The **detection** and **management** of **patients** with **chronic kidney disease** in primary care

A New Zealand consensus statement for the management of chronic kidney disease (CKD) in primary care has recently been developed. The statement reinforces the need to view CKD as a significant contributor to cardiovascular risk and recommends that targeted testing for CKD should be linked to routine cardiovascular risk assessments and diabetes testing. Earlier detection of CKD in high-risk groups, e.g. Māori and Pacific peoples and people with diabetes, is a clinical priority. A major challenge is identifying those patients with progressive CKD who require early and intensive intervention to prevent kidney failure and the eventual need for dialysis and/or kidney transplantation.

Chronic kidney disease in New Zealand

A consensus statement on the identification and management of chronic kidney disease (CKD) in primary care was agreed upon following the National Consensus Conference on CKD held in 2013 at Matakana. Discussions involved general practitioners, nurses, diabetes specialists and nephrologists. The CKD consensus statement has been reviewed by stakeholder groups. In this article we present the key points for health professionals working in primary care.

The challenge of chronic kidney disease

Chronic kidney disease is a general term used to describe any long-term condition that affects kidney structure and function, e.g. diabetic nephropathy, IgA nephropathy or polycystic kidney disease. However, declining kidney function is also a natural part of the ageing process. It is estimated that by the age of 70 years approximately 30% of the population will meet classification criteria for CKD.[1] The clinical challenge of CKD is to distinguish patients with progressively declining renal function due to disease from those with uncomplicated, age-related declining renal function.[2] Patients with untreated progressive CKD are at extremely high risk of experiencing a cardiovascular event, and if they live long enough they are likely to require dialysis and/or kidney transplantation.

Chronic kidney disease is a growing problem

The number of people in New Zealand with CKD is currently unknown, although based on overseas populations an estimate of 7–10% of the population would seem reasonable.[1] It has also been estimated that one in three people in the general population are at risk of developing CKD.[3] The burden of CKD on New Zealand communities is increasing and the number of people requiring dialysis has almost doubled since 2000; in 2012 there were reported to be 2469 people undergoing dialysis and 1520 people who had a successful kidney transplant.[1] Approximately half of all people in New Zealand requiring dialysis have diabetes as a primary cause of their condition.[1]

The impact of CKD in New Zealand is felt particularly among Māori and Pacific peoples as end stage kidney disease (stage 5 CKD – Figure 1, over page) is reportedly three to four times more common in these groups compared with people of European descent.[4] Earlier detection of CKD in high-risk groups is a health priority for primary care. The cost per annum for each patient undergoing dialysis ranges from $30 000 to $60 000.[1]

Defining and classifying chronic kidney disease

Chronic kidney disease is defined as the presence of structural or functional renal abnormalities, present for periods greater than three months, with implications for the patient's health.[5]

The Kidney Disease Improving Global Outcomes (KDIGO) criteria are used to classify CKD according to the patient's estimated Glomerular Filtration Rate (eGFR) and degree of albuminuria (Figure 1).[5] The KDIGO classification criteria do not include the cause of the patient's CKD. The term progressive CKD is used to describe patients with CKD whose eGFR is declining at a rate > 5 mL/min/year.[1]

In people with CKD the criteria used to classify stage 1 – 2 CKD differs from that used to classify stages 3 – 5. Patients who have stage 1 or stage 2 CKD must have some form of documented kidney disease, e.g. diabetic nephropathy or polycystic kidney disease as shown by imaging or biopsy abnormalities, or persistent proteinuria with or without haematuria. A patient's eGFR is then used to distinguish stage 1 CKD from stage 2 CKD, i.e. ≥ 90 mL/min/1.73m^2 (stage 1) or 60 – 80 mL/min/1.73m^2 (stage 2).[1] Patients with stages 3 – 5 of CKD have an eGFR ≤ 59 mL/min/1.73m^2, and evidence of kidney damage is not

required (Figure 1). It is important to note that the patient's eGFR will underestimate true GFR if the eGFR > 60 mL/min/1.73m², most likely due to the composition of the study population used to develop the equation from which eGFR is derived.

Age is included in the formula that calculates eGFR. Therefore in the general population eGFR declines by approximately 1 mL/min per year and many older patients will fulfil the criteria for stage 3 CKD without having any evidence of active or structural kidney disease. In these patients histology is likely to show age-related sclerotic changes to renal blood vessels, glomeruli and interstitium following biopsy.[1]

The kidneys are the canary in the coal mine

The risk of a person experiencing a cardiovascular event increases as their renal function declines. Between 40 – 50% of people with kidney failure die of cardiovascular disease (Figure 2).[6] The association between CKD and cardiovascular disease exists in part because two of the largest risk factors for CKD – diabetes and hypertension – are also associated with left ventricular hypertrophy and left ventricular diastolic dysfunction, both of which are predictive of myocardial infarction and stroke.[7] Coronary artery calcification, hyperlipidaemia, inflammatory processes, thrombosis, altered blood viscosity and endothelial dysfunction have also been suggested as mechanisms for the increased cardiovascular risk in people with CKD.[8] Albuminuria/proteinuria are markers of increased cardiovascular risk and renal injury.[1]

Detecting patients with chronic kidney disease in primary care

Most people with CKD stage 1 or 2 have no symptoms.[2] Therefore to increase detection of people with CKD it is recommended that primary care clinicians routinely offer kidney function testing for patients as part of routine CVD risk assessments and diabetes checks.[1]

Risk factors for chronic kidney disease

The major risk factors for CKD are:[1]

- Hypertension
- Proteinuria
- Diabetes
- Age over 60 years
- Body mass index (BMI) > 35
- Family history of CKD
- Māori, Pacific or Indo Asian ethnicity

- Cardiovascular disease resulting in reduced renal perfusion and endothelial dysfunction
- Prostatic syndrome/urologic disease which has the potential to cause obstructive nephropathy

Patients with risk factors for CKD should be assessed at least every one to two years.[2] For patients with diabetes this assessment should be performed at least annually.[2] Population screening for CKD in isolation is not recommended.

Diagnosing chronic kidney disease

Patients with stage 3 CKD may be asymptomatic, or may report nocturia, mild malaise or anorexia.[2] The signs and symptoms of stage 4 and 5 CKD are usually more obvious and include nausea, pruritus, restless legs and dyspnoea.[2]

Patients with CKD can be identified in primary care by requesting both:[1]

- A serum creatinine, which automatically generates an eGFR from the laboratory
- An ACR test; if a first void urine specimen, when the urine is most concentrated, is not possible then a random urine sample can be used[2]

Blood pressure measurements for patients at risk of developing CKD should also be performed where there is not a recent measurement recorded in the patient's notes.

Evaluating kidney test results

In patients with an eGFR < 60 mL/min/1.73m² testing should be repeated. Be mindful when performing follow-up tests that small fluctuations in eGFR occur naturally and these may not necessarily indicate that the patient's renal function is progressively declining.[2] A decline of 20% or greater in a patient's eGFR from baseline is considered to be clinically significant.[2] An eGFR < 45 mL/min/1.73m² is associated with an increased risk of renal and cardiovascular complications regardless of the patient's age.[2] When evaluating patients with suspected CKD it is particularly important to detect patients with progressive CKD whose kidney function decline may be as high as 10 – 20 mL/min per year.[1]

Albumin:creatine ratio testing is recommended in preference to protein:creatinine ratio (PCR) (mg/mmol) testing because ACR testing is considered to be a more sensitive and specific measure of changes in glomerular permeability than total urinary protein.[5] Albuminuria is classified according to Table 1.

Prognosis of CKD and by eGFR and Albuminuria Categories: KDIGO 2012

eGFR categories (mL/min/1.73m²) Description and range				Persistent albuminuria categories Urine ACR (mg/mmol) Description and range		
				A1	A2	A3
				Normal male < 2.5 female < 3.5	Microalbuminuria male 2.5 – 25 female 3.5 – 35	Macroalbuminuria male > 25 female > 35
G1	Normal or high	>90				
G2	Mildly decreased	60–89				
G3a	Mildly to moderately decreased	45–59				
G3b	Moderately to severely decreased	30–44				
G4	Severely decreased	15–29				
G5	Kidney failure	<15				

■ Low risk (if no other markers of kidney disease, no CKD) ■ Moderately increased risk ■ High risk ■ Very high risk

Figure 1: Classification and prognostic risk of chronic kidney disease (CKD) according to estimated Glomerular Filtration Rate (eGFR – mL/min/1.73m²) and presence of albuminuria (mg/mmol) adapted from KDIGO clinical guidelines, 2012[5]

	ACR < 10	ACR 10–29	ACR 30–299	ACR >300
eGFR >105	0.9	1.3	2.3	2.1
eGFR 90–105	Reference value	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.5	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	14	7.9	4.8	8.1

Figure 2: Risk of death due to a cardiovascular cause according to KDIGO criteria relative to a "healthy" person with an eGFR 90 – 105 mL/min/1.73m² and ACR < 10 mg/mmol, from the National Consensus Statement[1]

Table 1: Staging of albuminuria for males and females[2]

Stage of kidney damage	Male ACR (mg/mmol)	Female ACR (mg/mmol)
Normalbuminuria	<2.5	<3.5
Microalbuminuria	2.5 – 25	3.5 – 35
Macroalbuminuria	>25	>35

If the patient has microalbuminuria or macroalbuminuria (see referral criteria below) then this result should be repeated one to two times over the next three months to confirm a result.[2] If the patient has established macroalbuminura/proteinuria then the PCR needs to be quantitated as the proteinuria is usually non-selective and albumin will only comprise 50–60% of the proteinuria. Persistent proteinuria needs to be investigated.

The combination of a low eGFR and albuminuria/proteinuria means that the patient is at greater risk of developing end-stage renal failure, compared with patients who have a low eGFR, but no albuminuria or proteinuria.[1]

Referral to nephrology
General practitioners need to make the decision on an individual basis as to when to refer a patient with CKD to a nephrologist and/or diabetes services, and local guidelines may vary.[2] In younger patients a lower threshold for referral is usually appropriate. All patients with the following should be referred to a nephrologist:[1]

- Progressive CKD in patients with an eGFR < 45 mL/min/1.73[2]
- Evidence of intrinsic kidney disease, e.g. glomerulonephritis, polycystic kidney disease or interstitial nephritis

- Resistant hypertension and/or significant issues with blood glucose control and/or multiple vascular complications

If there is uncertainty concerning referral or management then telephone consultations and/or "virtual" referrals are highly recommended.[1] In general referral to a nephrologist is not necessary for patients who have:

- Stable eGFR ≥ 30 mL/min/1.73m[2]; and
- ACR < 30 mg/mmol with no haematuria; and
- Normal or controlled blood pressure

As CKD progresses alterations in bone mineral metabolism and calcium and phosphate homeostasis develop.[5] Anaemia will often occur in patients with severely reduced kidney function due to reduced renal synthesis of erythropoietin. Complications of advanced CKD will be managed by a renal team (Table 2), e.g. acidosis, metabolic bone disease, anaemia, malnutrition, infection risk and acute kidney injury (AKI).[2] Each patient should have an eGFR, serum electrolytes and quantification of proteinuria, and ideally have a recent renal ultrasound before being referred to a nephrologist. Consider discussing patients with a nephrologist if there is uncertainty regarding referral.[2]

Managing patients with chronic kidney disease in primary care

Most patients with stable CKD can be fully managed in primary care, particularly patients with stable stage 3 CKD or those patients aged over 75 years with early and stable stage 4 CKD.[2] The most important aspects of CKD management are:

1. Controlling blood pressure; and if the patient has diabetes

2. Controlling blood glucose

Patients with stable CKD (stage 3 – 4) have a five-year cardiovascular risk > 15%, if they do not have diabetes, which increases to > 20% if diabetes is also present. These patients need appropriate cardiovascular disease management and it is important that additional medicines, e.g. statins and aspirin, are initiated according to cardiovascular guidelines to reduce cardiovascular risk.

Complementary community-based care strategies involving nurse-led teams have been shown to improve outcomes in patients with moderate CKD who are at high-risk of progressing to kidney failure (see:" Delaying nephropathy in Māori and Pacific patients").

Software-based decision support, audit and patient recall systems are an important part of best practice in the management of CKD.

Lifestyle management of chronic kidney disease

Patients with CKD are able to reduce their rate of renal function decline through lifestyle modifications. Reductions in systolic blood pressure are often used to quantify the benefits of lifestyle modification in patients with CKD because this is known to have a renal-protective effect. Examples of lifestyle modifications and their approximate effect on systolic blood pressure include:[2]

- Reducing BMI to at least ≤ 30 kg/m² with an ideal target of ≤ 25 kg/m². Alternatively a waist circumference for males < 102 cm and a circumference < 88 cm for females. A 10 kg reduction in weight results in a reduction in systolic blood pressure of 5 – 20 mmHg.

- Moderate intensity physical activity ≥ 30 minutes/day results in a 4 – 9 mmHg reduction in systolic blood pressure

- Reducing dietary salt intake to ≤ 6 g/day results in systolic blood pressure of 2 – 8 mmHg. This can be achieved by choosing to consume fresh vegetables and fruit, fish, milk, unprocessed meats, and using less salt in cooking and at the dinner table.

- All patients with CKD can be advised to observe at least two alcohol-free days per week. Upper limits for alcohol consumption for females are no more than two standard drinks per day, and no more than ten standard drinks a week. Males should be encouraged to drink no more than three standard drinks per day, and no more than 15 standard drinks per week. Reducing alcohol consumption to moderate levels can result in a 2 – 4 mmHg reduction in systolic blood pressure.

Delaying nephropathy in Māori and Pacific patients: the DEFEND trial

General practices can produce clinically significant improvements in outcomes for patients at high-risk of progressing to kidney failure by instigating relatively simple complementary nurse-led interventions.

The DElay Future End-stage Nephropathy due to Diabetes (DEFEND) trial involved 65 Māori and Pacific patients aged from 47 – 75 years with type 2 diabetes, moderate CKD and hypertension.[7] Half the patients were randomised to usual-care (routine family doctor and renal/diabetes hospital outpatient care). The remaining patients received community care with monthly visits for one year by a member of a nurse-led team for blood pressure measurements, treatment compliance checks as well as monitoring for adverse effects. The study found that the community care resulted in clinically significant reductions in systolic blood pressure and proteinuria as well as delaying progression of left ventricular hypertrophy and diastolic dysfunction.[7] The success of the programme was attributed to Māori and Pacific health-care assistants providing culturally appropriate care, more frequent follow-up, frequent prompting for patients to take medicines, and reduced costs to the patients because of home visits.[7]

Smoking is an important modifiable risk factor for CKD progression.[9] The few studies that have been conducted on the effects of smoking cessation in patients with CKD have found that albuminuria is significantly decreased and progression of diabetic nephropathy slowed.[9] Encouraging smoking cessation in any patients with CKD is a priority of care.

Patients with CKD can be advised to maintain a normal daily intake of protein, i.e. 0.75 – 1 g/kg/day.[2] This equates to 60 – 80 g of protein a day for an 80 kg person, e.g. approximately 250 g of lean beef or chicken breast or 300 g of canned tuna.[10] High-protein diets, i.e. > 1.3 g/kg/day, are not recommended in patients with CKD at risk of progression due to the risk of further kidney damage.[5] Low-protein diets are also not recommended as insufficient dietary protein can lead to malnutrition, particularly in older patients.[5]

For further information see:
www.nutritionfoundation.org.nz/nutrition-facts/Nutrients/protein

Identifying patients at risk of progressive chronic kidney disease

Patients with progressive CKD require close supervision and will often need to be intensely managed.[2] Patients with CKD and risk factors should be regularly monitored (Table 2) for clinically significant reductions in renal function.[2] These risk factors include:

- Hypertension
- Proteinuria
- Obesity
- Diabetes
- Current smoker
- Aged over 60 years
- Family history of CKD
- Māori, Pacific or Indo-Asian ancestry

Pharmacological treatment of chronic kidney disease

Managing blood pressure is a cornerstone of CKD management both to slow the rate of CKD progression and to reduce the patient's cardiovascular risk.

The target blood pressure for patients with CKD is:[2]

- ≤ 130/80 mmHg for patients with diabetes or proteinuria with an ACR > 30 mg/mmol
- ≤ 140/90 mmHg for most other patients

However, blood pressure targets may need to be flexible and in older patients, e.g. aged over 70 years, a blood pressure target of < 150/90 mmHg may be reasonable.[1] When prescribing antihypertensive medicines to older patients doses should be gradually increased and the patient monitored for adverse effects such as dizziness, orthostatic hypotension, electrolyte imbalances and acute kidney injury (AKI).[5] Blood pressure control should also aim to reduce the levels of proteinuria by more than 50%.[2]

Angiotensin converting enzyme (ACE) inhibitors are the first-line treatment for controlling blood pressure in patients with CKD.[2] Angiotensin II receptor blockers (ARBs) are an alternative if ACE inhibitors are not tolerated.[2] The combination of ACE inhibitors and ARBs should be avoided when treating patients with CKD in primary care.[2] Follow-up in the early stages of treatment, i.e. two to four weeks, is useful to ensure the patient is responding adequately to antihypertensive treatment.[1]

Many patients will require multiple medicines to achieve blood pressure targets and this need increases as a patient's eGFR declines.[2] It is recommended that a calcium channel blocker be added to an ACE inhibitor or ARB as the second stage in managing hypertension in patients with CKD.[11]

For further information see: "Hypertension in Adults: The silent killer." BPJ 54 (Aug, 2013).

Glycaemic control
In patients with CKD and diabetes, glycaemic control is essential to prevent or delay the progression of the microvascular complications of diabetes, including diabetic nephropathy, and to reduce cardiovascular risk.[5] A HbA_{1c} target < 53 mmol/mol is generally appropriate for patients with CKD and diabetes, although in patients at risk of hypoglycaemia, e.g. older patients living alone, or in patients with co-morbidities or limited life expectancy, a target HbA_{1c} ≥ 53 mmol/mol may be more appropriate; this should be discussed with patients using a shared-decision making approach.[5]

In patients with advanced stage 4 and stage 5 CKD the risk of hypoglycaemia is also clinically relevant, and less intensive glycaemic control but with close monitoring is often required.[1]

The maximum dose of metformin in patients with an eGFR < 60 mL/min/1.73m² is metformin 1 g, daily.[12] Metformin should be avoided altogether in patients with an eGFR < 30 mL/min/1.73m² except under the close supervision of a nephrologist.[12]

For further information see: "Getting to know patients with type 2 diabetes and poor glycaemic control: One size does not fit all" BPJ 58 (Feb, 2014).

Treat hyperlipidaemia according to cardiovascular risk

Statin treatment for hyperlipidaemia should be discussed, where appropriate, with patients with CKD. The benefits of statin treatment in patients with CKD is relatively consistent in patients with a broad range of LDL cholesterol levels.[5] However, statins are less effective in patients with advanced CKD.[2] Fibrates should be avoided in patients with reduced renal function due to the increased risk of a myositis-like syndrome occurring.[12] The optimal lipid levels for patients with CKD are:[2]

- Total cholesterol < 4.0 mmol/L
- LDL cholesterol < 2.0 mmol/L
- HDL cholesterol ≥ 1.0 mmol/L
- Triglycerides < 1.7 mmol/L

Gout is common in people with chronic kidney disease

Chronic kidney disease is reported to be the third most prevalent risk factor for gout, following obesity and hypertension.[13] This is because reduced renal function in patients with CKD can result in uric acid levels being raised, causing gout symptoms in some patients.[14] According to international estimates 40 – 50% of patients with gout also have CKD.[15] Gout is associated with increased cardiovascular risk in patients with CKD. Gout is present in 11.7% and 13.5% of Māori and Pacific males, compared to 3.7% of European males, and 4% of Māori and Pacific females, compared to less than 1% of European females.[16]

Monitoring of renal function in patients with CKD and gout is particularly important as many of the medicines used to treat patients with gout are potentially nephrotoxic. Allopurinol is the first-line medicine used to reduce uric acid levels. Initial doses of allopurinol should be low and determined by eGFR in patients with CKD, and then slowly titrated to achieve a serum uric acid level of < 0.36 mmol/L.[17] This slow titration of allopurinol reduces the risk of patients experiencing the relatively rare allopurinol hypersensitivity syndrome. All non-steroidal anti-inflammatory drugs (NSAIDs) are associated with potentially nephrotoxic effects and should be used with caution to treat attacks of acute gout in patients with CKD. Oral prednisone is a treatment option for the management of acute gout attacks in patients with CKD.[12] Colchicine remains a useful treatment option in patients with stage 1 or 2 CKD, but should be avoided in patients with an eGFR < 60 mL/min/1.73m^2.[12]

For further information see: "Allopurinol dosing in renal impairment" BPJ 61 (Jun, 2014).

Monitoring patients with established chronic kidney disease

Patients with established CKD should have their eGFR and albuminuria assessed at least annually.[2] Albuminuria and eGFR measurements should be recorded more regularly for patients with an increased risk of progressive CKD. Patients with progressive stage 3 – 4 CKD have a much greater risk of developing renal failure.[1] These patients require intensive management with weekly or fortnightly review of risk factor management until their condition is stable.[1] Table 2 provides a recommended monitoring schedule for patients with established chronic kidney disease according to the degree of renal dysfunction.

Table 2: Monitoring and investigation schedule for patients with chronic kidney disease according to staging[2]

CKD staging	Frequency of review	Investigations requested
Stage 1 – 2	6 – 12 months; less frequently if the patient's eGFR is stable and risk factors controlled	Serum creatinine, ACR (or PCR), serum electrolytes, serum urate, HbA$_{1c}$ and lipids
Stage 3	Three to six-monthly	In addition to the above: FBC, serum ferritin, calcium, phosphate and parathyroid hormone
Stage 4	Three-monthly	In addition to the above: plasma bicarbonate
Stage 5	Monthly	Investigations usually determined in conjunction with a nephrologist

Preventing acute kidney injury

Most people who experience AKI have some degree of pre-existing CKD.[18] Medicines are a common cause of AKI in people with CKD and patients with an acute illness (e.g. a gastrointestinal illness, sepsis, and respiratory or urinary tract infection causing hypovolaemia) are at particular risk. In this context some medicines should be used with caution. For example the triple combination of NSAIDs, ACE inhibitors (or ARBs) and diuretics can cause AKI by interfering with homeostatic mechanisms needed to preserve kidney perfusion during acute illness.[19] Fluid and electrolyte maintenance is an important preventative strategy in people with CKD who are acutely unwell. People with established CKD should be advised to cease taking antihypertensive and oral hypoglycaemic medicines, especially metformin, if they develop acute illness with vomiting and diarrhoea, until they have recovered.

People with CKD are also at an increased risk of developing AKI when they undergo procedures involving radiocontrast media.[20] It may be necessary to temporarily withdraw potentially nephrotoxic medicines from patients with CKD who are undergoing contrast-enhanced imaging, particularly if they also have diabetes. The use of metformin is contraindicated in patients undergoing procedures involving iodine-containing contrast media, e.g. when investigating some cancers.[12]

For further information see: "Acute-on-chronic kidney disease: prevention, diagnosis, management and referral in primary care" BPJ 46 (Sep, 2012).
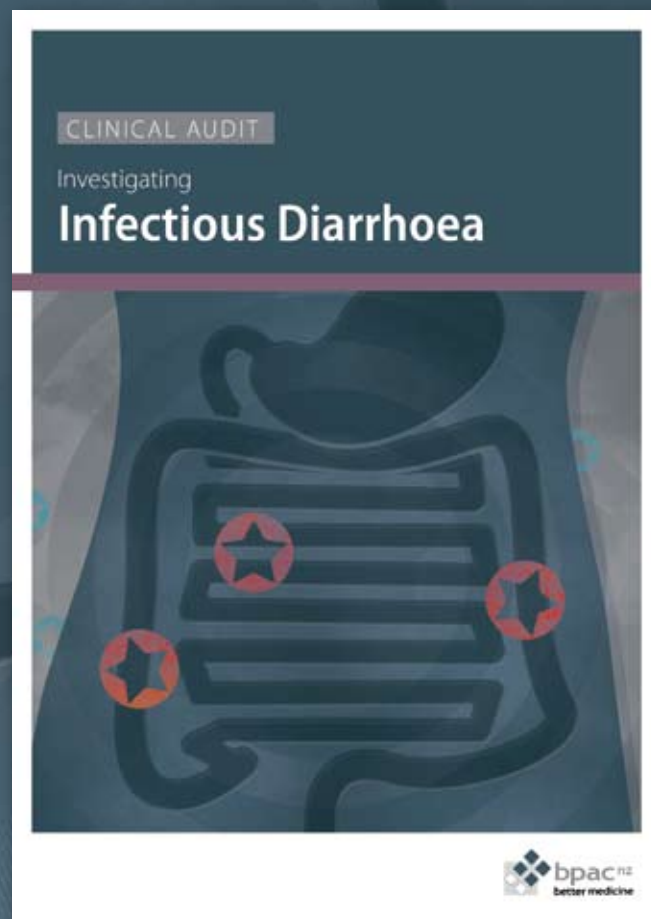
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