteinuria (UACR 330 mg/mmol) meets the Kidney Check Australia Taskforce’s recommended indications for referral to a nephrologist (Table 3).

Table 3. Recommendations for referral to a specialist renal service or nephrologist

<table>
<thead>
<tr>
<th>Referral to a specialist renal service or nephrologist is recommended in the following situations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• eGFR &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>• Persistent significant albuminuria (UACR ≥30 mg/mmol)</td>
</tr>
<tr>
<td>• A consistent decline in eGFR from a baseline of &lt;60 mL/min/1.73 m² (a decline &gt;5 mL/min/1.73 m² over a 6-month period, which is confirmed on at least three separate readings)</td>
</tr>
<tr>
<td>• Glomerular haematuria with macroalbuminuria</td>
</tr>
<tr>
<td>• CKD and hypertension that is hard to get to target despite at least three anti-hypertensive agents.</td>
</tr>
</tbody>
</table>

CONCLUSION
A subsequent biopsy confirmed a diagnosis of membranous glomerulonephritis. Graham was commenced on immunosuppressive therapy with cyclosporine.

REFERENCES
CASE 4
RUBY REFUSES DIALYSIS

Ruby, aged 82 years, is a resident at a nursing home. She attends outpatient dialysis at the local hospital 3 times a week. She was admitted to her nursing home 6 months ago because of increasing frailty and mobility problems.

Her past history includes ischaemic heart disease and mild congestive cardiac failure (CCF) following an acute myocardial infarct (AMI) 3 years ago. She has chronic lower back pain with right-sided sciatica and mild gastroesophageal reflux disease (GORD).

She commenced renal dialysis 2 years ago for chronic renal failure, presumably related to atherosclerosis, and has required renal dialysis since that time.

Ruby's general health has declined since her admission to the nursing home. She is now virtually bed- and chair-bound and has developed a chronic ulcer over her sacrum. She experiences considerable pain with movement and requires ambulance transportation to attend dialysis.

This morning she claims that she has had enough and refuses to go to dialysis. Ruby is usually lucid and coherent despite her physical frailty; however, over the last few weeks she has become slightly confused and irrational. She is uncharacteristically resistant to nursing attention and assistance with activities of daily living (ADLs). She asks to speak to you as her regular GP.

Ruby has become slightly vague in recent weeks but is determined not to get into the ambulance today. Her ACD states that if her quality of life deteriorated such that she was either bed-bound, confused or both, she would wish to cease dialysis. Ruby’s ACD states that in the event of a cardiorespiratory arrest, she is not to have cardiopulmonary resuscitation (CPR). Ruby had previously discussed this matter with her three children, who have also met with her renal physician and the social worker at the dialysis unit over the past few months.

The family feels comfortable supporting Ruby’s decision to withdraw from dialysis. They have requested that Ruby remain at her nursing home rather than be transferred to a hospital or hospice for palliative care.

QUESTION 2
What is Ruby’s life expectancy without dialysis?

QUESTION 3
Is withdrawing from dialysis euthanasia?

QUESTION 4
What are the general considerations regarding palliative care?

FURTHER INFORMATION
When Ruby first entered the nursing home, she and her family were encouraged to consider treatment limitations. She has a written advance care directive (ACD) and nominated her older daughter, who is a registered nurse, as her enduring medical guardian.
Withdrawal from dialysis is a significant decision in Ruby's life and has very definite and serious implications for her life expectancy. It is vital that an urgent meeting is held with Ruby and her family to discuss the implications of dialysis withdrawal for Ruby. For additional information about communicating prognosis and end-of-life issues see Resources for doctors section.

A small study reviewing the charts of 35 patients who withdrew from dialysis reported a mean survival time of 10 days (range 1–48 days). Other studies suggest that 75% of patients will die within 10 days or fewer following withdrawal from dialysis. Ruby's prognosis without dialysis may also be affected by other intercurrent medical problems, her level of hydration and the presence or absence of hyperkalaemia.

Withdrawal from dialysis is a common cause of death and in a 2008 Australian report was reported as the cause of 35% of dialysis-related deaths.

Withdrawing from dialysis is not an act of euthanasia. Euthanasia is defined as a deliberate act with the intention of ending a person's life in the context of serious illness. Withdrawing from treatment when the burden to the patient is outweighed by any benefit is considered ethically, legally and medically valid. Current guidelines specifically state that 'Withholding or withdrawing dialysis is not euthanasia. Equally it does not constitute physician-assisted suicide.'

Palliative care focuses on attaining the best quality of life for the person with advanced disease, where further active interventions are considered futile as the risks outweigh the benefits. Palliative care involves a careful and thorough clinical assessment, wise choice of symptom-directed care interventions and excellent nursing care, as well as spiritual and psychological support for the patient and close family members.

For Ruby, remaining in her nursing home, an environment that is familiar to her and being known to her carers, is likely to be of importance for her dignity, confidence, comfort and quality of life. If Ruby's decision is to remain in her nursing home, community palliative care resources can be utilised to assist the general practitioner (GP) and nursing home staff to provide the best possible care. Given the goals of care in a palliative care setting, any fluid restrictions can be relaxed a little.

In palliative care settings, reduced renal function complicates the choice of medications and doses suitable for symptom control, as many drugs require the kidneys for effective elimination of their metabolites.

**FURTHER INFORMATION**

Ruby's current medications include:
- paracetamol 1 g QID
- fentanyl 12 µg/hour patch every 3 days
- calcium 600 mg BD
- gabapentin 100 mg nocte
- oxycodone 2.5 mg every 4 hours PRN for breakthrough pain
- pantoprazole 40 mg daily.

**QUESTION 5**

Which of Ruby's medications can and/or should be continued?

---

**QUESTION 6**

Will pain be a problem for Ruby? How can it be managed in the nursing home?

---

**QUESTION 7**

What other symptoms associated with renal failure might require management?
These considerations should be taken into account when prescribing medications for patients. Ruby will probably progress quickly to a stage when she will not be able to take her usual medications or even oral symptom-management drugs, which may be prescribed for her. Hence, parenteral medication options should be considered early.

**ANSWER 5**

Paracetamol can be continued, although Ruby may need to take it as an elixir if she has any difficulty swallowing. No dose adjustment is required in renal failure. Although not a potent analgesic, paracetamol is considered a much safer option than non-steroidal anti-inflammatory drugs (NSAIDs). Other opioids (eg morphine, hydromorphone, oxycodone and their metabolites) are cleared by dialysis and rapidly accumulate after stopping dialysis.

Fentanyl is part of Ruby’s chronic pain management and should be continued. Palliative care guidelines recommend use of fentanyl or methadone where opioid-based pain management is required in renal failure. Fentanyl and methadone are considered the safest opioids because they do not have active renally excreted metabolites. Other opioids (eg morphine, hydromorphone, oxycodone and their metabolites) are cleared by dialysis and rapidly accumulate after stopping dialysis.

A low dose of gabapentin can be continued with care for neuropathic pain as long as Ruby can swallow. Care must be taken with higher doses in renal failure, as it accumulates and has significant adverse effects. The contents of the capsule can be administered in yoghurt or something similar if Ruby’s swallowing is impaired; however, there is no parenteral option.

Continued use of pantoprazole and calcium tablets is often limited by practical issues with swallowing and alertness so are often readily ceased.

**ANSWER 6**

Many doctors anecdotally regard death from renal failure as painless; however, it is now becoming clear that pain is often a significant problem for patients with advanced renal disease. Patients may experience pain from the discomfort associated with poor mobility, pressure areas or from other pre-existing medical conditions. With adequate palliative care and appropriate analgesia, death from ESRF/cessation of dialysis can still be ‘good’.

Ruby has chronic sciatica and there is the possibility of general discomfort arising from her increasing immobility and so management of pain will be important. Patients will also have difficulty taking oral analgesics as uraemia increases and alertness decreases.

As discussed previously, fentanyl and methadone are opioids without actively excreted renal metabolites and are, theoretically, the preferred options in renal failure. However, fentanyl patches are very slow to titrate and may be quite potent in opioid-naive patients. The parenteral formulation of fentanyl is also expensive and often difficult to access in the community. Methadone is very difficult to titrate, so hydromorphone is usually the opioid of choice for parenteral use, with allowances made for reduced dose or dosing frequency.

For Ruby, it would be appropriate to continue her usual fentanyl patch and to use hydromorphone as a breakthrough analgesic at a starting dose of 0.5 mg subcutaneously every 4 hours PRN. If multiple injections are required, a subcutaneously inserted butterfly needle can allow multiple doses of medication to be administered with minimal distress to the patient.

In an opioid-naive patient, hydromorphone 0.25–0.50 mg subcutaneously every 4 hours PRN would be an appropriate starting dose, remembering than in renal failure the duration of action may be significantly longer than the expected 4 hours. From a practical point of view hydromorphone is considered to be 5–7 times stronger than morphine.

If a patient not usually on opioids were to need frequent PRN doses of analgesia, consideration should be given to commencing a regular dose via a syringe driver (Figure 1). This would also allow concurrent infusion of an antiemetic and/or sedative if these medications were required. A syringe driver is a battery-driven portable device that allows a 24-hour infusion of compatible medications to be infused evenly via a subcutaneous butterfly needle. Some nursing homes are proficient in the use of syringe drivers and have their own machines, but most community palliative care teams can lend a device and provide education to nursing home staff on its use.

**Figure 1. Syringe driver**

**ANSWER 7**

Guidelines highlight that symptoms in patients with end-stage kidney disease are consistently under-assessed and not adequately managed. Symptoms that might need to be managed in renal failure are discussed below.

**Nausea and vomiting**

Haloperidol is recommended for uraemia-related nausea and vomiting. The starting dose is 0.5 mg twice daily subcutaneously PRN, up to a total daily dose of 7.5 mg. If used regularly, haloperidol could be added to other medications, such as hydromorphone, in a syringe driver.

Metoclopramide should be used with caution in renal failure because of a higher risk of extrapyramidal side effects, although it may still help if gastroparesis was a problem. Note, the maximum dose is 30 mg in 24 hours. Metoclopramide can be used in syringe driver combinations.

**Dyspnoea**

Low-dose opioids, as per pain recommendations, are appropriate medications for management of dyspnoea.
For anxiety and panic associated with dyspnoea, sublingual lorazepam at a dose of 0.5–1.0 mg every 4 hours PRN provides quick relief and is shorter acting than clonazepam. For increasingly more significant distress, clonazepam drops 0.25–0.5 mg every 6 hours sublingually can be used. Alternatively, midazolam 2.5 mg every 2 hours subcutaneously PRN, although more sedating and possibly amnesic for a short while, can be very helpful. Midazolam can also be added to a syringe driver for terminal agitation and its dose titrated to effect.

Uraemic pruritus (itch)
This can be difficult to resolve and in the terminal phase medications that may be used usually provide sedation. Ensure that the patient does not have another cause for itch such as allergies or scabies. Liberal use of bland skin moisturisers is advised. Gabapentin in low dose may be of some benefit early.

Restless legs syndrome
Antiparkinsonian drugs, such as levodopa, or gabapentin at low doses may be helpful; however, the patient may not be able to take these orally for very long. Occasionally, metoclopramide can cause restlessness, so if it is being used, it might need to be stopped.

In a rapidly deteriorating situation, management of restless legs with parenteral benzodiazepines may be the most appropriate option as in palliative sedation for myoclonus or terminal agitation. Clonazepam can be used orally or sublingually (oral liquid) once or twice daily in 0.5–1 mg doses, or subcutaneously (injection formulation) up to 4 mg a day in divided doses.

Terminal agitation
Haloperidol and clonazepam can be titrated for comfort with increased and PRN doses, but in Ruby’s case, the midazolam dose could be titrated up as required, incorporating it into the regular syringe driver regime.
At some point, the increasing uraemia will itself produce significant sedation. Hyoscine and/or glycopyrrolate for ‘death rattles’, if they occur, are compatible with hydromorphone, midazolam and haloperidol in a syringe driver.

It is important to note that although there is a parenteral formulation of clonazepam, it is usually given intermittently as a subcutaneous injection. This is because 50% of the clonazepam is absorbed into the infusion tubing if it made of polyvinyl chloride, and as the drug has a long half-life, intermittent doses are an effective option.

REFERENCES

RESOURCES FOR PATIENTS
- The Renal Resource Centre. Withdrawal from Dialysis Treatment. www.renalresource.com/pdf/Withdrawing%20from%20Dialysis%20Treatment%20RENL%20RESOURCE%20CENTRE.pdf
- www.racgp.org.au/guidelines/advancecareplans
- http://advancecareplanning.org.au
- www.renalresource.com

RESOURCES FOR DOCTORS
CASE 5
IRENE’S BLOOD PRESSURE IS DIFFICULT TO CONTROL

Irene, 59 years of age, is new to your practice and has presented for renewal of her prescriptions. She reports a history of hypertension and has osteoarthritis in both knees. Her current medications are amlodipine 10 mg once daily, metoprolol 50 mg twice daily and hydrochlorothiazide 12.5 mg daily. On examination, her seated blood pressure, using an appropriately sized cuff, is 164/88 mmHg in the right arm and 140/86 mmHg in the left arm with no postural drop.

QUESTION 1
Does Irene have resistant hypertension?

QUESTION 2
What other enquiries should you make in your history and look for in your examination as you assess Irene’s hypertension?

QUESTION 3
Which arm blood pressure recording should be used to guide Irene’s medical management?

QUESTION 4
How would you further investigate Irene?

FURTHER INFORMATION
Irene’s hypertension was first diagnosed 5 years ago during a ‘wellness check’ at work and was subsequently confirmed by three blood pressure measurements by her previous general practitioner (GP), after which she was commenced on amlodipine 5 mg daily. Her clinic and home blood pressure readings were ‘all right’ until last year when her blood pressure control worsened, necessitating an increase in her amlodipine dose (12 months ago) and subsequent commencement of metoprolol (6 months ago) and a thiazide diuretic (2 months ago). She reports good compliance with her medication. She is an ex-smoker (30 pack years), drinks 1–2 glasses of red wine with her evening meal, does not exercise regularly because of her knees and eats a lot of processed foods. Her father was diagnosed with type 2 diabetes at 48 years of age and had a myocardial infarction at 52 years of age. The only significant findings on physical examination were silver wiring of her retinal vessels, heart rate of 54 beats per minute, body mass index (BMI) of 31 kg/m² and waist circumference of 95 cm. Irene states that she has had some blood tests performed previously, but does not recall the results.
FURTHER INFORMATION
Irene returns 1 week later for a follow-up. A repeat blood pressure measurement in her right arm is 166/95 mmHg. Her 24-hour ambulatory blood pressure monitoring shows the following:
- daytime average 162/90 mmHg
- night-time average 156/85 mmHg
- 24-hour average 159/88 mmHg.
Irene’s blood tests reveal:
- sodium 136 mmol/L (reference range 135–150)
- potassium 3.8 mmol/L (3.5–5.0)
- urea 12.6 mmol/L
- creatinine 146 µmol/L (70–110)
- eGFR 38 mL/min/1.73 m²
- serum albumin concentration 38 g/L (32–40)
- total cholesterol 5.8 mmol/L
- HDL cholesterol 1.8 mmol/L
- LDL cholesterol 3.6 mmol/L
- triglycerides 1.6 mmol/L.

Her full blood count, the remainder of her biochemistry and her plasma aldosterone-to-renin ratio are normal. A urinalysis reveals 10 x 10⁶/L red and white cells and a UACR of 22 mg/mmol (<5.0 mg/mmol). Her ECG shows evidence of left ventricular hypertrophy. Records obtained from Irene’s previous GP showed that 2 years ago her serum creatinine was 125 mmol/L and eGFR was 40 mL/min/1.73 m².

QUESTION 5  
What is your diagnosis?

QUESTION 6  
What is Irene’s absolute cardiovascular risk (i.e., her risk of cardiovascular disease in the next 5 years)?

QUESTION 7  
What is Irene’s target blood pressure?

QUESTION 8  
How should Irene’s BP be managed?
Irene may have resistant hypertension, which is defined as blood pressure that remains above 140/90 mmHg in spite of concurrent use of three antihypertensive drugs from different classes (including a diuretic) for at least 1 month. Although Irene meets these criteria, it is important to first exclude pseudo-resistant hypertension, which is due to poor blood pressure measuring technique, white coat effect or poor adherence to medication. Careful measurement of Irene’s blood pressure with an appropriately sized cuff and concordance of her home and clinic blood pressure measurements suggest it is not due to poor technique and white coat effect, respectively. Assessment of Irene’s medication adherence would be very important before concluding that she has resistant hypertension.

The aims of history taking and physical examination should be to establish:

- the course and severity of hypertension
- the presence of end-organ damage (eg retinopathy, cardiac failure, proteinuria, reduced eGFR, CKD)
- cardiovascular risk
- the presence of clinical features suggestive of secondary hypertension, particularly chronic kidney disease (CKD), obstructive sleep apnoea and rare causes such as phaeochromocytoma, Cushing’s syndrome, hypothyroidism and aortic coarctation.

With regards to history taking, it is important to know how Irene’s hypertension was diagnosed, how well her blood pressure has been controlled, which antihypertensive agents have been trialled previously and, if relevant, the reasons for their discontinuation, how adherent she has been to her treatment regimen and whether she takes any medications known to increase blood pressure (Table 1). It is also important to determine if Irene has a personal or family history of premature hypertension, kidney disease, diabetes, dyslipidaemia and/or cardiovascular disease.

Lifestyle factors, such as sodium intake (processed food, added salt), physical activity, smoking, alcohol consumption and obesity, should be considered.
check Renal problems

**Table 1. Examples of medications/agents that interfere with blood pressure control**

- NSAIDs: conventional and COX-2 (most common)
- Sympathomimetics (eg nasal, oral decongestants, amphetamines)
- Oral contraceptives
- Bupropion
- Corticosteroids
- Hepatic enzyme inducers (eg rifampicin, antidepressants, monoamine oxidase inhibitors)
- Calcineurin inhibitors (eg tacrolimus, cyclosporine)
- Cholestyramine
- Erythropoiesis stimulating agents (eg erythropoietin, darbepoetin)
- Licorice
- Caffeine
- Alcohol
- Ginseng preparations
- Ephedra (ma huang)
- Melatonin

**ANSWER 3**

The National Heart Foundation guidelines recommend measuring blood pressure in both arms at the first assessment. The discrepancy in measurements between Irene’s left and right arms probably reflects an atherosclerotic lesion in the arm with the lower reading (ie her left arm). Diagnosis and management should always be guided by the readings from the arm with the higher measurement (in this case, Irene’s right arm).

**ANSWER 4**

Irene has hypertension and obesity, which are two of the seven recognised risk factors for CKD. The other risk factors are diabetes mellitus, smoking, family history of CKD, established cardiovascular disease and Aboriginal or Torres Strait Islander origin. The presence of any CKD risk factor warrants screening for the presence of CKD by requesting a urinary albumin-to-creatinine ratio (UACR) in a spot urine sample (preferably a first morning void) and an estimated glomerular filtration rate (eGFR), which is automatically reported by all Australian pathology laboratories with every serum creatinine request in an adult over the age of 18 years.

Irene should also have blood tests for a full blood count, general biochemistry, fasting lipids, urine microscopy/culture and plasma aldosterone-to-renin ratio. An aldosterone-to-renin ratio is best performed when patients are not taking any interfering drugs, including diuretics, beta-blockers, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Verapamil, hydralazine and prazosin do not interfere with the test. However, the investigation still has a good negative predictive value (for ruling out primary hyperaldosteronism) even when patients are on interfering medication.

Ambulatory blood pressure monitoring is often useful in situations where there is unusual variation between blood pressure readings in the clinic, suspected white coat hypertension (eg clinic hypertension in a person without evidence of target-organ damage), suspected hypotensive episodes (eg in those who are elderly or have diabetes) or, as in Irene’s case, resistant hypertension. Home blood pressure measurements are acceptable if ambulatory monitoring is not available. It is also important to try to obtain records of Irene’s previous blood tests.

Irene, therefore, has confirmed resistant hypertension with target-organ damage (CKD and left ventricular hypertrophy).

**Table 2. Risk of progressive CKD**

<table>
<thead>
<tr>
<th>Kidney function stage</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Albuminuria stage</th>
<th>Microalbuminuria (UACR mg/mmol) Male: 2.5–25; Female: 3.5–35</th>
<th>Macroalbuminuria (UACR mg/mmol) Male: &gt;25; Female: &gt;35</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>Normal (UACR mg/mmol) Male: &lt;2.5; Female: &lt;3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>45–59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>30–44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or on dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Green = low; yellow = moderate; orange = high; red = very high
**ANSWER 5**

On the basis of eGFR <60 mL/min/1.73 m² for at least 3 months and albuminuria in the microalbuminuric range, Irene has stage 3b CKD with microalbuminuria (Table 2).

The underlying cause of her kidney disease is uncertain at this stage. The most common causes of CKD in the community are diabetic kidney disease (DKD), chronic glomerulonephritis, hypertensive nephrosclerosis (including renovascular disease) and polycystic kidney disease. Irene’s ambulatory blood pressure readings are considerably elevated above the upper reference limits (24-hour average 135/85 mmHg, daytime average 140/90 mmHg, night-time average 125/75 mmHg).

**ANSWER 6**

Irene’s eGFR is <45 mL/min/1.73 m², indicating that she is automatically in the highest absolute cardiovascular risk category (ie >15% of cardiovascular disease within the 5 years). Using the Australian Absolute Cardiovascular Risk Calculator (www.cvdcheck.org.au/) to assess Irene’s risk level would lead to an erroneously low risk assessment (10% risk). Table 3 indicates the conditions that denote very high cardiovascular risk and for which use of the Australian Absolute Cardiovascular Risk Calculator is inappropriate.

<table>
<thead>
<tr>
<th>Table 3. People at very high cardiovascular risk (&gt;15% in 5 years) for whom use of the Australian Absolute Cardiovascular Risk Calculator is inappropriate</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Established cardiovascular disease</td>
</tr>
<tr>
<td>• Diabetes and age &gt;60 years</td>
</tr>
<tr>
<td>• Familial hypercholesterolaemia</td>
</tr>
<tr>
<td>• Serum total cholesterol above 7.5 mmol/L</td>
</tr>
<tr>
<td>• Severe hypertension (systolic ≥180 mmHg, diastolic ≥110 mmHg)</td>
</tr>
<tr>
<td>• Diabetes and microalbuminuria</td>
</tr>
<tr>
<td>• &lt;45 mL/min/1.73 m² or persistent proteinuria</td>
</tr>
</tbody>
</table>

**ANSWER 7**

According to the Kidney Health Australia-Caring for Australasians with Renal Insufficiency (KHA-CARI) and Kidney Check Australia Taskforce (KCAT) guidelines, Irene’s blood pressure target is <130/80 mmHg (Table 4) as she has CKD with microalbuminuria.

<table>
<thead>
<tr>
<th>Table 4. Recommended BP targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with…</td>
</tr>
<tr>
<td>Albuminuria (micro- or macro-)</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>CKD</td>
</tr>
<tr>
<td>All others</td>
</tr>
</tbody>
</table>

**ANSWER 8**

Lifestyle modification is important in the management of Irene’s blood pressure. She should be encouraged to follow a low salt (<100 mmol salt or 6 g salt or 2.3 g sodium per day), normal protein (0.75–1.0 g/kg/day) diet, high in vegetables and fruit and low in saturated fats. The KHA-CARI guidelines recommend that people with progressive CKD, particularly obese patients, should have an individualised diet intervention involving an accredited practicing dietician. Irene should also exercise regularly and moderate her alcohol intake. Such lifestyle interventions can achieve blood pressure reductions of 5–20 mmHg. Irene will also require additional antihypertensive therapy. Given that she has proteinuric CKD, it would be appropriate to commence either an ACEI or ARB. This could be prescribed as a combination medication with either the calcium channel blocker or the thiazide diuretic to minimise pill burden and optimise medication adherence. Initiation of an ACEI or ARB should always be followed by a repeat measurement of serum potassium and creatinine levels 5–7 days after commencement. If hyperkalaemia occurs, it should be managed by dietary potassium restriction. Serum potassium levels <6.0 mmol/L are acceptable.

An increase in serum creatinine following the commencement of an ARB or an ACEI is not unusual and is acceptable as long as the increase is ≤25% of the baseline value and stabilises within the first month. If creatinine increases by >25% of baseline within the first month, the ACEI or ARB should be ceased, as it suggests that the patient has functionally significant bilateral renal artery stenosis. If Irene’s blood pressure remains poorly controlled, consideration should be given to adding other classes of antihypertensive agents, including alpha₁ adrenoceptor antagonists, centrally acting alpha₂ adrenoceptor agonists and vasodilators. Consideration could also be given to changing her thiazide diuretic to a loop diuretic if her eGFR falls below 30 mL/min/1.73 m². The guiding principles for medical management of resistant hypertension are shown in Table 5.

**ANSWER 9**

As Irene has confirmed CKD, the KHA-CARI guidelines recommend that it is important to consider the underlying cause and to pursue the diagnosis sufficiently to exclude treatable pathology, such as...
obstruction, vasculitis and rapidly progressive glomerulonephritis.\(^4\)

Irene should have a renal tract ultrasound scan to assess the anatomy of her renal tract, specifically to assess kidney size and discrepancy and to exclude outflow obstruction. Her renal function should be monitored regularly. Although Irene’s likely diagnosis is hypertensive nephrosclerosis, it is reasonable to request urine and serum electrophoresis and serum free light chains.

Investigating for the possibility of underlying renal artery stenosis (eg with a renal artery duplex or spiral computed tomography) is not recommended in Irene’s case.\(^3,4\) Two large randomised controlled trials have shown that endovascular intervention for either uni- or bilateral atherosclerotic renal artery stenoses did not improve blood pressure control, antihypertensive agent requirements or renal function deterioration.\(^3,4\) Thus, investigation for renal artery stenosis should not be first line and should be reserved for rare cases associated with flash pulmonary oedema or rapidly deteriorating renal function.

**ANSWER 10**

In line with the recommendations of the KCAT and the KHA-CARI Guidelines,\(^3,4\) Irene should be referred to a nephrologist as she has CKD and hypertension that is difficult to get to target despite at least three antihypertensive agents (Table 6).

<table>
<thead>
<tr>
<th>Table 6. Recommendations for referral to a specialist renal service or nephrologist(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral to a specialist renal service or nephrologist is recommended in the following situations:</td>
</tr>
<tr>
<td>• eGFR &lt;30mL/min/1.73 m(^2)</td>
</tr>
<tr>
<td>• Persistent significant albuminuria (UACR ≥30mg/mmol)</td>
</tr>
<tr>
<td>• A consistent decline in eGFR from a baseline of &lt;60mL/min/1.73 m(^2) (a decline &gt;5mL/min/1.73 m(^2) over a 6-month period, confirmed on at least three separate readings)</td>
</tr>
<tr>
<td>• Glomerular haematuria with macroalbuminuria</td>
</tr>
<tr>
<td>• CKD and hypertension that is difficult to get to target despite at least three anti-hypertensive agents.</td>
</tr>
</tbody>
</table>

**ANSWER 11**

Renal denervation is aimed at reducing renally stimulated sympathetic activity; however, a recent randomised patient-blinded controlled trial of 535 participants failed to show a significant reduction in hypertension in patients treated with renal denervation.\(^15\)

Therefore, this therapy cannot be recommended.

**CONCLUSION**

Irene was referred to a nephrologist. Her blood pressure was ultimately controlled following lifestyle modification and a combination of amlodipine, metoprolol, perindopril, frusemide and methyldopa.

**REFERENCES**


**RESOURCES FOR DOCTORS**

CASE 6

ANNA HAS NAUSEA AND INCREASED URINARY FREQUENCY

Anna, aged 29 years, has been attending your practice since she and her husband moved to your large rural town 5 years ago. Anna is currently 8 weeks pregnant and today you are reviewing the results of her routine antenatal tests, which were done last week. Her blood results are normal. The results of her midstream urine (MSU) are shown in Table 1.

Anna is feeling well apart from mild nausea in the mornings. She has had an increase in urinary frequency since being pregnant, but no dysuria or suprapubic pain. Anna is normally very healthy and has no significant past medical history.

<table>
<thead>
<tr>
<th>Table 1. Anna’s MSU results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
</tr>
<tr>
<td>pH: 5.5</td>
</tr>
<tr>
<td>Protein: nil</td>
</tr>
<tr>
<td>Glucose: nil</td>
</tr>
<tr>
<td>Blood: nil</td>
</tr>
</tbody>
</table>

Antimicrobial sensitivity

Ampicillin/amoxicillin R (resistant)

Amoxicillin/clavulanic acid S (sensitive)

Cephalexin S

Trimethoprim S

Nitrofurantoin S

Norfloxacin S

QUESTION 1

How would you interpret Anna’s MSU results?

QUESTION 2

How would you manage Anna, given the above results?

QUESTION 3

What is your diagnosis? How will you manage Anna?

FURTHER INFORMATION

Anna completes the recommended treatment and her follow-up MSU result is normal. Her pregnancy progresses normally until 26 weeks, when she presents feeling ‘terrible’. She says she has felt feverish for 24 hours, is nauseated and has pain on her left side. The baby seems to be moving normally. On examination she has a temperature of 38.8°C, is mildly dehydrated and has left loin tenderness. Fundal height is appropriate for dates and the fetal heart rate is approximately 140 beats per minute.

<table>
<thead>
<tr>
<th>Table 2. Results of repeat MSU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
</tr>
<tr>
<td>pH: 5.4</td>
</tr>
<tr>
<td>Protein: nil</td>
</tr>
<tr>
<td>Glucose: nil</td>
</tr>
<tr>
<td>Blood: nil</td>
</tr>
</tbody>
</table>

Antimicrobial sensitivity

Ampicillin/amoxicillin R (resistant)

Amoxicillin/clavulanic acid S (sensitive)

Cephalexin S

Trimethoprim S

Nitrofurantoin S

Norfloxacin S

FURTHER INFORMATION

Anna’s repeat MSU results and antimicrobial sensitivity are shown in Table 2.
FURTHER INFORMATION
Anna is discharged 4 days after her admission. She has been prescribed nitrofurantoin 100 mg 12-hourly.

QUESTION 4
What follow up, if any, does she need during this pregnancy, with respect to her urine infection?

FURTHER INFORMATION
Anna has a normal delivery, giving birth to a healthy baby boy, Thomas, at 39 weeks gestation. She comes to see you for a postnatal checkup 6 weeks later. She is feeling well and has no urinary symptoms.

QUESTION 5
Does Anna require any further investigation for the UTIs she had during pregnancy?

CASE 6 ANSWERS

ANSWER 1
The presence of significant numbers of epithelial cells indicates contamination of the urine sample with cells from the distal urethra and/or perineum. Contaminated samples are frequently associated with false-positive urine culture results, as epithelial cells can carry large numbers of bacteria. Guidelines suggest that a positive culture in the presence of raised epithelial cells should be interpreted with caution. The urine test should be repeated with a carefully collected MSU sample.

ANSWER 2
Anna has asymptomatic bacteriuria, which is defined as bacteriuria (>100,000/mL) in the absence of specific symptoms of a urinary tract infection (UTI). Women should be offered routine screening for asymptomatic bacteriuria by MSU culture early in pregnancy. Dipstick testing (for leucocytes and nitrites) and urine microscopy alone (for the presence of bacteria and leucocytes) are screening methods shown to have high false-negative rates and should not be substituted for microscopy and culture. Screening and treatment of bacteriuria has been shown to be cost-effective.

According to UK studies, the incidence of asymptomatic bacteriuria in pregnant women is 2–5%. The risk is increased in those with a history of diabetes, previous UTIs or structural abnormalities of the urinary tract, and in mothers with lower socioeconomic status. If untreated, up to 30% of mothers may develop acute cystitis and up to 50% may develop acute pyelonephritis.

Escherichia coli is the most common pathogen isolated (approximately 80% of cases) in urine samples. Other pathogens include Staphylococcus saprophyticus, which is the second most common pathogen, as well as other gram-negative bacteria. Group B Streptococcus, although isolated less often, can cause asymptomatic bacteriuria in pregnancy, and women with this finding require treatment with penicillin during labour to help prevent neonatal sepsis.

Asymptomatic bacteriuria is associated with low birth weight and preterm delivery. A 2007 Cochrane review of 14 studies showed that treatment of asymptomatic bacteriuria with antibiotics reduces the risk of pyelonephritis and low birth weight but did not show a significant difference in the incidence of premature delivery.

Anna should be treated with an antibiotic according to her sensitivity testing results and taking into account any allergies. Appropriate choices are:

• cepalexin, 500 mg 12-hourly for 5 days (TGA pregnancy category A)

OR

• nitrofurantoin, 100 mg 12-hourly for 5 days (TGA pregnancy category A)

OR

• amoxicillin 500 mg + clavulanic acid 125 mg, 12-hourly for 5 days (TGA pregnancy category B1)
Although urinary alkalinisers are considered safe in pregnancy, they should not be used in combination with nitrofurantoin as this can result in a loss of treatment efficacy.\textsuperscript{2,11} A repeat urine culture should be performed at least 48 hours after treatment is completed to confirm clearance of the infection.\textsuperscript{10}

**ANSWER 3**

Anna has developed pyelonephritis, which is defined as significant bacteriuria in the presence of systemic illness and symptoms such as flank or renal angle pain, pyrexia, rigors, nausea and vomiting.\textsuperscript{2} Pregnant women with fever and pyelonephritis require hospital admission as there is a risk of preterm labour and maternal renal complications.\textsuperscript{2,12} Investigations usually include blood cultures; full blood examination; urea; electrolytes and creatinine (UCE); vaginal swab; MSU and urinalysis for proteinuria.\textsuperscript{2} Fetal wellbeing should be assessed with cardiotocography (CTG) monitoring. A specialist obstetrician should be involved if possible because of the risk of preterm labour. Consideration may need to be given to the use of antenatal steroids and/or tocolysis.\textsuperscript{8}

Anna should be commenced on empirical intravenous antibiotics until sensitivity testing is available.\textsuperscript{13} Intravenous gentamicin 4–6mg/kg for one dose then subsequent doses, determined by renal function, plus intravenous amoxicillin/ampicillin 2 g 6-hourly is recommended. In cases of penicillin allergy, gentamicin alone is usually sufficient. If gentamicin is contraindicated, intravenous ceftriaxone or cefotaxime are suitable alternatives.\textsuperscript{13}

Parenteral treatment should continue until the patient is afebrile for at least 24 hours, after which oral therapy can be commenced, guided by susceptibility testing results.\textsuperscript{13}

**ANSWER 4**

It is recommended that oral antibiotics are continued for 10–14 days, but this may need to be extended up to 21 days if improvement is slow.\textsuperscript{13} A repeat MSU should be done 48 hours after ceasing treatment to check that the infection has been cleared,\textsuperscript{13} and then at every subsequent pregnancy visit.\textsuperscript{2}

There is no consensus regarding the use of prophylactic antibiotics for recurrent UTIs in pregnancy. Some guidelines recommend antibiotic prophylaxis after two or more documented separate episodes of cystitis or pyelonephritis.\textsuperscript{2} Suitable antibiotic options are:\textsuperscript{2}

- **nitrofurantoin 50 mg oral at night**
  
  Note, caution should be exercised when administering nitrofurantoin at term or in cases of possible preterm birth. In these situations there is the possibility of producing haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and due to immature enzyme systems in the early neonatal period.

  **OR**

- **cephalexin 250 mg oral at night**

  **OR**

- **trimethoprim 150 mg oral at night.**

Avoid use in the first trimester and in pregnant women with established folate deficiency, low dietary folate intake, or in women taking folate antagonists.

A Cochrane review of 24 studies investigating the effectiveness of cranberry products for the prevention of recurrent UTIs has recently been published. The meta-analysis showed that cranberry products did not significantly reduce the occurrence of symptomatic UTI overall or for the subgroup of pregnant women with recurrent UTIs.\textsuperscript{14}

**ANSWER 5**

The incidence of asymptomatic bacteriuria in healthy, non-pregnant premenopausal women is 1–5%.\textsuperscript{16} Treatment of asymptomatic bacteriuria does not decrease the frequency of symptomatic UTI or prevent further episodes of bacteriuria.\textsuperscript{15} Additionally, asymptomatic bacteriuria has not been shown to be associated with detrimental long-term outcomes (eg hypertension, renal failure, genitourinary cancer or decreased survival).\textsuperscript{16} For these reasons, screening for or treatment of asymptomatic bacteriuria in premenopausal non-pregnant women is not recommended.\textsuperscript{4,16} Following guideline recommendations and not treating asymptomatic bacteriuria helps reduce antimicrobial resistance.\textsuperscript{17}

Anna is asymptomatic after the birth of her baby and does not require a screening MSU at this visit. She should be screened as early as possible in any subsequent pregnancies, as 6–8% of women experience recurrent pyelonephritis during a subsequent pregnancy.\textsuperscript{18–20}

People with structural abnormalities of the urinary tract are more likely to develop an upper urinary tract infection. Referral for investigation of an underlying abnormality of the renal tract is advisable for:\textsuperscript{12}

- men, following their first episode of acute pyelonephritis
- women, following two or more episodes of acute pyelonephritis
- all people with a urinary tract infection caused by a *Proteus* species.

There are no commonly accepted guidelines regarding referral for investigation of an underlying abnormality of the renal tract for women develop pyelonephritis during pregnancy. In pregnancy, significant physiological changes occur in the urogenital tract (eg bladder volume increases and detrusor tone decreases), which increase the potential for pathogenic colonisation. Most pregnant women develop ureteric dilatation due to a combination of progestogenic relaxation of ureteric smooth muscle and pressure from the expanding uterus. The overall effect is increased urinary stasis, compromised ureteric valves and vesicoureteric reflux, facilitating bacterial colonisation and ascending infection.\textsuperscript{9} In the absence of evidence-based guidelines, the general practitioner will need to use clinical judgement when considering investigation for underlying renal tract abnormality. Urinary tract ultrasonography could be considered, whereas computed tomography (CT) urogram has a higher cost and involves significant radiation exposure and probably cannot be justified.
REFERENCES


Renal Problems

In order to qualify for 6 Category 2 points for the QI&CPD activity associated with this unit:

- read and complete the unit of check in hard copy or online at the gplearning website at http://gplearning.racgp.org.au
- log into the gplearning website at http://gplearning.racgp.org.au and answer the following 10 multiple choice questions (MCQs) online
- complete the online evaluation.

If you are not an RACGP member, please contact the gplearning helpdesk on 1800 284 789 to register in the first instance. You will be provided with a username and password that will enable you access to the test.

The expected time to complete this activity is 3 hours.
Do not send answers to the MCQs into the check office.

This activity can only be completed online at http://gplearning.racgp.org.au

If you have any queries or technical issues accessing the test online, please contact the gplearning helpdesk on 1800 284 789.

For a Full list of abbreviations and acronyms used in these questions please go to page 3.
For each question below select one option only.

Which of the following statements regarding hypertension is CORRECT?

A. Resistant hypertension is defined as blood pressure that remains above 130/80 mmHg in spite of the concurrent use of three antihypertensive drugs.
B. Melatonin and ginseng preparations do not affect blood pressure.
C. Sympathomimetics (eg nasal and oral decongestants, amphetamines) and oral contraceptives do not interfere with blood pressure control.
D. Diagnosis and management of hypertension should always be guided by the readings from the arm with the higher measurement.
E. Alcohol use does not affect blood pressure control.

QUESTION 1

Jane, aged 25 years, is 7 weeks pregnant. Her recent MSU result following a routine antenatal visit showed the following:

- microscopy: leucocytes 9 x 10⁶/L (normal <10)
- erythrocytes 2 x 10⁶/L (<10)
- epithelial cells 0
- culture: Org 1: E. coli >10⁸ organisms/L
- antimicrobial sensitivity: ampicillin/amoxicillin R (resistant); amoxicillin/clavulanic acid S (sensitive); cephalxin S; trimethoprim S; nitrofurantoin S; norfloxacin S. She has no urinary symptoms.

Which of the following options would be appropriate management for Jane?

A. No further action is required with respect to this MSU result.
B. Repeat the MSU test.
C. Prescribe trimethoprim 300 mg daily for 5 days.
D. Prescribe cephalxin 500 mg twice daily for 5 days.
E. Prescribe cephalxin 1000 mg twice daily for 10 days.

QUESTION 2

People with resistant hypertension require multiple antihypertensive agents to bring their blood pressure within target or close to target.

People with diabetes are at increased risk of developing diabetic kidney disease (DKD). Which of the following statements regarding DKD is the most CORRECT?

A. The Nephron study reported that every second patient with diabetes will most probably have DKD.
B. Risk factors for DKD, other than diabetes, include having a strong family history of DKD (especially involvement of a first-degree relative), being overweight or obese and being over 60 years of age.
C. Levels of DKD have remained stable in the last 2 decades in Australia.
D. Statements A, B and C are correct.
E. Statements A and B are correct.

QUESTION 3

People with diabetes are at increased risk of developing diabetic kidney disease (DKD). Which of the following statements regarding DKD is the most CORRECT?

A. The Nephron study reported that every second patient with diabetes will most probably have DKD.
B. Risk factors for DKD, other than diabetes, include having a strong family history of DKD (especially involvement of a first-degree relative), being overweight or obese and being over 60 years of age.
C. Levels of DKD have remained stable in the last 2 decades in Australia.
D. Statements A, B and C are correct.
E. Statements A and B are correct.

QUESTION 4

Melanie, 84 years of age, is a nursing home resident who wants to stop attending outpatient dialysis sessions. Melanie was an only child and never married. She has no known family/relatives. Past medical history includes polio at age 6 years, acute myocardial infarct (10 years ago), heart failure diagnosed 2 years ago and several transient ischaemic attacks/strokes in the last 3 months, which have reduced her mobility and rendered her bed- and chair-bound. She experiences major pain with any movement. Which of the following statements is correct?

A. Allowing Melanie to withdraw from dialysis is tantamount to euthanasia.
B. Without dialysis Melanie would be expected to have a mean survival time of 10 days.
C. Withdrawal from dialysis is considered a rare cause of death in Australia.
D. Withholding or withdrawing dialysis is ‘physician-assisted suicide’.
E. Melanie’s prognosis without dialysis will not be influenced by any other factors (eg illness).
QUESTION 5
Pain is a common symptom in patients with chronic kidney disease (CKD). Which of the following statements regarding pain management in people with chronic kidney disease is the most CORRECT?
A. The principles of pain management are to treat the cause of the pain using non-opioid analgesia initially.
B. Paracetamol should not be used in people with CKD.
C. NSAIDs are suitable for people with chronic kidney disease when used at reduced doses.
D. Morphine can be safely used for people with CKD.
E. Fentanyl, which is renally excreted, should not be used in CKD.

QUESTION 6
Jennifer, aged 72 years, presents with swelling of both ankles. The problem arose after her routine flu immunisation 6 weeks ago. Examination reveals pitted oedema half-way up her knees. She was diagnosed with diabetes mellitus 12 years ago for which she receives insulin. Hypertension was diagnosed 15 years ago for which she received a low dose diuretic and an ACEI inhibitor until recently when she was also prescribed amlodipine. Recent reports indicate an eGFR of 41 mL/min/1.73 m² and a urine albumin:creatinine ratio of 31 mg/mmol. Which of the following statements is the most CORRECT?
A. Jennifer’s medication(s) could be contributing to her swollen ankles.
B. Jennifer’s swollen ankles could be symptomatic of a new and as yet undiagnosed illness.
C. On the basis of the presenting information, Jennifer has CKD.
D. All of the above.
E. None of the above.

QUESTION 7
Which of the following statements CORRECTLY describes the management of symptoms associated with CKD and/or end-stage kidney disease (ESKD)?
A. Fatigue is common, with the main reversible cause being anaemia secondary to reduced erythropoietin (EPO) synthesis; it may be treated with synthetic EPO-analogues.
B. Nausea is common in ESKD; the preferred first-line treatment is levoemepromazine.
C. Pruritus should be treated with gabapentin or antihistamines.
D. Dyspnoea should be managed using non-pharmacological options.
E. Restless legs syndrome is treated with gabapentin at normal doses.

REFERENCES


