REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Sterile Pyuria

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Pyuria is defined as the presence of 10 or more white cells per cubic millimeter in a urine specimen, 3 or more white cells per high-power field of unspun urine, a positive result on Gram's staining of an unspun urine specimen, or a urinary dipstick test that is positive for leukocyte esterase.[1] Sterile pyuria is the persistent finding of white cells in the urine in the absence of bacteria, as determined by means of aerobic laboratory techniques (on a 5% sheep-blood agar plate and MacConkey agar plate).

Sterile pyuria is a highly prevalent condition, and population-based studies show that 13.9% of women and 2.6% of men are affected.[2] Specific populations have a higher risk of this condition; for example, the frequency of detection of sterile pyuria was 23% among inpatients in one study (excluding those with urinary tract infection), and sterile pyuria is more common among women than among men because of pelvic infection.[3] Subsequent to initial detection, the costs of laboratory, radiographic, and invasive evaluation in such large populations can have a considerable effect on health care expenditures.[4]

Although colony counts greater than 100,000 colony-forming units (CFU) per milliliter in voided urine have historically been used to distinguish bacterial urinary tract infection from colonization,[5] many U.S. laboratories currently report bacterial colony counts of more than 1000 CFU per milliliter in urine as being diagnostic of bacteriuria.[6] It is important to consider that lower bacterial counts can be associated with urinary tract infection. Contemporary studies indicate that a colony count of 100,000 CFU per milliliter would differentiate clinically significant from clinically nonsignificant infections and thus reduce the number of positive cultures by 38% relative to the number of cultures that would be considered positive with the 1000 CFU per milliliter cutoff point. Use of the higher cutoff point as the "level to treat" could also decrease the use of antibiotics.[6]

In this article, we review causes of sterile pyuria and describe a clinical approach to its evaluation.

CAUSES OF STERILE PYURIA

SEXUALLY TRANSMITTED INFECTIONS

In 2008, it was estimated that 500 million people worldwide were infected with sexually transmitted viruses such as herpes simplex virus type 2 (HSV-2) and human papillomavirus (HPV) or had sexually transmitted infections such as gonorrhea, chlamydia, syphilis, mycoplasma, and trichomoniasis.[7] More than 300,000 U.S. cases of infection with *Neisseria gonorrhoeae* are reported to the Centers for Disease Control and Prevention each year.

In men, the majority of sexually transmitted infections cause symptomatic urethritis and, less commonly, epididymitis or disseminated gonococcal infection.

Many women may be asymptomatic initially, and pelvic inflammatory disease may develop without symptoms.[8]

Gonorrhea and Chlamydia

Historical and current studies indicate that gonorrhea is a cause of sterile pyuria.[9,10] In asymptomatic men, urine tests to detect leukocyte esterase have a sensitivity of 66.7% for the diagnosis of gonorrhea and 60.0% for the diagnosis of chlamydia. Commercially available nucleic acid hybridization tests provide rapid detection of *N. gonorrhoeae* and *Chlamydia trachomatis*.[11]

In an Australian study, 1295 symptomatic men with nongonococcal urethritis and pyuria were evaluated for sexually transmitted diseases. *C. trachomatis* was detected in 401 men (31%), and *Mycoplasma genitalium* was diagnosed in 134 men (10%).[12] A Japanese study involving 51 men showed that the 16S ribosomal RNA gene of *Ureaplasma urealyticum* (quantified by means of a real-time polymerase-chain-reaction [PCR] assay) was associated with the presence of symptoms of urethritis and higher leukocyte counts in first voided urine.[13]

Genital Herpes and Herpes Zoster

Genital vesicular eruption, which is characteristic of HSV-2 infection, extrudes white cells into urine. Pyuria may be associated with HSV-2–associated urethritis and cervicitis.[14] The diagnosis of genital herpes is determined by means of HSV PCR, an antigen-detection immunofluorescence test, or an enzyme immunoassay.[15]

In a 12-year study involving 423 patients with herpes zoster, 17 patients (4%) manifested changes in lumbosacral dermatomes and voiding dysfunction. Twelve patients with cystitis-associated symptoms (3% of all the patients with herpes zoster) had pyuria.[16]

HPV and Human Immunodeficiency Virus Infections

In one study, among 114 patients with biopsy-proven HPV infection, 14 patients (12.3%) had an intraurethral lesion.[17] A British survey tested 3123 urine samples obtained from male and female respondents who were 18 to 44 years of age. HPV DNA was detected in 29.0% of samples obtained from women and in 17.4% of samples obtained from men.[18] The respondents were not screened by means of measurement of leukocytes.

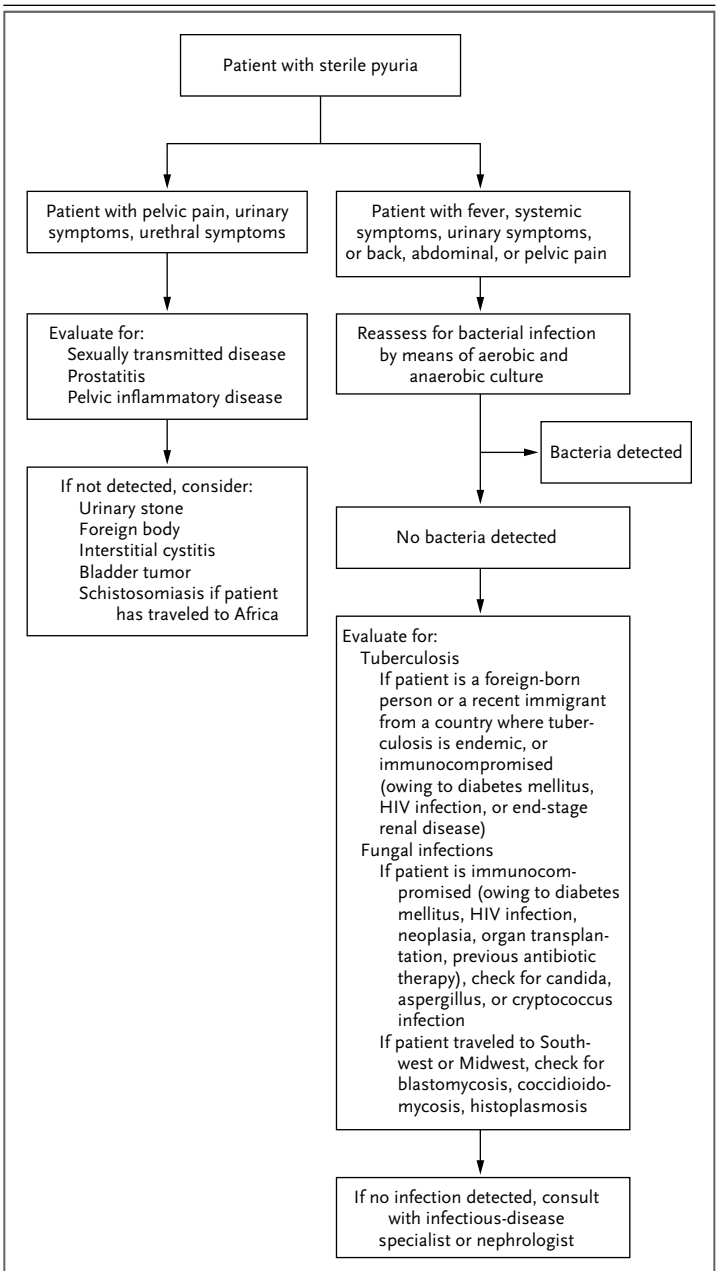

Figure 1. Clinical, Epidemiologic, and Laboratory Assessment of a Patient with Sterile Pyuria.

However, one study showed that male patients with HPV infection can have urethral discharge containing inflammatory cells.[19]

Pyuria is associated with advanced human immunodeficiency virus (HIV) infection. In one study, among 104 patients with untreated HIV infection, 13% had pyuria.[20]

Table 1. Causes of Sterile Pyuria.*

Causes related to infection
Current use of antibiotics
Recently treated urinary tract infection (within past 2 wk)
Gynecologic infection
Urethritis due to chlamydia, *Neisseria gonorrhoeae*, mycoplasma, or ureaplasma
Prostatitis
Balanitis
Appendicitis (if the appendix lies close to a ureter or the bladder)
Viral infection of the lower genitourinary tract
Genitourinary tuberculosis
Fungal infection
Parasitic disease such as trichomoniasis or schistosomiasis
Causes not related to infection
Presence or recent use of a urinary catheter
Recent cystoscopy or urologic endoscopy
Urinary tract stones
Foreign body such as surgical mesh in the urethra or a retained stent
Urinary tract neoplasm
Pelvic irradiation
Urinary fistula
Polycystic kidney
Rejection of a renal transplant
Renal-vein thrombosis
Interstitial nephritis or analgesic nephropathy
Papillary necrosis
Interstitial cystitis
Inflammatory disease such as systemic lupus erythematosus or Kawasaki's disease

* The information is adapted from Dieter.[41]

OTHER VIRAL INFECTIONS

Viral infections such as adenovirus,[21] BK polyomavirus,[22] and cytomegalovirus[23] may cause hemorrhagic cystitis in immunocompromised children. However, these infections are typically not associated with pyuria.

GENITOURINARY TUBERCULOSIS

Nearly 10,000 tuberculosis infections are reported in the United States each year.[24] Genitourinary tuberculosis, the most common form of nonpulmonary tuberculosis after lymphadenopathy, accounts for 27% of cases (range, 14 to 41). Hematuria and pyuria are typical findings in genitourinary tuberculosis. This condition can infect the kidneys, ureters, bladder, prostate, and genitalia.[25] Genitourinary tuberculosis can cause renal calyceal destruction, calyceal obstruction, or hydronephrosis, or all of these conditions.

Since the incidence of tubercular infection is 13 to 26 times as high among foreign-born persons and recent immigrantsas among non-Hispanic whites, clinical suspicion of tuberculosis infection should be higher in these patients when they present with sterile pyuria. In the United States, the incidence of tubercular infection is also higher among Asians, Hispanics, and blacks than among whites.[24] In addition, nonpulmonary tuberculosis is more common in ethnic minority groups.[24,26]

The tuberculin skin test is helpful in determining whether a person has been exposed to tuberculosis, but false positive results often occur in patients who have received the *Mycobacterium bovis bacilli* Calmette–Guérin (BCG) vaccine, and a false negative skin test may occur in patients with impaired T-cell function. Interferon-γ–release assays are whole-blood tests that are not affected by BCG immunization.[27]

M. tuberculosis may also be identified on urine culture. However, in a study involving 42 patients in whom there was suspicion of genitourinary tuberculosis on the basis of radiologic abnormalities, mycobacteria were isolated in the urine acid-fast bacilli culture in only 13 of 35 patients (37%) and bladder biopsy was positive in 11 of 24 patients (46%), whereas urinary PCR for *M. tuberculosis* was positive in 33 of 35 patients (94%).[28]

FUNGAL INFECTIONS

Candida infections are a common source of urosepsis in hospitalized patients, especially those who are immunocompromised.[29,30] *Candida albicans* is the most prevalent species; however, *C. glabrata*, *C. tropicalis*, *C. krusei*, and other candida species can also cause infection.

Speciation is important because of differences in antifungal susceptibility.[30] Notably, patients with diabetes are prone to candida infections, patients who have received transplants are vulnerable to aspergillosis, and patients with HIV infection may be susceptible to cryptococcuria. Blastomycosis, coccidioidomycosis, and histoplasmosis are associated with intense environmental exposures (e.g., disruption of the environment by construction, sandstorms, or tornadoes

Table 2. Diagnosis and Management of Causes of Sterile Pyuria.*

Condition	Recommendation
Tuberculosis	
Diagnosis	Increased risk among persons with exposure to tuberculosis in the family or environmental exposure, among immigrants and members of minority ethnic groups, and among persons who are immunocompromised because of diabetes or HIV infection. Diagnostic tests include the tuberculin skin test, interferon-γ–release assay, or both; urine cultures for tuberculosis; PCR assay; and computed tomographic urography or intravenous pyelography.
Treatment	First-line drug therapy for 3–6 mo with a combination and various dose schedules of isoniazid, rifampin, ethambutol, and pyrazinamide. Modification of treatment in patients with HIV infection (consult with an infectious-disease specialist regarding patients with allergy to medication, drug resistance, or complex disease).
Gonorrhea and chlamydia	
Diagnosis	Nucleic acid amplification test with a first-catch urine sample (equivalent to a urethral swab in detecting infection).
Treatment	In patients with gonorrhea: ceftriaxone (250 mg intramuscularly) and either azithromycin (1 g orally in a single dose) or doxycycline (100 mg orally twice a day for 7 days). Increase dose in patients with antibiotic-resistant strains. In patients with chlamydia: azithromycin (1 g orally in single dose) or doxycycline (100 mg orally twice a day for 7 days). An alternative regimen is erythromycin base (500 mg orally four times a day for 7 days).
Mycoplasma and ureaplasma	
Diagnosis	Culture is difficult because of growth requirements of the organism. No internationally validated and approved nucleic acid amplification test to detect *M. genitalium* is currently available.
Treatment	Azithromycin, levofloxacin, or moxifloxacin. Duration of treatment not defined.
Genital herpes	
Diagnosis	Identification of vesicular lesions, cell culture, and PCR assay.
Treatment	Acyclovir (400 mg orally three times a day for 7–10 days) or acyclovir (200 mg orally five times a day for 7–10 days) or famciclovir (250 mg orally three times a day for 7–10 days) or valacyclovir (1 g orally twice a day for 7 days).
Trichomoniasis	
Diagnosis	Evaluate patient for HIV infection and other sexually transmitted diseases; examine the patient's sex partner. Use wet-mount slide for microscopic visualization of motile *Trichomonas vaginalis* parasites. Culture on InPouch TV (BioMed Diagnostics). Nucleic acid amplification test.
Treatment	Metronidazole (2 g orally in a single dose) or tinidazole (2 g orally in a single dose). Treat patient's sex partner if trichomoniasis is diagnosed in patient.
Fungal infections	
Diagnosis	Candida, aspergillus, and cryptococcus infections are seen in patients with coexisting conditions such as diabetes, immunosuppression, and organ and bone marrow transplantation, as well as in patients who are receiving multiple antibiotics, glucocorticoids, or both over long periods of time. The risk of blastomycosis, coccidioidomycosis, and histoplasmosis is increased among persons in regions where these infections are endemic, particularly in the Midwest and Southwest. Perform microscopic examination of urine to detect fungal elements, budding yeast, and hyphae. Perform fungal cultures of urine and obtain biopsy of the bladder and prostate. Evaluate for filling defects (fungal balls in renal collecting system and bladder) and the presence of a renal mass.
Treatment	Antifungal drugs include fluconazole, posaconazole, echinocandins, and amphotericin B. Use and dosage are dependent on fungal species and drug sensitivity. If the patient has coexisting conditions such as diabetes mellitus or immunosuppression, or if the patient has undergone organ or bone marrow transplantation, he or she may require more than one antifungal drug as well as antibiotic treatment.
Schistosomiasis	
Diagnosis	Increased risk among persons who have lived in or visited Africa because of possible infection from freshwater in southern and sub-Saharan Africa. Microscopic examination of urine for *Schistosoma haematobium* eggs, bladder biopsy, and serologic testing for antischistosomal antibody. Use of PCR is investigational.
Treatment	Praziquantel (40 mg per kilogram of body weight per day orally in 2 divided doses each day over 1 or 2 days).
Pyuria in absence of defined infection	Consultations with internist, nephrologist, infectious-disease specialist, or urologist, or all of these specialists. Abdominal, renal, pelvic, and bladder imaging and renal biopsy.

* The information is based on Wise,[31] Vinkeles Melchers et al.,[34] guidelines from the Centers for Disease Control and Prevention,[42,43] and Shipitsyna et al.[44] HIV denotes human immunodeficiency virus, and PCR polymerase chain reaction.

or exposure to a high concentration of bird excrement). All these fungal infections may cause genitourinary infection with associated pyuria.[31]

Urine microscopy may show budding yeast forms or hyphae, but identification of fungus requires special culture medium and from 3 days to 3 weeks for speciation.[32] In patients with candida or aspergillus infections, imaging studies may reveal filling defects in the collecting system or bladder caused by fungal materials that are referred to as "fungal balls."

PARASITIC INFECTIONS

Trichomonas vaginalis is one of the most common human parasitic infections in the United States and the most prevalent nonviral sexually transmitted infection. Infection can be diagnosed by identification of the motile parasite during microscopic examination of a wet-mount preparation of cervicovaginal secretions in women and urethral discharge in men, but PCR is more sensitive. In one study, 46 of 205 male partners of women with confirmed trichomonas infection (22%) had culture-detected infection, whereas 201 of 205 male partners (98%) had infection detected by means of PCR.[33]

An estimated 119 million people in the world are infected with *Schistosoma haematobium*.[34] Transmission requires the contamination of water by egg-containing feces or urine, a specific freshwater snail as intermediate host, and human contact with water inhabited by the intermediate host snails.[35] The urogenital system is affected in 75% of infected persons. Radiographic studies may show calcification of the bladder wall or ureter. Diagnosis has been based on microscopic examination of urine, but this method is dependent on the skill of the observer and is known for low sensitivity. A recent study showed that real-time PCR has 100% sensitivity as an indicator of infection intensity.[34]

In a 10-year study involving more than 25,000 ill travelers from endemic areas, 410 cases of schistosomiasis were identified; 83% of the infections were acquired in Africa. A total of 63% of the patients with schistosomiasis presented within 6 months after travel.[36]

INFLAMMATORY AND AUTOIMMUNE CONDITIONS

The cause of the combination of interstitial cystitis and the painful bladder syndrome, which occurs primarily in women, is unclear. In an evaluation of 122 patients in whom this condition was suspected, 22 (18%) had detectable leukocyte esterase with a negative nitrite indicative of sterile pyuria and prodromal inflammatory changes in the bladder.[37]

Kawasaki's disease often manifests with sterile pyuria, microscopic hematuria, and proteinuria associated with renal involvement. In one study, sterile pyuria, which is typically associated with more severe systemic inflammation, was identified in 40 of 133 patients (30%).[38] In another study, sterile pyuria was identified in 215 of 946 patients with systemic lupus erythematosus (23%).[39] In addition, analgesic nephropathy can cause sterile pyuria in association with chronic interstitial nephritis and renal papillary necrosis.[40]

INFLAMMATION OUTSIDE THE URINARY TRACT AND OTHER UROLOGIC CONDITIONS

One study involving 210 patients who were hospitalized for infections outside the urinary tract (e.g., pneumonia, bacterial septicemia, intraabdominal infection, enteritis, and female genital tract infections) identified 31 patients (15%) with sterile pyuria.[3] In addition, pyuria may be associated with radiation cystitis, urinary stones, foreign bodies, stents, transvaginal mesh, urinary fistulae, polycystic kidney disease, renal-transplant rejection, and intrinsic renal disease.[41]

EVALUATION OF PATIENTS WITH STERILE PYURIA

As noted above, the differential diagnosis of sterile pyuria is broad (Fig. 1). A complete history and physical examination with consideration of the factors listed in Table 1 are required to identify the potential causes of genitourinary inflammation. Specific evaluation for sexually transmitted infections is warranted. Evaluation to detect bacterial, fungal, and parasitic infections is indicated in patients with a clinical history that suggests specific infections.

Abdominal, renal, and bladder imaging should be considered for evaluation of febrile or otherwise symptomatic patients. Inflammatory conditions near the urinary tract as well as systemic diseases should be included in the differential diagnosis (Table 2). Sterile pyuria has his-

torically been considered to be suggestive of genitourinary tuberculosis, but a wide variety of other causes must be considered.

Criteria for successful treatment of conditions that cause sterile pyuria include curtailment or resolution of symptoms, a negative culture, or a negative PCR assay. Pyuria may persist because of underlying inflammatory changes.

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Disclosure forms provided by the authors are available with the full text of the article at NEJM.org.

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