



The detection and investigation of pyuria

Each month we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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The detection of persistent significant pyuria in a fresh urine specimen is usually an indicator of inflammation or infection within the renal tract. In patients with urinary symptoms, the presence of pyuria is most commonly associated with a urinary infection. Pyuria is found in more than 96% of adult patients with urinary symptoms plus bacteriuria, i.e. a urinary tract infection (UTI).

In the general practice setting, pyuria is most commonly identified by urinary dipstick testing. However, pyuria is most accurately confirmed by urine microscopy, performed as part of a midstream urine (MSU) investigation (i.e. microscopy, culture and sensitivity), where it is defined as more than 8000 to 10,000 leucocytes per mL of urine or two to five leucocytes per high powered (40x) field in a centrifuged specimen.¹

Urinalysis

Urinary dipsticks are the most convenient way to initially screen for urinary abnormalities. They are quick to use and low in cost, and give results that are easy to interpret without specialised equipment, and are reasonably accurate.

Commercial dipsticks have a strip to show pyuria by detecting the presence of leucocyte esterase, an enzyme found in primary neutrophil granules. Another strip indicates bacteriuria by detecting nitrite, which is formed from urinary nitrate by the nitrate reductase found in enterobacteriaceae (Figure 1). Pyuria almost always accompanies clinically significant UTIs in adults. The urinary nitrite strip is capable of detecting most of the common organisms that cause UTI. False negative results, however, are not uncommon, and are due to a lack of urinary nitrate substrate or the presence of pathogenic organisms lacking nitrate reductase, such as *Staphylococcus*, *Enterococcus* and *Pseudomonas* species.²

Both reagent strips are used in screening for UTI, and ideally both strips are positive in true infection. However, in most symptomatic clinical settings, a positive result for either test is suggestive of UTI and indicates the need to send an MSU specimen for microscopy (Figures 2 and 3), culture and sensitivity testing before starting broad spectrum antibiotic therapy. By most reports these dipstick tests have only moderate sensitivity,

IN SUMMARY

- Urine dipstick testing is an important screening tool in general practice.
- Dipstick findings of urinary leucocytes or nitrite are suggestive of urinary tract infection (UTI).
- If pyuria on dipstick is persistent but UTI is not confirmed by repeated midstream urine culture, further investigation is warranted, including testing for proteinuria and haematuria, assessing renal function and performing a renal ultrasound.
- Persistent sterile pyuria also warrants further simple investigation.
- Patients require referral to a nephrologist if they have any significant, persistent abnormality such as proteinuria, haematuria, sterile pyuria or impaired renal function detected.

continued



Figure 1. A commonly available urinary multidipstick.

acceptable specificity and poor positive predictive value, but an acceptable negative predictive value – so that, if both strips are negative, UTI is unlikely.¹⁻³ Formal culture followed by antibiotics is indicated, however, in symptomatic patients with negative dipstick results who are in high risk subgroups. Such patients include women who are pregnant, at increased risk of complications or treatment failure, or have prolonged or recurrent signs or symptoms, and all men.²

In patients with supportive dipstick results, empirical antibiotics may be

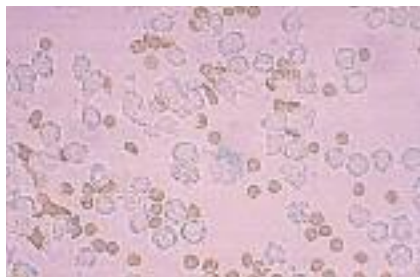


Figure 2. Urine microscopy of MSU from a patient with a urinary tract infection, showing white and red blood cells and clumps of bacteria.

appropriate in some uncomplicated clinical groups presenting with urinary symptoms, such as nonpregnant females. Formal MSU is still recommended though, because this provides the best definitive diagnosis of UTI and helps to guide treatment by providing the identities of the infecting organisms and their antibiotic sensitivities.

The investigation of urinary abnormalities is summarised in the flowchart on page 65.

Contamination of urine specimen

Contamination of the urine during specimen collection is generally not a significant problem in dipstick testing. For an MSU investigation however, a careful collection technique to avoid contamination is essential. Most collecting laboratories will provide clear patient directions to obtain a clean midstream sample. This is particularly important in female patients. Contamination of the urine specimen from the vulva or female genital tract can be avoided by simple measures. Menstruating women should insert a fresh tampon and wash the vulval area before collecting the specimen.

Causes of pyuria

A UTI is by far the most common cause of pyuria, but urinary white cells also occur in other common settings encountered in general practice. Leucocytes in the urine may originate from sites of

inflammation other than the urinary tract, particularly by contamination from the female genital tract, such as in vaginitis or sexually transmitted disease. If a sexually transmitted disease is suspected, the patient should be examined and a swab taken: rapid culture techniques are available for some types of infection, such as chlamydia.

Leucocytes may persist for a time in the urine after the UTI has cleared spontaneously or following treatment. Sterile pyuria (pyuria with negative bacterial growth on MSU) may indicate an insufficiently or only partially treated UTI, when antibiotics have suppressed but not totally eradicated the infecting bacteria. Hence, it is important to ascertain if there has been any recent use of antibiotics, which may indicate a partially treated infection. If this is the case, the antibiotic course should be completed and the MSU specimen recollected after an antibiotic-free period. A medication history may also be useful if there is a possibility of interstitial nephritis, but this is usually associated with changes in serum urea and creatinine and not only abnormal urinalysis.

Of special note, persistent sterile pyuria may be a sign of renal tuberculosis, which should be considered and excluded in migrant populations and other previously exposed or high risk populations. Thus racial origin and history of previous exposure to tuberculosis may be relevant. If tuberculosis is not thought of as one of the differential diagnoses, then it will be missed. A negative routine urine culture does not exclude tuberculosis because mycobacteria require specific culture conditions. If there is any suspicion of tuberculosis then three early morning urine specimens must be sent to the laboratory for specific mycobacterial culture.



Figure 3. Urine microscopy showing red blood cells.

Persistent pyuria

Patients with recurrent, persistently abnormal dipstick results who have a

Investigating pyuria

Patient presents with urinary signs or symptoms

Dipstick urinalysis shows pyuria and/or nitrites

- Confirm by urine microscopy and culture (MSU)
- Give empirical antibiotics in certain uncomplicated cases (see text)

Negative MSU culture

Positive MSU culture, confirming urinary tract infection

Normal result on repeat full urine dipstick testing

Abnormal result on repeat full urine dipstick testing, indicating persistent pyuria

Symptoms persist

Symptoms and urinary abnormalities subside

Negative repeat MSU culture, indicating sterile pyuria

Positive repeat MSU culture

Reinvestigate and refer to urologist if required

No further treatment

- Arrange:
- creatinine and calculated GFR
 - testing of three morning urine samples for mycobacteria
 - laboratory assessment of urinary protein and blood
 - formal microscopy for casts and crystals
 - renal ultrasound

Determine antibiotic sensitivities of bacteria

Treat as standard urinary tract infection

If results abnormal, refer to nephrologist

If results normal, repeat dipstick in 3 to 6 months

continued

Table 1. Some possible diagnoses underlying sterile pyuria

- Vaginitis, with contamination of urine sample with vaginal leucocytes
- Urethritis
- Prostatitis
- Recent urinary infection after antibiotic use
- Pregnancy
- Acute febrile episodes
- Atypical infections
 - chlamydia
 - ureaplasma urealyticum
 - tuberculosis
 - fungal infection
- Uroepithelial tumour
- Renal or perirenal abscess
- Genitourinary trauma
- Interstitial nephritis, acute or chronic
- Papillary necrosis
- Analgesic nephropathy
- Nephrolithiasis
- Nephrocalcinosis
- Polycystic kidney disease
- Vesicoureteric reflux
- Anatomical abnormalities
- Foreign bodies
- Renal transplant rejection
- Cyclophosphamide therapy

negative urine culture should be investigated further. Repeated full urine dipstick testing should be followed by repeated MSU (microscopy, culture and sensitivity) studies, with the addition of urinary tuberculosis culture in selected patients. Other important investigations are dipstick or laboratory urinary protein estimation (spot urinary protein or urine albumin: creatinine ratio), dipstick check for haematuria and serum creatinine and urea estimation, with calculation of the glomerular filtration rate (GFR) – expressed as creatinine clearance – by the Cockcroft–Gault formula (see the box on this page).

Renal ultrasound is an appropriate noninvasive investigation to detect

The Cockcroft–Gault formula

Glomerular filtration rate (GFR), expressed as creatinine clearance, is an accurate index of kidney function and can be calculated from the serum creatinine by use of the Cockcroft–Gault formula:

$$\frac{(140 - \text{age [in years]}) \times \text{weight [in kg]} \times 0.85 \text{ (if female)}}{814 \times \text{serum creatinine (mmol/L)}} = \text{Estimated creatinine clearance (GFR) [mL/min]}$$

The normal value for creatinine clearance is 80 to 100 mL/min

kidney stones, structural lesions, polycystic kidneys or kidney scarring, and does not expose the patient to x-rays. Intravenous pyelogram radiography is not recommended unless the patient has demonstrably normal kidney function on blood testing (creatinine, Cockcroft–Gault formula estimate of GFR) and is known to be not pregnant, diabetic or allergic to intravenous dye.

Patients with any significant abnormality of the above (e.g. dipstick urinalysis greater than or equal to ‘++ protein’; spot urinary albumin: creatinine ratio more than twice normal, or calculated GFR less than 60 mL/min) warrant referral to a nephrologist. These findings are likely to represent significant underlying renal disease with the potential to progress.

Sterile pyuria

Sterile pyuria is an uncommon diagnosis in general practice, and is a term usually reserved for patients where repeated urine examinations have shown ongoing pyuria but routine MSU cultures have not revealed concomitant urine infection. A diagnosis of ‘isolated sterile pyuria’ implies that proteinuria, haematuria, documented urine infection or elevation of serum creatinine (and consequential abnormal calculated GFR) does not accompany the pyuria.

Patients with repeated evidence of sterile pyuria, especially if associated with proteinuria, haematuria or casts, usually have inflammatory disease of the kidneys. The focus in such patients should be on diagnosing the nature of the underlying renal disease, although it

may be difficult to ascertain a definitive diagnosis.⁴ Table 1 lists some of these possible diagnoses. In isolated sterile pyuria, however, the causes are generally benign.

Conclusion

Examination of the urine provides some of the most important, and often only, early signs of ongoing renal injury. Abnormalities in the urine, such as protein, excessive white or red blood cells and nitrates, are important urinary abnormalities to detect, confirm and, where appropriate, further investigate. Sterile pyuria, found on repeated testing, may be an indication of underlying renal disease, and warrants referral to a nephrologist. MT

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Further reading

1. Australian Kidney Foundation and ANZSN. Early referral of patients with renal disease. In: *The CARI guidelines (Caring for Australians with Renal Impairment)*. Part 2. (www.cari.kidney.org.au).