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Criteria for the Diagnosis of Urinary Tract Infection and for the Assessment of Therapeutic Effectiveness*

Summary: Three parameters – urinary symptoms, pyuria, and bacteriuria – can be used independently or in combination to define the presence of urinary tract infection. Using these parameters, several approaches to defining urinary infection in various clinical contexts are discussed. Similarly, approaches to the definition and classification of therapeutic outcomes after antimicrobial treatment are explored. Further research is needed to more precisely evaluate the effectiveness of various criteria for diagnosis and cure of urinary infection.

Zusammenfassung: *Kriterien zur Diagnose einer Harnwegsinfektion und zur Beurteilung des Therapieerfolges.* Die drei Parameter, Symptome, Pyurie und Bakteriurie, können unabhängig voneinander oder in Kombination zur Definition einer Harnwegsinfektion verwendet werden. In der Arbeit werden mehrere Möglichkeiten diskutiert, wie mit diesen Parametern in verschiedenen klinischen Situationen eine Harnwegsinfektion definiert werden kann. Ähnliches gilt für die Definition und Einteilung der Therapieergebnisse nach der Antibiotikatherapie. Weitere Untersuchungen sind erforderlich, um die Effektivität der verschiedenen Diagnose- und Therapieerfolgskriterien besser beurteilen zu können.

Introduction

Although a variety of microorganisms, including viruses, ureaplasmas, *Chlamydia* and parasites may infect the urinary tract, the overwhelming majority of urinary tract infections (UTIs) are caused by bacteria. In fact, more than 95% of these infections result from either a member of the *Enterobacteriaceae*, *Pseudomonas aeruginosa*, Enterococci or *Staphylococcus saprophyticus* species. This review will focus upon defining the presence of bacterial urinary tract infections caused by these species, as well as defining their eradication after antimicrobial therapy. The consensus definitions presented here were the result of the deliberations of an expert committee convened by the Infectious Disease Society of America and Food and Drug Administration.

Hypothetical States of Urinary Tract Colonization and Infection

In considering how one might define the presence of bacterial urinary tract infections, three parameters have been most frequently utilized: 1) the presence of urinary symptoms suggesting infection; 2) the presence of indicators of urinary tract invasion by microorganisms (pyuria, haematuria, or an immune response); and 3) the presence of bacteriuria on urine cultures. As summarized in Table 1, one or more of these factors may be present in various circumstances [1]. Bacteriuria, for example, may be present without evidence of urinary symptoms or urinary tract invasion as measured either by pyuria or an immune response. This condition could result from contamination of a specimen or, if real, might be considered colonization of the urinary tract and in most instances would not warrant antimicrobial therapy. Bacteriuria, however, may be accompanied by evidence of tissue invasion (pyuria or an immune response) without evidence of clinical symptomatology. This condition could be considered true asymptomatic infection of the urinary tract, a condition which may warrant therapy in selected circumstances. Most commonly, bacteriuria, evidence of urinary inflammation (pyuria) and urinary symptoms present concurrently, a circumstance usually indicative of a symptomatic urinary tract infection. In some patients, evidence of urinary tract invasion or inflammation, i.e. pyuria, may be unaccompanied by bacteriuria. Pyuria in such patients may be caused by chlamydial or mycoplasmal infections or may result from noninfectious disease processes. Finally, the presence of urinary symptoms in some patients may not be associated with either pyuria or bacteriuria.

It is evident from the foregoing considerations that none of these three separate criteria for urinary tract infections can be used alone to indicate the presence of bacterial infection of the urinary tract. On the other hand, requiring

Table 1: Hypothetical states of bacterial colonization and infection in the urinary tract.

	Bacteriuria	Symptoms	Pyuria
Colonization	+	–	–
Asymptomatic infection	+	–	+
Symptomatic infection	+	+	+
Inflammation without infection	–	–	+
Symptoms without infection	–	+	–

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Table 2: Criteria for classification of urinary tract infections by clinical syndrome.

Category	Criteria	
	Clinical	Laboratory
Acute uncomplicated UTI in women	– Dysuria, urgency, frequency, suprapubic pain – No urinary symptoms in last four weeks prior to this episode – Females – No fever or flank pain	– ≥ 10 wbc/mm^3 – ≥10^3 cfu/ml uropathogens in MSU
Acute uncomplicated pyelonephritis	– Fever, chills – Flank pain on exam – Other diagnosis excluded – No history or clinical evidence of urological abnormalities	– ≥ 10 wbc/mm^3 – ≥ 10^4 cfu/ml uropathogens in MSU
Complicated UTI and UTI in men	– Any combination of symptoms in one and two above – One or more factors associated with complicated UTI (see below)*	– ≥ 10 wbc/mm^3 – ≥10^5 cfu/ml uropathogens in MSU
Asymptomatic bacteriuria	– No urinary symptoms	– ≥ 10^5 cfu/ml in two MSU cultures > 24 h apart – ± > 10 wbc/mm^3

* Factors associated with complicated UTI include: any UTI in a male; indwelling or intermittent urinary catheter; > 100 cc of post-void residual urine; obstructive uropathopy; vesicoureteral reflux or other urological abnormalities; azotaemia (even without structural abnormalities; renal transplantation).

the presence of all three criteria (symptoms, pyuria, bacteriuria) may exclude some patients whose symptoms are truly caused by bacterial urinary tract infection. Thus, any definition used will be imperfect and optimal definitions can be established only by comparing the sensitivity and specificity of various diagnostic methods with one another or with a "gold standard". To define bacterial urinary tract infections, the two most commonly used "gold standards" have been repeatedly positive cultures of midstream urine (MSU) or a culture of a suprapubic aspirate of urine; both of these approaches differentiate true infection from specimen contamination. From the point of view of the clinician, relevance must also be considered. In general, too much emphasis has probably been placed upon documenting the presence or absence of bacteriuria in diagnosing urinary tract infections. In most instances, treatment is warranted for symptomatic urinary tract infections and thus attention should be directed primarily toward criteria for defining when to initiate therapy. Therapy is less often indicated for the treatment of asymptomatic infections [2].

Clinical Syndromes Associated with Urinary Tract Infection

Urinary tract infection encompasses a broad range of clinical entities that differ in terms of clinical presentation, degree of tissue invasion, epidemiological setting, requirements for successful antimicrobial therapy and propensity for recurrence [3,4]. The most useful diagnostic criteria for specific clinical syndromes may differ, and hence it is important to categorize definitions of infection by type of clinical presentation. Based upon epidemiological considerations, it would seem most useful to subdivide urinary tract infections into three separate categories: acute uncomplicated cystitis in women; acute uncomplicated pyelonephritis in women, and complicated urinary tract infections in men and women (Table 2). The latter group can be further subdivided into more precise categories designating specific types of complicated infections, i.e., patients with urinary stones, patients with prostatitis and so forth.

Although symptoms are imperfect indicators of urinary tract infection, selected symptoms suggest specific clinical syndromes. Thus, in acute uncomplicated infections in women, symptoms typically include dysuria, urgency, frequency and suprapubic pain. Fever and flank pain are usually absent. Gross haematuria may be present. In acute uncomplicated pyelonephritis, the cardinal symptoms are fever, chills, and flank pain. Patients may or may not complain of any of the symptoms enumerated under acute uncomplicated cystitis. In complicated urinary tract infections in men or women, any of the symptoms noted under the prior two categories may occur alone or in various combinations. In addition, one or more of the factors considered indicative of complicated UTI (Table 2) should be present. It should be noted that in infants or elderly patients, the symptoms of urinary tract infection may be nonspecific. Frequently, fever may be the only sign noted in infants. In contrast, in adults or elderly patients, fever may be absent.

Relationship of Pyuria to Urinary Tract Infection

To be considered a true infection, a symptomatic episode should be associated with signs of urinary tract invasion by microorganisms. Although this could theoretically be demonstrated on the basis of a serological test (a specific immune response to the infecting organism) or on the basis of a biopsy demonstrating mucosal invasion by microorganisms, in practical terms in the clinical arena this is demonstrable only as the presence or absence of pyuria (and, in some patients, haematuria). In adult patients with urinary symptoms, the presence of pyuria

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generally correlates very closely with proven bacterial urinary tract infection, assuming appropriate techniques for its measurement are utilized. Unfortunately, the usual method for quantitating the number of leukocytes in the urine in many laboratories is to count the number of white blood cells per high power field in the resuspended sediment of a centrifuged aliquot of urine. Using this method, as many as 50% of patients with proven urinary tract infection will not have pyuria (> 5 leukocytes/HPF) with a coefficient of variation of approximately 40% [1]. In contrast, the finding of > 10 leukocytes per cubic millimeter when the unspun urine is examined in a counting chamber (such as a haemocytometer) is a much more accurate and reproducible method [1]. Using this method, more than 96% of symptomatic men and women with significant bacteriuria and either complicated or uncomplicated UTIs have > 10 leukocytes per cubic millimeter in their urine while fewer than 1% of asymptomatic nonbacteriuric individuals have evidence of pyuria. The latter may not hold true in chronically catheterized patients, who more often have pyuria in the absence of bacteriuria [5]. In addition, most acutely symptomatic women with pyuria but without significant bacteriuria do have true urinary infection with bacterial pathogens present in colony counts less than 100,000/ml on midstream urine culture (as confirmed by suprapubic aspiration) [6]. In paediatric patients, it should be noted that pyuria sometimes accompanies fever and, considered alone, may not be as specific an indicator of urinary tract infection as it is in adult patients.

The Presence of Bacteriuria: Use of Quantitative Urine Cultures

Quantitative urine cultures have been widely used as a means of defining urinary tract infection. In most circumstances, urine cultures are collected by the clean catch midstream technique. Collection by urethral catheterization or suprapubic aspiration are acceptable alternatives often used in research studies, but they are not often used in clinical practice and hence will not be discussed further. In more than 95% of UTIs, the infecting microorganism is a member of the *Enterobacteriaceae*, *P. aeruginosa*, Enterococci, or in the case of young women, *S. saprophyticus* species. In contrast, the organisms that commonly colonize the distal urethra and skin of both men and women and the vagina of women – *Staphylococcus epidermidis*, diphtheroids, lactobacilli, *Gardnerella vaginalis* and a variety of anaerobes – rarely cause urinary tract infection [7]. Thus, the *identity* of the bacterial species found in urine cultures should be a major factor in determining whether an infection is present or not. The major problem in interpretation of urine cultures arises because approximately 10–20% of females harbour *Enterobacteriaceae* in their vaginal and periurethral areas at any point in time [7]. In these women, urine cultures collected by the voided technique may be contaminated with vaginal *Enterobacteriaceae* as well as normal flora, making interpretation of the culture difficult.

Apart from the presence or absence of a uropathogenic species, the other major criterion for interpreting culture results is the number of colony-forming units per milliliter (cfu/ml) of bacteria found in a urine culture. It is of interest to note that in few other circumstances in clinical microbiology are the number or organisms actually quantitated. *Kass* and others first demonstrated that quantitative cultures of the urine separated individuals into two groups, those who consistently had large numbers of bacteria in their urine ($\geq 10^5$ cfu/ml) and usually experienced morbidity on that basis (hence the term significant bacteriuria) and those with few bacteria in their urine, which were predominantly contaminants [8].

Although the concept of significant bacteriuria has proved very useful for research in urinary tract infections, interpretation of colony counts in clinical practice must take the patient's clinical presentation and the epidemiological setting into account. Studies indicate that in women with acute uncomplicated urinary infection, the traditional diagnostic criterion of $\geq 10^5$ cfu/ml has a very high diagnostic specificity but a very low sensitivity [9–11]. Indeed, approximately one-third of women with a clinical syndrome of acute dysuria, frequency, and urgency; pyuria on urinalysis; and a good clinical response to antimicrobial therapy have infections with $10^2 - 10^4$ cfu/ml of a urinary pathogen as demonstrated by suprapubic aspiration [9]. Since a large number of infected women would not be judged as infected, and thus not treated, if this diagnostic criterion were used, other definitions seem preferable in this setting. In this type of patient, $\geq 10^2$ cfu/ml of a uropathogen provides the highest combined sensitivity and specificity for the diagnosis of acute UTI. By using a colony count cut-off of $\geq 10^3$ cfu/ml, a higher specificity (0.95) can be obtained without much sacrifice in sensitivity (0.80). Additionally, $\geq 10^3$ cfu/ml can be reliably detected by microbiological techniques available in most clinical microbiology laboratories. Thus, it may be practically expedient to use this cut-off rather than the $\geq 10^2$ cfu/ml criterion.

The diagnostic significance of specific bacterial colony counts in patient groups other than women presenting with acute dysuria have been less extensively studied. In studies of the patients with acute uncomplicated pyelonephritis whose diagnosis is ultimately confirmed by positive blood cultures, it was found that approximately 80% have $\geq 10^5$ cfu/ml, 10–15% have between $10^4 - 10^5$ and the remaining patients have smaller numbers of bacteria in their midstream urine culture [12]. Thus, $\geq 10^4$ cfu/ml of a uropathogen in an MSU culture could certainly be considered excellent evidence of infection in patients with suspected acute uncomplicated pyelonephritis.

In male patients, most of whom have complicated urinary tract infections, it has been demonstrated that a diagnostic threshold of $\geq 10^4$ cfu/ml in a clean catch specimen

provides an increased sensitivity (as compared with $\geq 10^5$ cfu/ml) without sacrificing specificity [13]. The problem of contamination of urinary specimens in men is infrequent as compared with clean void specimens in women [14].

More rigid criteria appear appropriate for the evaluation of patients with asymptomatic bacteriuria. In this circumstance, accepting lower numbers of bacteria as diagnostic is associated with diagnostic inaccuracies (and hence lack of specificity). In asymptomatic persons, two consecutive MSU cultures yielding the same organism in numbers $\geq 10^5$ cfu/ml has a specificity $> 95\%$ and a sensitivity $> 95\%$, and is thus an excellent criterion in this group [15,16].

Criteria for Defining Urinary Tract Infection in Specific Patient Groups

Based on the above considerations, proposed definitions for the diagnosis of urinary tract infections are outlined in Table 2. Both clinical and microbiological criteria are used in all of the definitions proposed, and different definitions are proposed for specific clinically and epidemiologically defined groups.

Criteria for Resolution of Urinary Tract Infections

Unfortunately, there have been few systematic evaluations of various means of defining treatment failures after antimicrobial therapy for urinary tract infection. The criteria utilized for defining cure vary widely. Some investigators focus entirely upon microbiological criteria, others upon clinical criteria and some include both parameters. There are few comparative data to determine which outcome criteria are the most meaningful. For example, in women with acute urinary infection whose symptoms resolve after antimicrobial therapy, what is the significance of persistence or recurrence of the original infecting strain without associated symptoms? Conversely, in patients whose microorganisms are eradicated, of what consequence is the presence of persistent urinary symptoms or persistent pyuria or both? In the absence of data addressing these issues, criteria for evaluating the response to therapy must be developed on an empirical basis. One reasonable system involves defining each patient's outcome as a clinical cure or failure and as a microbiological cure or failure. Clinical failures are defined as the presence of urinary symptoms, pyuria, and $\geq 10^3$ cfu/ml of a uropathogen at any time up to and including the final outcome visit. Thus, all clinical failures are in essence judged to be microbiological failures. Microbiological failures are defined as noted above for clinical failures, or by the persistence of $\geq 10^5$ cfu/ml of uropathogen in the midstream urine at any time through the four to six week follow-up visit in an asymptomatic patient (with or without associated pyuria).

Microbiological and clinical failures can be subdivided into early onset (less than five to nine days post treatment) and late onset (greater than five to nine days post treatment) and into same strain or different strain based on speciation, antibiogram, or alternative means such as serotyping. While "different strain" recurrences clearly represent reinfection (whether they occur early or late), the interpretation of "same strain" recurrences is more difficult and may be different in different patient groups. Thus, in complicated urinary tract infections with a tissue-based focus of infection (an infected stone, for example) early same strain recurrence probably signifies relapse and signals a need for longer term treatment [17]. In women with acute uncomplicated infection, however, early same strain recurrence may represent "reinfection" of the urinary tract from organisms persisting in the vaginal or fecal reservoir. Although these various outcomes may be difficult to differentiate unambiguously it seems reasonable to classify the type and timing of treatment failures by use of a system such as the one proposed here.

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