

Improved Classification of Urinary Tract Infection: Future Considerations

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Article info

Keywords:

Antibacterial treatment of urinary tract infections
Antibiotic resistance
Classification of urinary tract infections
European Section of Infection in Urology
Metagenomic sequencing
Microbiome
Microbiota
Urinary tract infections

Abstract

The current European Association of Urology and European Section of Infection in Urology classification of urinary tract infections (UTIs) is a working instrument useful for daily patient assessment and clinical research. This new classification of UTI is based on clinical presentation, risk factors, and severity scale. Symptomatic UTIs are classified as cystitis, pyelonephritis, and urosepsis, considering that the urosepsis syndrome is the most severe form and that pyelonephritis is more severe than cystitis. The risk factors are phenotyped according to the ORENUC system: O indicates no known risk factors; R, risk of recurrent UTIs but without risk of a more severe outcome; E, extraurogenital risk factors; N, relevant nephropathic diseases; U, urologic resolvable (transient) risk factors; C, permanent external urinary catheter and unresolved urologic risk factors. Although clinical findings, culture tests, and microscopy remain the standard methods for diagnosing UTIs, improved detection of bacteria by novel diagnostic technologies, such as metagenomic sequencing (MGS), might change this paradigm in the future. Applying a culture-independent MGS technology allows detection of rich bacterial communities in urologic patients with “sterile” urine. However, the clinical relevance of detecting difficult-to-culture bacteria needs to be established by well-designed clinical studies.

Patient summary: The current European Association of Urology Section of Infection in Urology classification of urinary tract infections (UTIs) is useful for patient assessment. Symptomatology and urine culture remain the standards for diagnosing UTIs. Novel technologies will further explore the interactions between the host and microorganisms in the urogenital tract.

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1. Introduction

Urinary tract infections (UTIs) are among the most frequent bacterial infectious diseases imposing a substantial financial burden on the society [1]. UTIs account for nearly 7 million office visits and 1 million emergency department

visits, resulting in 100 000 hospitalizations in the United States each year [2]. It is the 15th most common condition seen by family physicians and is the diagnosis code for 2% of family medicine visits [3].

UTIs are more common in women than in men. In the United States, nearly one in three women will have had at

least one episode of UTI by age 24 yr [2]. In the United Kingdom, it is estimated that half of all women will have a UTI episode at least once in their lifetime, whereas only 1 in 2000 healthy men will develop a UTI episode each year [4]. In Sweden, about half of all women have at least one episode of acute cystitis during their lives, although the true incidence is most likely higher [5]. According to surveys of antimicrobial use for health care–associated infections (HAIs) in European long-term care facilities, symptomatic UTIs were the main types of infection, accounting for 31.2% of all HAIs in 2010 and 22.3% in 2013 [6]. The Global Prevalence Infection in Urology (GPIU) studies have shown that 10–12% of patients hospitalized in urologic wards suffer from HAIs [7].

The main objectives of disease classification are (1) to organize current knowledge, (2) to provide a basis for guidelines on diagnosis and treatment, (3) to provide a framework for design of research projects, and (4) to provide a framework for registration of clinical activity [8].

2. Classification of urinary tract infection

2.1. The concept of significant bacteriuria

Many microorganisms are continuously threatening to infect the urinary tract, but their virulence is balanced by host-protective mechanisms. Microbiological culture and microscopy are considered the gold standards for evaluating urologic disorders caused by infections, with an additional amplification system being used when sexually transmitted pathogens are suspected [1,9].

The term *significant bacteriuria* was introduced by Kass in 1960 on the assumption that bacteria tend to multiply to very large numbers in the urine, usually exceeding 10^5 colony-forming units (CFU) per milliliter [10]. This provided the means for differentiating between contamination of the voided specimen and true UTI. This concept was generally accepted. Recommendations for antibacterial therapy were based on the culture test results [1], thus, the distinction between significant bacteriuria and contamination was based on “the distribution of bacterial counts in non-bacteriuric and bacteriuric populations” [10]. In 1982, however, Stamm et al demonstrated that 10^2 CFU/ml of a known uropathogen in the midstream sample of urine (MSU) of women was already indicative of lower UTI [11]. In fact, no fixed bacterial count can be considered conclusive for significant bacteriuria in all kinds of UTI and under all circumstances [12]. According to European Association of Urology (EAU) guidelines, the critical number of uropathogens in MSU should exceed 10^4 CFU/ml in men and vary in women from $\geq 10^3$ CFU/ml in acute uncomplicated cystitis to $\geq 10^5$ CFU/ml in complicated UTIs [1]. The lower the CFUs in MSU, the higher the likelihood of contamination. In a suprapubic bladder puncture specimen, any count of bacteria is considered diagnostic [1]. The underlying idea has always been that urine from healthy persons is sterile, and a negative urine culture has usually excluded an infection.

2.2. Pathogenesis of urinary tract infections

Most UTIs are caused by the ascent of microorganisms through the urethra, although some microorganisms can reach the urinary tract by hematogenous or lymphatic spread [1].

Based on classical diagnostic methods, most UTIs are considered monomicrobial. The microbial spectrum is similar in uncomplicated upper and lower community-acquired UTIs, with *Escherichia coli* as causative pathogen in 70–95% of cases and *Staphylococcus saprophyticus* in 5–10% [13,14]. Occasionally, other Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella* sp, are isolated [15]. The microbial spectrum of complicated UTIs is broader and includes species of *Pseudomonas*, *Enterococcus*, *Staphylococcus*, *Serratia*, and *Providencia* and fungi [16]. It can also vary depending on geographical region, time period, and medical specialties in health institutions. However, *E coli* is the most common health care–associated uropathogen in hospital departments across the United States [17], Latin America [17], and Europe [17,18] and, in a European multicenter 1-d prevalence study, across a variety of urologic departments throughout Europe [19,20]. In addition, *Candida albicans* may cause ascending infections if an indwelling catheter is present or following extensive antibiotic therapy [1,21,22].

Hematogenous infection of the urinary tract is restricted to a few relatively uncommon microorganisms in urine, such as *S aureus*, *Candida* sp, *Salmonella* sp, and *Mycobacterium tuberculosis*, all of which tend to cause primary infections elsewhere in the body [1].

The bacterial etiology of UTI differs markedly between uncomplicated and complicated UTIs [23]. This is mainly due to the fact that bacteria causing uncomplicated UTIs are highly selected clones with an array of virulence factors [24].

2.3. Classifications of urinary tract infection

Classification of UTI is important for clinical decisions, research, quality measurement, and teaching. Traditionally, UTIs are classified based on clinical symptoms, laboratory data, and microbiological findings and usually have been divided into uncomplicated and complicated UTIs, and urosepsis [1]; however, most UTIs are uncomplicated.

The most widely used current classifications of UTI are those developed by the US Centers for Disease Control and Prevention in 1988 and updated in 2008, the Infectious Diseases Society of America (IDSA) and the US Food and Drug Administration in 1992, and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in 1993. The limitations of these classifications have been critically reviewed elsewhere [8]. In short, although the purpose of the CDC classification was to define and report health care–associated (nosocomial) UTI including symptomatic UTI, asymptomatic bacteriuria, and other infections of the urinary tract, both the IDSA and ESCMID classifications were mainly developed for the evaluation of new anti-infective drugs in clinical studies using the concept of uncomplicated and complicated UTI. In the CDC classification, the diagnosis of symptomatic UTI is based on clinical

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