best tests

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Microbiology of infected wounds
Interpreting urine dipsticks

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CONTENTS

Microbiological assessment of INFECTED WOUNDS

When to take a swab and how to interpret the results

Identifying and managing infection in wounds is an important aspect of primary care practice. However, many issues relating to the aetiology of infection and the sampling of wounds remain controversial, with limited expert consensus. Most wound infection is diagnosed clinically, with laboratory testing used to provide further information to guide management. It is only necessary to swab a wound if there are clinical signs of infection and the wound is deteriorating, increasing in size or failing to heal. Swabbing a wound that is not infected results in the unnecessary identification and analysis of organisms which are colonising the wound, rather than causing an infection.

Characteristics of a wound

A wound is defined as any injury that damages the skin and therefore compromises its protective function. An acute wound is generally caused by external damage to the skin, including abrasions, minor cuts, lacerations, puncture wounds, bites, burns (heat, cold, friction, chemical) and surgical incisions. A wound is defined as being chronic if it has failed to heal (i.e. achieved anatomical and functional integrity) within three months.[1] The most common type of chronic wound is an ulcer, usually on the lower leg, and usually associated with underlying diabetes or vascular causes.

The aim of good wound care is to promote healing, prevent infection and ideally to achieve a good cosmetic result for the patient.[2] The immediate treatment of wounds, including dressings and follow-up care, is a crucial aspect of wound management, and is usually undertaken by the Practice Nurse team. The focus of this article is on identifying wound infection and interpreting the results of microbiological analysis of a wound swab.

Wound healing

Wounds heal by either primary closure, as in the case of a clean, fresh wound, with well-approximated edges which are sutured together, or by contraction and epithelialisation, such as for a wound left open due to loss of skin or contamination.[2] Normal wound healing requires a sufficient supply of blood to the affected tissues. A delay in healing can be caused by a number of factors, both local (related to the wound itself) and systemic (related to the patient and their clinical condition). Many of these factors not only delay healing but increase the likelihood of infection developing in the wound.

Local factors which may delay wound healing include:[3, 4]

- The underlying cause and severity of the wound
- A delay in the patient presenting for medical attention
- The presence of necrotic tissue in the wound – this can promote the growth of bacteria, especially anaerobes
- The presence of foreign bodies in the wound
- Impairment of the local circulation
- The site of the wound, e.g. wounds near the anal area are at increased risk of contamination
- A haematoma or any "dead space" in a wound – this can provide a ideal environment for bacterial growth
- Oedema in the tissues surrounding the wound
- Continued trauma or pressure to the wound site

Systemic factors which may delay wound healing include: [1, 3]

- Predisposing medical condition, e.g. diabetes, which compromises the health of the skin and increases the risk of infection
- Older age
- Obesity
- Smoking
- Poor nutrition
- Immunosuppression associated with either an illness, e.g. AIDS, or medicine, e.g. chemotherapy, corticosteroids.

Colonisation versus infection

All open skin wounds are colonised by bacteria, however, this does not mean that all wounds are infected. Inflammation occurs in all wounds during healing, regardless of whether they are infected, and a certain level of swelling, erythema and increased warmth at the site is normal and should not be confused with clinical infection. When skin is broken, its protective defence mechanisms are impaired, and the environment becomes more conducive for bacteria, which increase in number. These bacteria come from three main sources; the environment (e.g. dust, foreign bodies, bacteria on hands, clothing and equipment), the surrounding skin (normal skin contains colonising bacteria, referred to as commensals) and from the mucous membranes (gastrointestinal, oral and genitourinary).

The significance of biofilms

Several factors determine the progression of a wound from contamination to infection, including the bacterial load, the types of bacteria present and their synergistic action and virulence.[1, 5] Wounds are initially colonised with skin commensals (bacteria which reside symbiotically on the skin). If the wound does not heal, over time it will be colonised by different pathogenic species. The polymicrobial populations then interact synergistically, making it difficult to isolate a particular causative organism for a wound infection.[5]

Biofilms are communities of bacteria, embedded in an extracellular polysaccharide matrix. A biofilm forms when bacteria attach to a wound and form a micro-colony over time. Bacteria within a biofilm are physically protected from the host environment and can communicate with each other (quorum sensing). This leads to bacteria changing their phenotypes, resulting in increased virulence and greater likelihood of causing infection. The biofilm becomes an impediment to the healing of chronic wounds, and bacteria in a biofilm are 50 – 1000 times more resistant to conventional antimicrobial treatment than unattached bacteria.[5] However, this is an area of controversy as more recent research suggests that the significance of biofilms is not fully understood, and they may also have a beneficial effect in wound healing.[6] Biofilms can be physically removed through debridement of the wound, e.g. as part of the management of a chronic diabetic foot wound.

Wound infection can be classified on a spectrum of five progressively more severe stages:[1, 5]

1. **Contamination** occurs when non-replicating bacteria enter the wound.
2. **Colonisation** occurs when the bacteria begin replicating and adhere to the wound site, but do not cause tissue damage. The healing process of the wound is not delayed by colonisation alone, and in some cases, colonisation can enhance the healing process.
3. **Local infection or critical colonisation** occurs when the number of bacteria is greatly increased and begins to overwhelm the host immune system. The wound does not heal, but tissue invasion has not yet occurred. During this stage, the granulation bed in the wound appears unhealthy, e.g. atrophied, deep red or grey discolouration, with increased discharge, but there is no sign of invasion of the surrounding tissues. Delayed healing may be the only clinical sign.
4. **Spreading invasive infection** occurs when the bacteria overwhelm the patient's immune system and begin to invade and damage the surrounding tissue. Signs and symptoms of infection occur, such as erythema, pain and purulent discharge.
5. **Septicaemia** occurs when the infection spreads throughout the body via the blood stream and causes systemic symptoms such as fever, chills and tachycardia.

Red flags for wound care

Specific wound features or patient factors greatly increase the risk of infection or other complications. Referral for hospital assessment should be considered if a patient presents with high risk features, such as:[7, 8, 9]

- Rapidly developing tissue necrosis or gangrene
- Extensive cellulitis, or cellulitis of the face, hands, over joints or periorbital area
- Systemic illness without another obvious cause
- Clinical signs suggestive of osteomyelitis, e.g. deep bone pain, fever or chills
- Pain unrelieved by analgesics such as paracetamol or codeine
- A non-healing or worsening wound in a patient with diabetes
- Suspected malignancy of the wound

There should be a lower threshold for both referral and treatment in patients with co-morbidities such as diabetes or vascular disease, or if psychosocial factors are present that may increase the risk of infection, e.g. inability to adequately care for a wound at home, unsanitary living conditions.

Tetanus immunisation status should be established in all patients who present with a wound, and vaccination given where necessary.

When and how should a wound be swabbed?

Microbiological assessment can be important in the management of infected wounds. Information on the microbiological species present in the wound is useful for determining antibiotic choice and predicting response to treatment. However, these results are only significant if interpreted in the context of a wound that is infected, as non-pathogenic, colonising bacteria will also be detected.

A wound should only be swabbed if there are clinical signs of infection and the wound is deteriorating, increasing in size or failing to heal.[10]

The classic clinical signs of infection in an acute wound include:[10]

- New or increased pain
- Swelling
- Erythema
- Purulent exudate (or serous exudate with inflammation)
- Malodour
- Localised warmth around the site of the wound

Signs of spread of a localised wound infection include extension of erythema (and development of cellulitis), abscess formation, lymphangitis, crepitus in the soft tissues and breakdown or dehiscence (splitting open) of the wound.

In people with diabetes or with other conditions where perfusion and immune response are diminished, classical clinical signs of infection are not always present,[9] so the threshold for suspecting infection should be lower. In addition, the classical clinical signs of infection in acute wounds may not always be obvious in patients with chronic wounds, and more subtle signs of infection can help indicate whether a chronic wound is infected. These signs include discolouration of the granulation tissue, "foamy" granulation tissue, contact bleeding, tissue breakdown (particularly new tissue) and epithelial bridging (where there is incomplete epithelialisation).[11]

How do you swab a wound?

In primary care, a swab is the most common method used for sampling a wound. Although biopsy or aspirates of pus are the "gold standard" techniques, wound swabs can provide acceptable samples for bacterial culture provided that the correct technique is used.

If the wound is not purulent it should be cleaned prior to swabbing. Some literature suggests that cleaning the wound before sampling is unnecessary, however, if the wound is not clean it often leads to the isolation of multiple organisms which may not be relevant and can generate laboratory results reporting "mixed bacterial flora" rather than individual species.[12] Cleaning removes the organisms present in the surface material, which are often different from those responsible for the pathology, and allows for more accurate culture results. Wounds should be washed with sterile saline and then superficially debrided with a cotton, alginate or rayon-tipped swab.[1, 4] Ideally, the patient should not have received recent antibiotic treatment before swabbing a wound as this can affect the microbiological results.

The recommended swabbing procedure is as follows:[1]

1. Apply sterile saline to moisten the head of the swab to increase the adherence of bacteria
2. Pass the swab over the wound area in a zigzag motion while twisting the swab so that the entire head of the swab comes into contact with the wound surface
3. Swab from the centre of the wound outward to the edge of the wound
4. The swab should be pressed firmly enough that fluid is expressed from the wound tissue (this may be painful for the patient)
5. Repeat the process with a separate swab if a pocket or sinus is present in the wound

Once the sample has been collected it should be labelled with the patient identification details, date and time of the sample and wound site. On the request form record relevant clinical information such as the site and type of wound, the indication for taking a swab and any medication that the patient is taking that may affect the result, e.g. systemic antibiotics, topical antibacterials applied to the wound, corticosteroids. It is also important to make it clear on the request form that the sample is from a wound rather than a superficial skin lesion (this will alert the laboratory to select the appropriate culture media).

The sample should be transported as quickly as possible to the laboratory; ideally it should be processed within 48 hours. The swab should be stored at room temperature if same-day processing is not possible.

When should empiric antibiotics be prescribed?

Immediate treatment with empiric antibiotics is usually necessary for patients with acute wounds, where the risk of infection and complications is increased, e.g. a mammalian bite or a contaminated wound.[13] In addition, the threshold for empiric antibiotic treatment may be lower if there are medical conditions, e.g. diabetes, or psychosocial factors present which may increase the risk of infection and complications. Depending on the patient and clinical circumstances, a wound swab may still be required in addition to empiric antibiotics and the antibiotic choice altered if necessary once the results become available.

In some situations, antibiotics should not be prescribed to a patient with a suspected infected wound until the results of the laboratory assessment are available so that the appropriate antibiotic can be prescribed, e.g. in a patient with a chronic leg ulcer where there is likely to be a large number and variety of bacteria present.

For information on recommended antibiotic regimens for common wounds and complications, including diabetic foot infection, bites, abscesses and cellulitis, see "Antibiotic guide for common infections", available from: **www.bpac.org.nz**

Interpreting the results of a wound swab analysis

Most laboratories will provide information on the bacteria cultured from a wound swab, the number of organisms grown (either quantitatively or semi-quantitatively), and the antibiotic susceptibility of the grown organisms, which should guide treatment.

The flora of wounds

Approximately half of all infections in soft-tissue, community-acquired wounds are polymicrobial, and approximately one-quarter of infections in these type of wounds are caused by *Staphylococcus aureus*.[10] Bacterial infection with multiple species produces a synergistic effect, leading to increased production of virulence factors and greater delays in healing (see "The significance of biofilms"). The presence of an organism in an infected wound does not necessarily mean that it has caused the infection, and in practice it is not possible to differentiate between pathogenic and non-pathogenic organisms.

Certain kinds of wounds have characteristic bacterial flora, for example:

Superficial burns do not usually become infected, unless other systemic factors are present. When infection does occur, the most commonly reported microbes from a burn wound in the days immediately following the injury are *S. aureus* and other Gram-positive organisms. Later, Gram-negative organisms such as *Pseudomonas aeruginosa* or coliforms, e.g. *E. coli* may be implicated.[13, 14]

Bite wounds often contain more exotic flora, reflecting the source of the bite.[10] They are commonly polymicrobial, with very high microbial loads. *Staphylococcus spp*, *Peptostreptococcus spp* and *Bacteroides spp* are the most common microorganisms in wounds from human and animal bites.[13] Less commonly, organisms such as *Pasteurella multocida*, *Capnocytophaga canimorsus*, *Bartonella henselae* and *Eikenella corrodens* will be present.[13]

Surgical wounds from a "clean" surgery, i.e. non-emergency surgery that does not enter the gastrointestinal or genitourinary tract, do not usually become infected. However, when infection does occur, antibiotic-resistant organisms, such as methicillin resistant *Staphylococcus*

aureus (MRSA) and vancomycin resistant enterococci, are more commonly encountered, reflecting hospital-acquired flora.[10]

Diabetic foot infections are frequently associated with *S. aureus*, *Staphylococcus epidermidis*, *Streptococcus spp.*, *P. aeruginosa*, *Enterococcus spp*. and coliform bacteria.[13] With good laboratory technique, anaerobes can be isolated in up to 95% of people with severe diabetic lower leg infections, most commonly *Peptostreptococcus*, *Bacteroides* and *Prevotella spp*. However, the clinical significance of the type of microorganism present is reduced if there are limited signs of infection, which is common in people with infected diabetic ulcers.[13] Delayed healing is more likely to occur in people with diabetic foot infections, even when less pathogenic microorganisms are present.[15]

Deeper penetrating wounds are associated with a wider range of bacteria, representing the increased likelihood of foreign bodies in the wound. Referral is often necessary for exploration of the wound if it fails to heal.

Is species or number of organisms more significant?

There is some debate as to whether the type of bacteria or the overall density of the bacteria affects healing rates more significantly. It is likely that both factors play a role, however, the more widespread opinion is that organism type has the greater effect on wound healing. It is thought that aerobic or facultative pathogens in particular, such as *S. aureus*, *P. aeruginosa*, and beta-haemolytic streptococcus are the primary causes of delayed healing and infection in both acute and chronic wounds.[13]

Laboratories may provide either a quantitative or semi-quantitative result for bacterial load. A quantitative result gives the estimated number of organisms per gram of tissue or per mm^3. Organism load above 100 000 per gram of tissue or per mm^3 is considered significant, and is likely to reduce healing times significantly. Semi-quantitative analysis is based on grading bacterial growth as scant, light, moderate or heavy (or 1+, 2+, 3+ or 4+), of which moderate and heavy usually indicate significant bacterial counts (i.e. greater than 100 000 per gram).[13]

Antibiotic choice and susceptibility

Susceptibility testing is performed for all of the potential pathogens isolated from the swab. A "susceptible " report means that the organism should respond to treatment with the recommended antibiotic as long as there is a good blood supply to ensure adequate tissue levels of the antibiotic. This may not always be the case, e.g. if necrotic tissue is present. When an organism is reported as resistant to a particular antibiotic it is important to assess the clinical response, if treatment has already commenced, with consideration given to changing the antibiotic if necessary.

In slower-developing infections or wounds that have failed to resolve over time, antibiotic choice should be directed by the relevant susceptibilities provided by the laboratory analysis.

If empiric antibiotic treatment is prescribed, i.e. without swabbing, or before receiving the results of the wound culture, it is important to be aware of local antibiotic susceptibility, to guide treatment choice. Susceptibility differs by geographical area, as well as in different rest homes or long-term care facilities, e.g. MRSA is more common in some locations.

For information on nationwide susceptibilities and resistance, see: **www.surv.esr.cri.nz** (search antimicrobial resistance)

In addition to antibiotic treatment, wound cleansing, surgical debridement and correct dressing is essential to reduce the microbial load, and likelihood of infection.

Think twice before using mupirocin (Bactroban)

Mupirocin 2% (Bactroban) is a topical antibacterial treatment. When it first became available in New Zealand, it could be purchased in pharmacies (as a pharmacy-only "restricted" medicine). Its frequent use led to increased bacterial resistance to mupirocin, and as a result, mupirocin became a prescription-only medicine. Mupirocin remains active against some MRSA strains and as such, it is recommended that it should be reserved for use only when susceptibility testing shows MRSA to be present.

What should you do if a wound infection does not resolve?

If signs of infection are not reduced 48 – 72 hours after initiation of antibiotic treatment for an acute wound, a swab should be taken to reassess the wound flora and relevant susceptibilities. If a wound fails to heal within four to six weeks following treatment, particularly if antibiotics were used, discussion with a wound specialist is recommended.

In some cases, a non-healing wound may raise the suspicion of malignancy and this should be investigated.

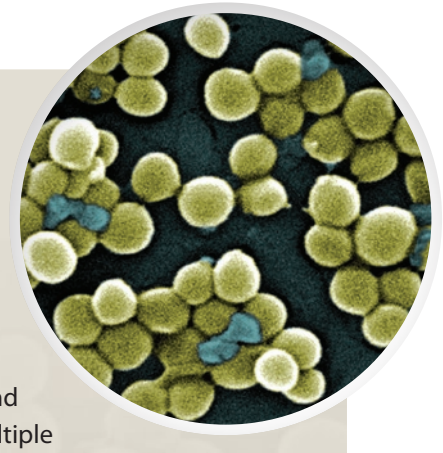
Is this wound malignant?

Chronic wounds can degenerate into malignancy, and conversely a malignancy may present as, or be mistaken for, a chronic wound.

It is estimated that approximately 3% of malignant lesions masquerade as a chronic wound. Primary malignancy should be considered in a patient with an ulcer which has developed over a relatively short time.[18] The typical example of this type of malignancy is a basal cell carcinoma, normally caused by sun exposure. Presentation varies, but the classic appearance is a "rodent ulcer", which has raised pearly edges and central atrophy or ulceration. A pearly, shiny nodule with prominent capillary networks is also common. A basal cell carcinoma may also present as an eczema-like patch. Only advanced cancers appear as wound-like, having outgrown their blood supply and eroded.

A chronic wound that develops into a malignancy is referred to as a Marjolin's ulcer.[19] The incidence varies, but it is estimated that approximately 2% of chronic wounds undergo malignant transformation.[18] Marjolin's ulcer is most commonly associated with burn wounds, but has been reported in various other types of chronic, non-healing wounds, such as lower leg ulcers. The ulcer is usually present for more than six months, but may be present for up to several decades, as it slowly undergoes malignant change. The most common resulting malignancy is a squamous cell carcinoma,[19] which is a slow-growing cancer derived from the epithelial cells.

MRSA: the super-villain of the 21st Century



CDC/ Janice Haney Carr/ Jeff Hageman, M.H.S.

Staphylococcus aureus is the most frequently isolated bacterial pathogen in wounds. Although non-pathogenic colonisation is common,[16] *S. aureus* is an important cause of both acute and chronic wound infection. Methicillin-resistant *S. aureus* (MRSA) are a subclass of *S. aureus* that are resistant to all classes of penicillins and cephalosporins.

There appears to be limited biological or clinical difference between MRSA and non-resistant staphylococcus with the exception of resistance. Adhesion ability, colonisation and infectivity, modes of transmission and survivability are all similar.[16] However, the difficulty in treating infections caused by MRSA mean that the MRSA infections are associated with higher mortality.

MRSA was first seen in New Zealand in 1975.[16] Traditionally, MRSA was almost exclusively hospital-acquired; however, since the 1990s community-acquired MRSA has been increasing in prevalence. Infections caused by MRSA are most common in hospitals, prisons, residential care and other areas where multiple people, often with lowered immune response live in close proximity.

Depending on the severity of the infection and the clinical situation, patients with MRSA infection in a wound may require referral to hospital for IV antibiotic treatment, usually with vancomycin. Patients with soft tissue infections that can be treated in the community are usually prescribed oral co-trimoxazole or clindamycin, but discussion with a clinical microbiologist or infectious disease specialist may be useful.[17]

Other factors that may indicate a malignant wound include:[18]

- Excessive granulation tissue that extends beyond the wound margin
- Wounds with an irregular base or margins
- Wounds with a change in discharge, bleeding or with outward (exophytic) growth

A punch biopsy of the wound should be taken if there is a suspicion of any malignancy; particularly if the wound has been present for longer than three months or developed rapidly and has not responded to treatment or is increasing in size.[18]

The biopsy site is important. If malignancy is suspected, the biopsy site should be on the wound margin and must include tissue from the wound bed and surrounding, non-damaged skin.[18, 20]

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Interpreting **urine dipstick tests** in adults

A reference guide for primary care

A urine dipstick positive for haematuria or proteinuria is a relatively common occurrence in primary care. For many patients there may be a transient, e.g. urinary tract infection (UTI), or benign explanation for their results, however, persistent positive results require further investigation. Management is determined by the presence of associated symptoms, risk factors for malignancy and additional investigations to identify a urological or nephrological cause.

Haematuria on dipstick

Haematuria can be classified as visible, also known as macroscopic or gross haematuria, or non-visible, also known as microscopic haematuria.[1] Haematuria can originate from numerous sites including the kidney, ureter, bladder, prostate, urethra or other structures within the urogenital tract.

Urine dipsticks are a rapid and relatively sensitive (>80%) method for detecting haematuria in a freshly voided sample of urine.[2] However, as well as intact red blood cells (RBC), urine dipstick may also detect haemoglobin from lysed RBC caused by haemolytic conditions, or myoglobin from crush injuries, rhabdomyolysis or myositis. As a consequence, reports of specificity range from 65 – 99%.[3] Significant haematuria occurs at readings of 1+ or above, and trace levels should be considered negative.[1]

Urine microscopy is not routinely required for confirming a dipstick diagnosis of haematuria.[1] However, in some situations, after clinical evaluation, urine microscopy may be useful in helping to distinguish haematuria from haemoglobinuria and myoglobinuria and to detect dysmorphic red blood cells and urinary casts indicating a medical renal cause.

Visible haematuria (macroscopic)

Visible haematuria is primarily associated with urological conditions. Rarely, similar changes in urine colouration may be due to other causes such as haemoglobinuria, myoglobinuria, beeturia (after eating beetroot), porphyria or medicines, e.g. rifampicin and chlorpromazine.[1] Haemoglobinuria can occur with haemolytic anaemia, which may be accompanied by rapidly developing pallor, splenomegaly and jaundice due to an increased concentration of bilirubin. Myoglobinuria is usually associated with rhabdomyolysis.

Non-visible haematuria (microscopic)

Transient, non-visible haematuria is common and, depending on the studied population, may be reported in as many as 39% of people.[3] It is associated with a mixture of urological and glomerular causes. Persistent, non-visible haematuria is defined as urine positive on two out of three consecutive dipsticks, e.g. over a one to two week period. It is estimated to occur in 2.5 – 4.3% of adults seen in primary care.[3]

Assessing haematuria

Haematuria can be symptomatic or asymptomatic. Relevant lower urinary tract symptoms include dysuria, frequency, urgency and hesitancy. Table 1 (over page) provides guidance when considering causes for haematuria. Anticoagulant and anti-platelet medicines are more likely to exacerbate, rather than cause, haematuria. Therefore patients who are taking these medicines who present with haematuria require investigation.[1]

Clinical suspicion of significant urological disease should be raised in people with haematuria with the following risk factors:[4]

- History of recurrent visible haematuria
- Age over 40 years
- Current smoker or recent history of smoking
- History of recurrent urinary tract infection (UTI) or other urological disorders
- Occupational exposure to chemicals or dyes
- Previous pelvic irradiation
- History of excessive analgesic use
- Treatment with cyclophosphamide

Risk factors specific for bladder cancer include; family history, smoking, male gender and occupational exposure

to carcinogens, e.g. benzenes, organic solvents or aromatic amines (also see: "Suspected UTIs and cancer risk in males", Page 15).[5]

A clinical history and examination may indicate a possible source of bleeding. As urinary tract infection (UTI) is a common cause of haematuria, this should first be considered and excluded. Non-visible haematuria is often transient so persistence should be confirmed by the presence of two out of three positive dipstick tests, seven days apart.[6]

Investigating visible haematuria

If UTI or other obvious causes have been excluded, imaging of the urinary tract is indicated (see "Urinary tract imaging informed decision making" and Figure 1, Page 14). Assessment by an Urologist and cystoscopy will also be required in the majority of cases, although in young people (age less than 40 years with no risk factors for urothelial malignancy) cancer is unlikely to be the cause. If investigations are normal, i.e. do not suggest a urological cause, a nephrology opinion is required to exclude a medical renal cause, with urgency dependent on the continuing level of haematuria.

Investigating non-visible haematuria with urinary tract symptoms

Non-visible haematuria is regarded as significant once transient causes, e.g. urinary tract infection (UTI) or exercise, or benign causes, e.g. menstruation, have been excluded. Urinary tract imaging is indicated for all patients of any age with recurrent, symptomatic, non-visible haematuria (see "Urinary tract imaging – informed decision making" and Figure 1, Page 14).[1, 6, 11] Urological assessment and cystoscopy is also required for patients aged over 40 years, or for patients with risk factors for urothelial malignancy.[1] When lower urinary tract symptoms are present in males aged over 40 years, digital rectal examination of the prostate and PSA testing should be undertaken. Incidental, non-visible haematuria may be present when prostatic cancer is diagnosed, usually as a result of associated benign prostatic hypertrophy. Typically, prostate cancer does not cause haematuria unless it is at an advanced stage.[12]

Baseline assessment of blood pressure and renal function with testing of creatinine (eGFR), ACR / PCR and urine microscopy for urinary casts and dysmorphic red cells are also recommended to identify patients with a renal medical cause for non-visible haematuria.[1, 6]

Table 1: Causes of haematuria that may be considered when assessing a positive dipstick[7]

Common in primary care	Transient/other	Do not miss	Consider
■ Urinary tract infection ■ Urinary tract or kidney stones ■ Prostatitis	■ Menstruation ■ Exercise-induced ■ Benign prostatic hyperplasia ■ Mild trauma ■ Pseudohaematuria, e.g. beeturia	■ Urinary tract, kidney or prostate malignancy ■ Cardiovascular: – Kidney infarction – Kidney vein thrombosis – Prostatic varices ■ Acute glomerulo-nephritis ■ Severe infection: – Infective endocarditis – Kidney tuberculosis ■ Papillary necrosis ■ IgA nephropathy	■ Urethral prolapse ■ Foreign body ■ Radiation cystitis ■ Familial: – Thin basement membrane disease – Adult polycystic kidney disease

Investigating asymptomatic non-visible haematuria

Age over, or under 40 years is used to determine the likelihood of there being a urological or renal medical explanation for asymptomatic non-visible haematuria.[1] For patients at higher risk of a urological cause, e.g. age over 40 or younger with risk factors for urothelial malignancy, urinary tract imaging is indicated (see "Urinary tract imaging – informed decision making). For those at low risk of a urological cause, renal ultrasound is indicated and a nephrology opinion is recommended under any of the following circumstances:[11]

- eGFR < 30 mL/min/1.73m^2 – Stage 4 or 5 CKD
- eGFR declining by > 5 mL/min in the previous year or > 10mls/min over the last five years
- Significant proteinuria ACR ≥ 30 mg/mmol or PCR ≥ 50 mg/mmol (proteinuria ≥ 0.5 g/24 hours)
- Uncontrolled hypertension ≥ 140/90 mmHg
- Unexplained visible haematuria following urological assessment where no cause was found

Primary care monitoring of unexplained haematuria

Primary care surveillance of unexplained haematuria requires annual assessment of urine dipstick, serum creatinine (eGFR) and urine albumin:creatinine ratio (ACR), or urine protein:creatinine ratio (PCR). This should be conducted until two consecutive negative urinalyses occur.[13] Patients with stable chronic kidney disease (CKD) should be monitored according to their stage of CKD. Patients should be referred back to urology if haematuria persists, or urinary tract symptoms develop or increase.

For further information see: "Making a difference in chronic kidney disease" BPJ 22 (Jul, 2009).

Urinary tract imaging – informed decision making

A computed tomography urogram (CTU) is regarded as the current gold standard for imaging in the investigation of visible and non-visible haematuria. However, some regions have reduced access to CTU and funding constraints mean that intravenous urogram (IVU/IVP) and ultrasonography still have a role when investigating patients at lowest risk of renal tract malignancy.

A CT should be performed in at least three phases; a non-contrast phase to detect urinary stones, a contrast phase to evaluate structural, vascular, or infectious abnormalities of the renal parenchyma, and a delayed excretory phase to outline the collecting system. This is often referred to as a triphasic-CT , CTU/IVP or CT-Haematuria.

The non-contrast phase of CT can detect renal stones with sensitivity of 94% to 98%, compared with 52% to 59% for IVU.[15] CT is superior to ultrasound and IVU for detecting renal masses.[16]

CTU is the most comprehensive radiological method for evaluating the urinary tract for urolithiasis, renal masses, and urothelial neoplasms in a single examination.[13] Cystoscopy is still required to exclude a cause for haematuria located in the bladder.

Women who are pregnant, or people who have a suspected allergy to the contrast media, may not be suitable for CTU imaging. Pre-existing renal dysfunction may also be a contraindication for CTU.

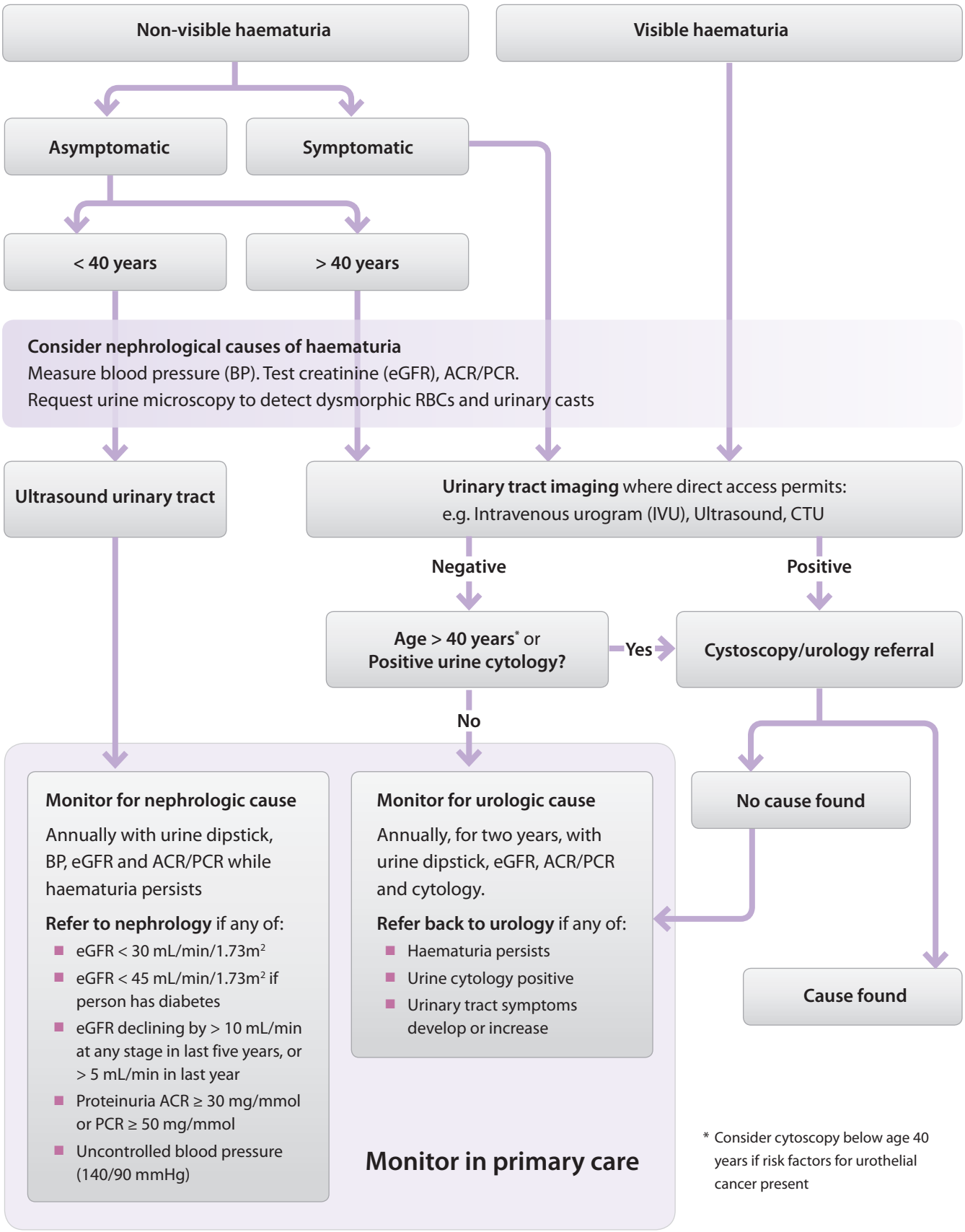


Figure 1: Investigation and referral algorithm for significant haematuria in adults once UTI and benign causes have been excluded[1, 6, 13, 14]

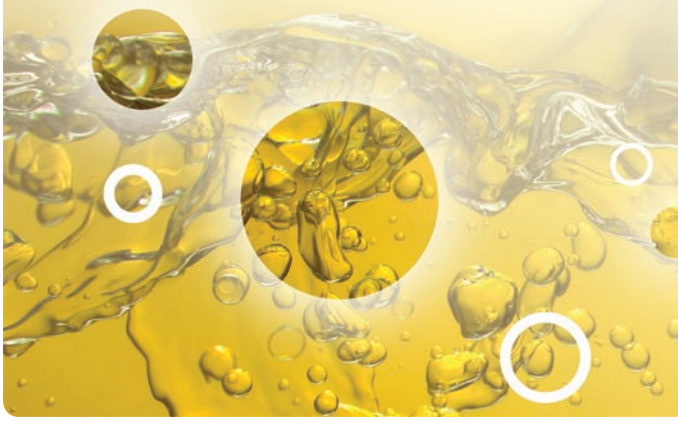
Suspected UTIs and cancer risk in males

Urinary tract cancer (kidney and bladder) has a higher incidence in males than females. In New Zealand, in 2009, there were 581 urinary tract cancer registrations for males, compared to approximately 300 for females.[8] Treatment is often curative if there is an early diagnosis when the malignancy is localised to the kidney and the immediately adjacent tissue. Renal cancer is rare in people aged under 35 years, and bladder cancer is rare below age 50 years.[9] Visible haematuria is a common symptom of urinary tract cancer.

When examining males with a suspected UTI, consider the possibility of malignancy, especially in patients with risk factors for cancer. Urine culture is recommended in all males with suspected UTI (in contrast to guidance for females with uncomplicated UTI) to confirm a diagnosis and guide treatment.[10] Males with a UTI that does not respond to antibiotic treatment, or who have persistent haematuria, should be referred to an Urologist.[10]

Factors that increase the risk of UTI in males include:[10]

- Age > 65 years
- Institutional care
- Bladder outlet obstruction
- Previous urinary tract surgery or recent procedures, e.g. prostate biopsy
- Anal intercourse
- Immunodeficiency



Urine cytology should not be routinely used in the initial investigation of haematuria

Urine cytology is a non-invasive method of testing for bladder cancer, however it is not a "rule-out" test due to low sensitivity of 40–76%.[18] The test detects cancerous cells shed from any part of the urothelium. Reports of specificity are as high as 98%.[18] The sensitivity of urine cytology for detecting cancer is influenced by the type of tumour present. Large, or high-grade tumours, or carcinoma in situ are more likely to shed cells and the sensitivity for detecting these is high, however, sensitivity for low-grade cancer is reported to be 11%.[18] As 60% of urothelial tumours are reported to present as low-grade and early-stage lesions, this has important implications for the use of urine cytology as a detection tool for bladder cancer.[18] Urine cytology results are also dependent on operator skill and it is important to have an experienced pathologist interpret the results.[17]

Cystoscopy is the preferred technique for excluding bladder cancer as the cause of haematuria as it is reported to have a specificity for malignancy of over 90% and the added advantage of being able to detect stones, vascular abnormalities and infectious lesions, which can also cause haematuria.[18] Furthermore, a study where 182 patients underwent 405 cytologies found that no patients with a positive cytology had a negative cystoscopic/radiological evaluation.[17] This suggests that the addition of cytology to an investigation of haematuria is unlikely to significantly increase the rate of cancer detection when all high-risk patients proceed to cystoscopy and radiology. The role of urine cytology as an investigation of haematuria is therefore being increasingly questioned.[18] It should not be used as part of a routine evaluation.[12] It is acknowledged, however, that some regional guidelines include urine cytology to aid triaging for cystoscopy. There may still be a role for cytology in circumventing the need for cystoscopy in high-risk patients likely to require surgery, or as a monitoring method for patients with an undiagnosed cause of haematuria and patients with a history of bladder cancer.[18]

Proteinuria on dipstick

People with normal kidney function excrete less than 150 mg of protein per day in their urine, approximately 20 mg of which is albumin.[24] Persistent protein excretion significantly above this level is a marker for kidney disease, and kidney disease progression, and indicates an increased risk for cardiovascular events.[25]

Urine dipstick is a highly specific (97 – 100%) method for detecting proteinuria, however, the sensitivity of the test for detecting low-end, but clinically significant proteinuria is reported to be 32 – 46%.[26] Therefore in people diagnosed with, or suspected of having diabetes, a more sensitive technique, i.e. albumin:creatinine ratio (ACR), is recommended to quantify proteinuria.[25]

Proteinuria on dipstick in primary care is frequently an incidental finding and is often benign and transient.[26] However, the presence of proteinuria can also suggest endothelial/glomerular injury. The first step in assessment should be to consider the possibility of a false positive result, which can be caused by alkaline urine (pH >7), gross haematuria, mucus, semen or leukocytes.[26]

Confirm persistent proteinuria

Proteinuria may be transient or persistent. Transient, mild proteinuria can be caused by recent strenuous exercise, standing for long periods (orthostatic proteinuria), pregnancy, UTI and acute febrile illness.[26] Congestive heart failure is a more serious cause of proteinuria that can also be transient. Orthostatic proteinuria is typically absent in the morning, occurs in the afternoon and is seen mainly in young adults.[26]

Transient proteinuria can be confirmed by a repeat dipstick result which is negative, in the absence of any suspected transient cause. Persistent proteinuria can be confirmed by two or more consecutive positive dipsticks over a one to two week period.[27]

If persistent proteinuria on dipstick is present an ACR or PCR should be performed to quantify the level of

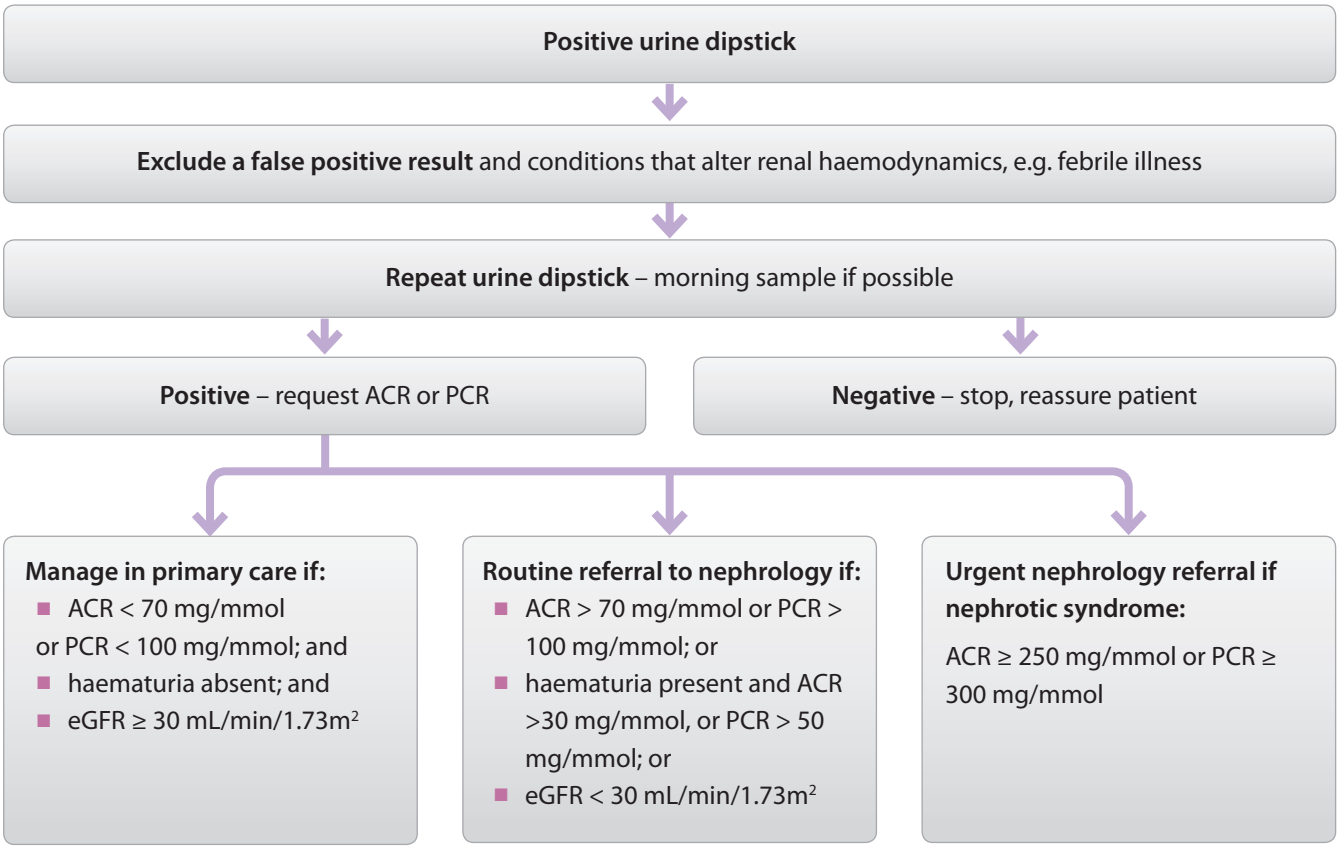


Figure 2: Investigating urine dipstick positive for proteinuria in primary care[26]

Table 2: Causes of proteinuria that may be considered when assessing a positive dipstick[7]

Common in primary care	Transient/other	Do not miss	Consider
■ Diabetes ■ Hypertension ■ Obesity ■ Medicines, e.g. NSAIDs	■ Contamination by vaginal secretions ■ UTI ■ Orthostatic proteinuria ■ Exercise ■ Fever	■ Congestive heart failure ■ Glomerulonephritis ■ Nephrotic syndrome ■ Acute tubular damage ■ Pre-eclampsia	■ Congenital tubular disease, e.g. polycystic kidney disease ■ Multiple myeloma ■ Systemic lupus erythematosus (SLE) ■ Myoglobinuria ■ Haemoglobinuria ■ Amyloidosis

proteinuria (Figure 2). ACR is the preferred method for quantifying proteinuria as it has greater sensitivity than a protein:creatinine ratio (PCR) for low concentrations of protein, and albumin is the predominant protein excreted in the majority of proteinuric kidney diseases (see "Always quantify proteinuria when eGFR or serum albumin are low", over page).[25] Spot (random) urine samples are generally sufficient, although early morning collection is preferable, as the sample will be more concentrated.[25] Timed urine collection is not required as spot sampling accurately reflects 24 hour albuminuria and proteinuria.[25]

Major causes of persistent proteinuria

Table 2 provides guidance when considering causes for proteinuria in primary care.

Follow-up investigations of confirmed proteinuria

Routine referral to nephrology is indicated for all patients with ACR > 70 mg/mmol or PCR > 100 mg/mmol.[28]

Urgent referral is required if nephrotic syndrome is suspected, i.e. proteinuria is in the nephrotic range (ACR ≥ 250 mg/mmol or PCR ≥ 300 mg/mmol), or if serum albumin is < 25 g/L, or oedema is present.[29, 28] Patients with haematuria and proteinuria (ACR > 30 mg/mmol or PCR > 50 mg/mmol) also require referral to nephrology.

Proteinuria and cardiovascular risk

People with CKD are at increased cardiovascular risk and are far more likely to die due to a cardiovascular cause than they are of progressing to end-stage renal failure.[11] A meta-analysis of 26 studies found evidence of a dose-response relationship between albuminuria and the risk of coronary heart disease (CHD).[36] Individuals with microalbuminuria had 50% greater risk of developing CHD and the risk in those with macroalbuminuria was increased more than 200%.[36] This study provides evidence that evaluation of proteinuria may be a useful future addition to cardiovascular risk assessment in primary care. People with diabetes and over nephropathy (ACR ≥ 30 mg/mmol) are classified as having a five-year cardiovascular risk greater than 20% and require intensive management to reduce risk factors.[37]

IgA nephropathy and thin basement membrane disease

IgA nephropathy (Berger's disease) is the most common form of primary glomerulonephritis. It is estimated to occur in up to 6 – 10% of the general population, although many of these people may not present for medical care, so will remain undiagnosed.[19, 20] Peak incidence occurs in the second or third decade of life.[21] In approximately one-third of those affected, IgA nephropathy is characterised by episodes of visible haematuria coinciding with intercurrent infections, usually of the upper respiratory tract (synpharyngitic haematuria), proteinuria, hypertension and progressive renal dysfunction.[22] Synpharyngitic haematuria is almost diagnostic of IgA nephropathy. A minority of people with IgA nephropathy progress to end-stage kidney disease. As for all people with chronic kidney disease (CKD), the main markers of progression are the presence and degree of proteinuria and development of hypertension. The degree of scarring on renal biopsy strongly correlates with risk of progression. Treatment is aimed at blood pressure control, i.e. ACE inhibitors and/or angiotensin-II receptor blockers (ARB), and reduction of proteinuria. Immunosuppression in IgA nephropathy is controversial

Patients with IgA nephropathy who only have non-visible haematuria and no, or minimal, proteinuria, normal blood pressure and normal renal function, have the same prognosis as the general population.

Thin basement membrane disease, also known as benign familial haematuria, is the most common reason for persistent haematuria in children and adults.[23] It is characterised by uniform thinning of the glomerular basement membrane and mild proliferative glomerulonephritis.[22] People with thin basement membrane disease often have lifelong glomerular haematuria, but have minimal proteinuria and normal renal function. It is common for multiple family members to be affected.[22]

Always quantify proteinuria when eGFR or serum albumin are low

Albumin comprises 60% of the body's total plasma protein.[38] It is the predominant protein excreted by people with diabetes, hypertension and many glomerular diseases and is also a marker for disease progression.[25] Urine albumin quantification by ACR provides increased sensitivity and precision for detection of lower, but clinically significant levels of protein than does total urine protein quantification via PCR.[25] This is particularly important for people with diabetes who are at increased risk of kidney disease.

It is recommended that all patients with an eGFR < 60 mL/min/1.73m^2 have proteinuria quantified by measuring ACR.[25] In addition all patients require proteinuria quantification where there is a clinical suspicion of nephrotic syndrome, e.g. serum albumin is low (hypoalbuminaemia).

The diagnostic criteria for nephrotic syndrome are:[29]

- ACR > 250 mg/mmol or PCR > 300 – 350 mg/mmol or proteinuria > 3 – 3.5 g/24 h
- Serum albumin < 25 g/L
- Clinical evidence of peripheral oedema

If non-visible haematuria is present, a sample should be sent for urine microscopy.[30] Red blood cell casts and dysmorphic red blood cells are likely to be caused by glomerular disease.[3, 31] Non-glomerular causes of proteinuria with haematuria include tubulointerstitial, renovascular or metabolic processes and generally occur without red blood cell casts and dysmorphic red blood cells.[31]

Renal function should also be assessed and serum electrolytes measured.[30] If eGFR is stable and ≥ 30 mL/min/1.73^2, haematuria is absent and ACR < 70 mg/mmol, or PCR < 100 mg/mmol then the patient can be managed in primary care.[28] If eGFR < 30 mL/min/1.73^2 and haematuria is present the patient should be referred to nephrology regardless of the level of proteinuria.[28]

Patients with proteinuria who are not referred to a Nephrologist should have blood pressure, urinalysis and renal function assessed every 6 – 12 months.[32] Hypertension should be treated to a target of less than 130/80 mmHg.[33] Some guidelines recommend a lower blood pressure target of 125/75 mmHg for the treatment of proteinuria, however, this target should be approached with caution as a systolic target less than 120 mmHg is associated with an increased risk of adverse events in people with diabetes.[32, 33]

Request further testing if multiple myeloma is suspected

The index of suspicion for multiple myeloma should be increased in patients aged greater than 60 years with any bone pain, and fatigue and/or weight loss, with or without hypercalcaemia.[34] There may be accompanying laboratory evidence of anaemia and renal impairment. Serum protein electrophoresis and serum-free light chain assay are recommended by international guidelines when investigating suspected myeloma. Urine-free light chain assays are no longer considered appropriate in this situation.[35] A practical approach is to first request serum protein electrophoresis and then if an increase in immunoglobulins is found, to discuss the need for further testing with a haematologist. Protein dipstick is an inappropriate test to exclude multiple myeloma due to its inability to detect light-chain immunoglobulins.

Interpretation of leukocyte esterase and nitrites on dipstick in females

Urine dipstick testing is not required to diagnose a UTI, but in practice it is often performed and the presence or absence of leukocyte esterase and nitrites can provide additional information.

Leukocyte esterase is an enzyme released by neutrophils and macrophages. A urine dipstick positive for this enzyme indicates pyuria (an increased number of leukocytes). Urinary tract infections including cystitis and urethritis are common causes of pyuria. Also consider sexually transmitted infections such as chlamydia. Pyuria is frequently associated with haematuria, as both are symptoms of inflammation.[39] The presence of leukocyte esterase on dipstick may also be due to non-infectious renal diseases such as glomerulonephritis. Contamination of samples by vaginal secretions may cause a false-positive result.

Nitrites are generally found in urine due to reduction of nitrates to nitrites by Gram-negative bacteria such as *E. coli*. The detection of bacteria in urine by nitrite positive dipstick is also dependent on nitrates from the patient's diet (vegetables) and sufficient bladder incubation time. Gram positive uropathogens such as *Staphylococcus saprophyticus* and Enterococcus do not produce nitrate reductase and therefore when infection is due to these bacteria, the dipstick will be negative for nitrite.

Management of UTIs is not discussed in this article. For further information see "Laboratory Investigation of UTI", bpac^{nz}, 2006.

How to collect and store urine samples

Clean-catch, midstream urine collection is the recommended method of collecting a sample for a urine dipstick test in both males and females. It generally results in an uncontaminated sample, and there is no evidence that prior cleansing of the external genitalia reduces contamination.[3] If it is necessary to collect urine from patients with an indwelling urinary catheter, a small quantity of initial urine should be drained and the collection drawn from the sampling port.[40]

If further (laboratory) analysis of the sample is required, it should be appropriately labelled, and stored in a fridge until collected. Analysis delays greater than two hours are reported to produce unreliable results.[31]

N.B. The nitrite dipstick reagent is sensitive to air exposure and containers of strips should be sealed whenever possible.[31]

Best Practice Tip: Do not store blood and urine samples in the same bag. Even small amounts of urine leakage can be drawn into the vacuum tube containing the blood specimen and contaminate it. Urine specimens should be placed in a "ziplock" biohazard bag that is in turn placed in another biohazard bag with any other samples from the patient. Printing separate forms for urine samples will encourage this practice.

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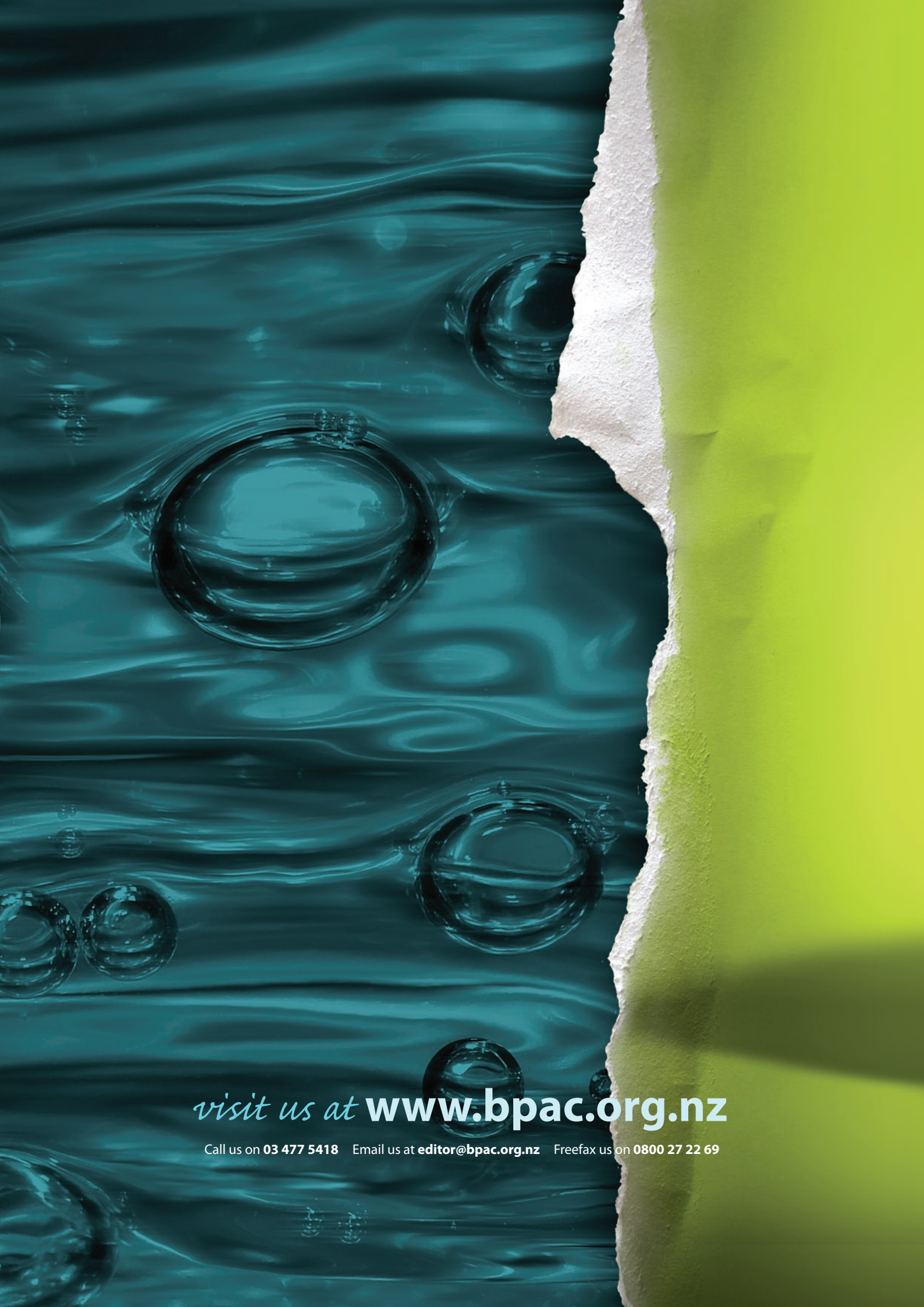

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