



Understanding the causes of pyuria for better therapy

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ABSTRACT

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

CAUSES OF STERILE PYURIA

Sexually Transmitted Infections

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, 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. 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].

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. [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 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.

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%).

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]

CONCLUSION

A complete history and physical examination with consideration of the factors listed are required to identify the potential causes of genitourinary inflammation putting in view of the Sterile Pyuria. 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 and management of Causes of Sterile Pyuria. Sterile pyuria has historically 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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