ASSESSMENT OF STERILE PYURIA IN PRIMARY CARE

In this article the author looks at the condition sterile pyuria and considers what causes it, how it can be identified in primary care and who should be referred for specialist treatment

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Sterile pyuria can be broadly defined as the presence of leucocytes in the urine in the absence of demonstrable urinary tract infection. It is a relatively common problem, with a wide range of causes, encountered frequently in both primary and secondary care settings, although there is no data to suggest the estimated prevalence in either a community or hospital setting. Indeed, the medical literature, in all it's vastness, contains remarkably little research or guidance regarding this problem, leaving many primary care physicians in the dark as to how best to manage their patients. This results in inconsistent management, ranging from ignoring the finding completely to over-investigation and possibly unnecessary secondary care referral.

There are many overlaps between the finding of sterile pyuria and that of asymptomatic non-visible haematuria – both are fairly common incidental findings, both with relatively low risk of significant underlying pathology, but both with potential causes that we would not want to miss. The recommended management of non-visible haematuria in primary care is now well described,[1] but guidance on sterile pyuria is entirely absent. This article aims to provide a framework for assessing patients with sterile pyuria, but in the absence of a good evidence base must represent basic guidance only, with individualised management decisions required when faced with this problem in primary care.

BOX 1: CAUSES OF STERILE PYURIA[2]

Common	Uncommon	Rare
Urinary Tract Infection	Bladder Cancer*	Genito-Urinary Tuberculosis**
Sexually Transmitted Infection (especially chlamydia)	Interstitial Cystitis	Schistosomiasis**
Post-menopausal atrophic vaginitis / trigonitis	Renal disease	Sarcoidosis
Balanitis	Lupus	Kawasaki Disease
Prostatitis	Ketamine abuse*	Cyanotic congenital heart disease
Appendicitis or Diverticulitis		
Renal Calculi		
Non-Urological Infections e.g. Pneumonia		

*: usually but not exclusively also with non-visible or visible haematuria

**: rare causes in a UK population but common causes on a global perspective

How can we define sterile pyuria?

If we take a pragmatic approach, it is easiest to define sterile pyuria along similar lines to those recommended for non-visible haematuria. Thus, a suggested working definition for use in primary care is:

Urine dipstick positive for leucocytes in the absence of dipstick haematuria or nitrites, with subsequent MSU showing no bacterial growth

Again, to be consistent with non-visible haematuria guidelines,[1] it would appear sensible to consider a dipstick showing only a trace of leucocytes to be a negative result, which can be safely ignored, and to treat '+' or greater as a positive result. There is no prognostic difference between '+' or '+++' of red blood cells for patients with non-visible haematuria – it is not known whether the same applies in sterile pyuria, but it would seem to be a reasonable assumption. An MSU is sent to allow urine culture to detect the presence of organisms, and not to confirm the presence of leucocytes, which may degrade while in transit to the laboratory, thus creating a false negative result.

If pyuria is seen on microscopy in the absence of prior dipstick analysis, it is unclear on the exact threshold for clinical significance, although a value of >10 white blood cells per µL of urine may be sensible.

It is important to ensure that a urine specimen is taken clean catch and mid-stream to reduce the risk of contamination. Urine from catheters or urostomies will almost always contain white cells and cannot therefore be interpreted except in the context of symptoms, e.g. of suspected infection.

Causes of sterile pyuria (see Box 1)[2]

Infectious causes

The very name, sterile pyuria, is potentially misleading, as the commonest cause for the finding is undoubtedly

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infection of some sort. This may be a partially treated urinary tract infection (even one dose of antibiotic before urine collection), a recently treated UTI (pyuria often remains for one-two weeks after clearing infection), a UTI with fastidious or slow growing atypical organisms that fail to grow during standard laboratory culture, or a sexually transmitted infection, particularly chlamydia in the asymptomatic sexually active person. Patients with typical symptoms of a UTI and sterile pyuria should be treated empirically with antibiotics and urine retested after treatment to ensure resolution of the pyuria (i.e. treating for probable UTI with a fastidious organism).

Other, symptomatic infective causes are also possible – urethritis (due to chlamydia or gonorrhoea), prostatitis, balanitis and vulvo-vaginitis can cause pyuria, but symptoms should make these diagnoses apparent. Likewise, extrinsic irritation of the ureters or bladder by appendicitis or diverticulitis may cause pyuria.

On a global scale, infection with tuberculosis (TB) or schistosomiasis are common causes of pyuria, but clearly these conditions are rare in a UK population without other risk factors. Genito-urinary TB is often asymptomatic, but may present with urinary symptoms (especially frequency and urgency), loin pain (from upper tract obstruction), haematuria and non-specific symptoms such as fever, weight loss, night sweats and malaise. The diagnosis should be considered in patients with sterile pyuria who have previous contact with active TB, recent arrival from a high risk country, the immuno-compromised or health care workers in settings with high TB prevalence. Testing for TB should be reserved for those considered to be at risk, based on symptoms and these risk factors – urine should be cultured for acid and alcohol fast bacilli (AAFB) using three early morning urine specimens, and upper-tract imaging (e.g. ultrasound) should be performed.

Schistosomiasis haematobium infection (a tropical disease also known as Bilharzia) may cause sterile pyuria, as well as cystitis like symptoms or haematuria and a travel history should be taken for persistent unexplained pyuria. High risk areas are Africa (especially Lake Malawi) and the Mediterranean part of the Middle East, particularly in people who have been swimming in open water. Urinary symptoms may develop many years after the original infection. If schistosomiasis is considered a possibility, urine microscopy for ova plus sending blood for ELISA antigen testing is recommended, but it would be worth discussing with the local microbiology department prior to testing to ensure appropriate tests are performed.

Non-urological infections can also cause sterile pyuria.[5] A small study of 210 patients (adults and children) admitted to hospital with a variety of conditions including pneumonia, intra-abdominal infections and bacterial septicaemia, found pyuria in almost one-third of cases.

Non-infectious causes

Non-infectious pathology of the urinary tract may cause sterile pyuria – tumours of the kidney or bladder can be responsible, although the exact risk associated with isolated asymptomatic sterile pyuria, whilst not stated in the medical literature, is likely to be extremely low. Intersitial cystitis, or painful bladder syndrome, may also be a cause of sterile pyuria, but will present with the typical symptoms of this condition – suprapubic pain (especially with a full bladder), dysuria and urinary frequency. This condition should be suspected on clinical grounds and requires further urological investigation.

In older women, decreased oestrogenisation of the vulva, vagina and bladder can lead to a degree of inflammation, making sterile pyuria a relatively common finding. In this situation, treatment of women with symptomatic atrophic vaginitis with topical oestrogen therapy can lead to resolution of sterile pyuria. However, it is difficult to justify treatment in the absence of symptoms, purely to see clearance of white cells from the urine.

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Sterile pyuria is a common finding in pregnancy – usually due to contamination by physiological vaginal discharge. It is vital, however, to confidently exclude the possibility of urinary tract infection, as asymptomatic bacteriuria is such an important preventable cause of pre-term labour. If pyuria is found, it is worth repeating the urine specimen after cleaning the vulva and rigorously ensuring a true clean catch specimen. This

TABLE 1: RENAL CAUSES OF STERILE PYURIA:

Papillary necrosis (e.g. secondary to analgesic nephropathy, diabetic nephropathy, sickle cell disease nephropathy)
Tubulo-interstitial diseases (interstitial nephritis, lupus nephritis, sarcoidosis)
Structural causes (e.g. polycystic kidney disease)

requires the patient to part the labia with one hand, while holding the urine container with the other, and aiming the stream into the container. If pyuria persists despite this method, it is worth informing the midwife or obstetrician responsible.

Sterile pyuria can be a presentation of asymptomatic renal disease (see Table 1) and this should be considered for all patients. Referral to a nephrologist should be considered in patients with sterile pyuria associated with: significant proteinuria (ACR>30mg/mmol) or deteriorating renal function. To exclude renal causes, all patients with unexplained sterile pyuria should have an assessment of estimated glomerular filtration rate (eGFR), urinary albumin: creatinine ratio and blood pressure. In the past, urine microscopy for the presence of casts (precipitant of protein, formed in the renal tubules and excreted in the urine) was recommended, but most laboratories perform this rarely and false negatives are highly likely, and this test should not be requested from primary care.

Ketamine, a dissociative anaesthetic, has been increasingly prevalent in the UK as a recreational drug.[3] It is associated with urinary symptoms including severe pain, frequency, haematuria and dysuria. It can occasionally present with sterile pyuria4 and should therefore be considered as a possible cause, especially in young people (peak age of ketamine use is 16-34 years). Patients with urinary symptoms with sterile pyuria and / or haematuria should be strongly encouraged to discontinue ketamine use.

BOX 2: INVESTIGATION OF STERILE PYURIA IN PRIMARY CARE

Investigation	Core	Optional
MSU for microscopy and culture	x	
Urine test for chlamydia and gonorrhoea (e.g. NAAT test)	x*	
eGFR / albumin : creatinine ratio / blood pressure	x	
Upper tract ultrasound	x	
Urine culture for AAFB		x
Urine microscpy for schistosomiasis ova		x

*: in patients who are sexually active

Investigating sterile pyuria

Again it seems reasonable to mirror the guidance from the British Association of Urological Surgeons and the Renal Association (www.renal.org) on the assessment of non-visible haematuria – namely, that symptomatic patients with sterile pyuria warrant investigation. However, asymptomatic patients found to have sterile pyuria should have urine retested after a short interval (ensuring an appropriate clean catch, mid-stream specimen is obtained) such as two-four weeks. If this is again positive, further basic investigations are warranted, but if a third negative specimen is obtained after another interval, then two out of three positive results would warrant further investigation.

All symptomatic patients with unexplained sterile pyuria should be referred to secondary care (typically Urology, Gynaecology or Nephrology) for assessment

Basic primary care investigations are detailed in Box 2. There are a limited number of simple tests that should be considered for all patients, with testing for TB and schistosomiasis reserved for patients considered to be at risk. Imaging of the upper tracts, using ultrasound, is useful to exclude pathology such as a renal tumour, hydronephrosis, renal calculi, or signs of previous infection such as pyelonephritis or TB. If ultrasound is normal, there is no need to proceed to more detailed imaging (e.g. CT Urogram) unless there are other features such as loin pain, haematuria or reduced eGFR (especially where renal papillary necrosis is a possibility. This condition, where the tips of the renal medulla undergo ischaemic necrosis occurs most commonly as part of diabetic nephropathy, in sickle cell disease or in patients with analgesic nephropathy, due to long term use of analgesics such as co-codamol.

Specialist referral

All symptomatic patients with unexplained sterile pyuria should be referred to secondary care (typically Urology, Gynaecology or Nephrology) for assessment

TABLE 2: CORE ASSESSMENT PRIOR TO UROLOGICAL (OR GYNAECOLOGICAL) REFERRAL

Urinalysis and laboratory analysis of a formal clean catch mid stream specimen of urine
A full history of urological (and gynaecological) symptoms
Basic examination – urological/ gynaecological
Appropriate investigation for a sexually transmitted disease, particularly chlamydia
Upper tract imaging with renal ultrasound

– Table 2 details the core elements of primary care assessment prior to this referral. Sterile pyuria in association with visible haematuria, or with persistent new onset storage symptoms (urgency / frequency / nocturia), or with bladder pain, should be considered red flags and prompt urgent or twoweek wait referral, particularly for the exclusion of underlying bladder cancer.

The question of whether to refer all patients with persistent unexplained asymptomatic sterile pyuria is more difficult to answer categorically. Many urologists will feel that all of these patients should be investigated, while many primary care physicians, often more comfortable with 'dealing with uncertainty' will take a more pragmatic approach if basic investigations are reassuring. There is no evidence to tell us which of these is the correct approach, and thus referral cannot be considered mandatory. However, if in doubt, it is not unreasonable to refer patients for a urological opinion, if only for reassurance of both patient and doctor.

Caption

References:

1. Kelly JD, Fawcett DP, Goldberg LC. *BMJ* 2009; 338: a3021.
2. Dieter RS. *Comp Ther* 2000; 26 (3): 150-152.
3. Winstock AR, Mitcheson L, Gillatt D, Cottrell AM. *BJU Int* 2012; 110: 1762-1766.
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5. Hooker JB, Mold JW, Kumar S. *J Am Bd Fam Med* 2014; 27: 97-103.

SUMMARY OF KEY POINTS

1. Despite the name, sterile pyuria still, in many cases, is caused by an infection of some sort
2. In older women, decreased oestrogenisation of the vulva, vagina and bladder can lead to a degree of inflammation, making sterile pyuria a relatively common finding
3. Sterile pyuria is also a common finding in pregnancy due to contamination by vaginal discharge – it is vital to exclude undiagnosed urinary tract infection
4. All symptomatic patients with unexplained sterile pyuria should be referred to secondary care for assessment
5. Sterile pyuria in association with visible haematuria, or with persistent new onset storage symptoms, or with bladder pain, should be considered red flags and prompt urgent or 2 week wait referral.
6. Public health messages to encourage reporting of significant symptoms, tools to assist assessment of the risk of cancer, urgent referral pathways, referral guidelines and GP access to relevant investigations are the key levers to assist the UK to improve outcomes