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European Association of Urology

Guidelines View

Keep it Simple: A Proposal for a New Definition of Uncomplicated and Complicated Urinary Tract Infections from the EAU Urological Infections Guidelines Panel

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Urinary tract infections (UTIs) are among the most prevalent bacterial infections encountered in both community and health care settings, contributing significantly to administration of antibiotics in medical practice [1]. UTIs exhibit a wide spectrum of heterogeneity in terms of their underlying causes, clinical manifestations, and disease progression, ranging from relatively benign cases with mild symptoms (cystitis) to severe and potentially life-threatening conditions (such as pyelonephritis, bacteremia, and septic shock).

UTIs are commonly categorized into uncomplicated and complicated types [2]. According to historical definitions, uncomplicated UTIs occur in healthy, nonpregnant women, while all other UTIs fall under the category of complicated UTIs. This classification is straightforward to comprehend, yet it carries inherent risks, as it may significantly impact initial patient management and treatment selection. According to this classification, for instance, UTI in a young woman with high-grade fever and pyelonephritis would be considered uncomplicated, whereas UTI in a young man with cystitis would be classified as complicated. This scenario poses a risk of mismanagement, as in the first case, the young female patient with pyelonephritis may be undertreated with antibiotics not optimal for pyelonephritis, while the young man with cystitis might receive broad-spectrum antibiotics for several days because all UTIs in males are considered to be complicated.

The concept of uncomplicated and complicated UTI was initially delineated in 1992 by the Infectious Diseases Society of America and the European Society of Clinical Microbiology and Infectious Diseases [3]. The aim was to standardize study cohorts for evaluations of new anti-infective drugs, with complicated UTIs defined as those occurring in the presence of catheterization or urinary tract abnormalities. Over time, subsequent recognition of many risk factors such as age, immunosuppression, and diabetes might have allowed more optimized antimicrobial treatment. However, the fundamental definition of complicated UTIs remains associated with the presence of predisposing conditions rather than clinical signs of systemic infection. Recent years have seen further expansion of the criteria defining complicated UTIs, especially in research guidelines. According to the US Food and Drug Administration 2018 guideline, complicated UTIs are characterized by a clinical syndrome involving pyuria and a documented microbial pathogen, accompanied by local and systemic signs and symptoms, occurring in the context of urinary tract abnormalities or catheterization [4]. This expanded and widely used definition underscores a combination of local and systemic manifestations in combination with risk factors. Pyelonephritis is included as a subset of the complicated UTI category, rendering the term "uncomplicated pyelonephritis" obsolete [5,6].

Despite, or perhaps precisely because of, these refinements, uncertainties persist, as evidenced by variations in defining complicated UTIs across studies, leading to disparities and challenges in interpreting study results [7,8]. However, real-life patient management cannot be

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https://doi.org/10.1016/j.eururo.2024.05.007

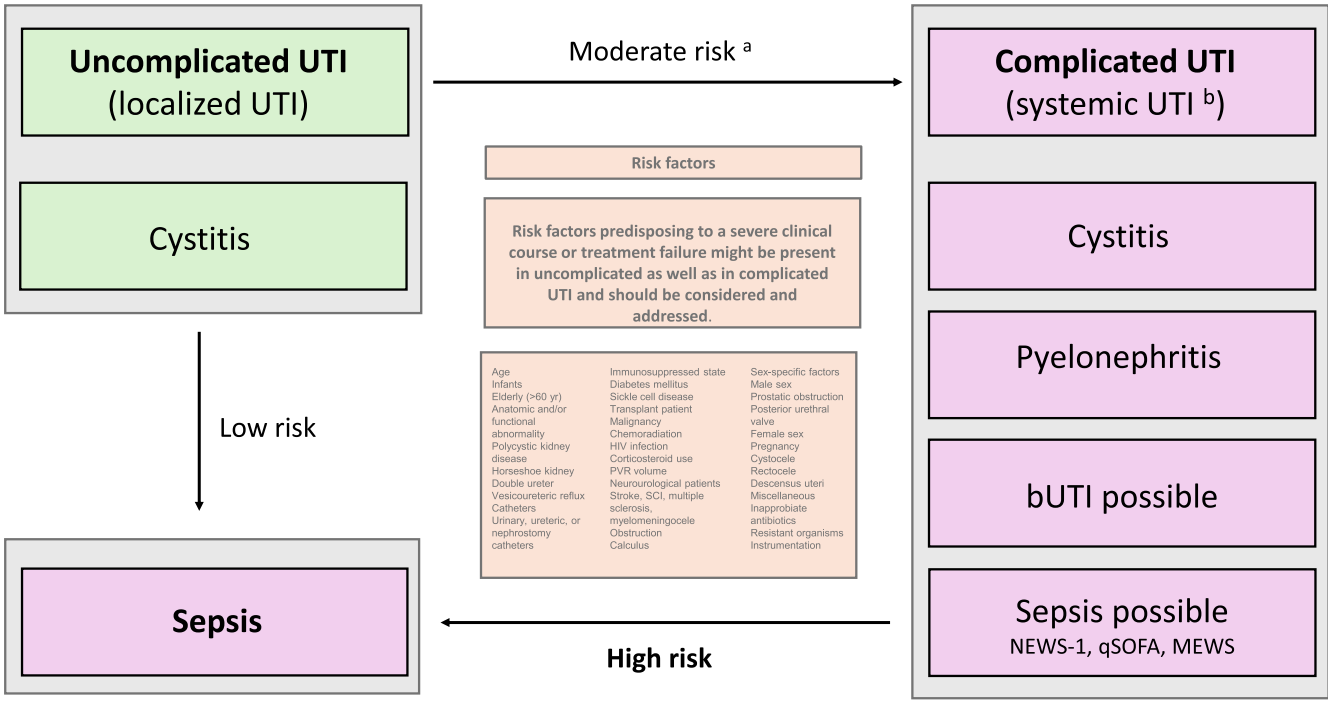

Fig. 1 – Concept of uncomplicated and complicated urinary tract infections (UTIs). Both uncomplicated and complicated UTIs are associated with risk factors that increase the likelihood of challenging clinical progression and hinder treatment effectiveness. Sepsis represents the most severe UTI outcome. Patients with uncomplicated UTIs generally face a low risk of direct progression to sepsis. The risk of developing a systemic infection is moderate and depends on specific risk factors. Patients with clinical suspicions of sepsis, flagged by warning scores such as National Early Warning Score (NEWS), Quick Sequential Organ Failure Assessment (qSOFA), or Modified Early Warning Score (MEWS), have the highest risk of sepsis onset. bUTI = bacteremic UTI; HIV = human immunodeficiency virus; PVR = postvoid residual; SCI = spinal cord injury. [a]Depending on risk factors. [b]Fever (temperature >38 °C), chills, or malaise.

compared to retrospective studies. For example, laboratory results are not available at a patient's first visit and pyelonephritis might still be considered as an uncomplicated UTI in clinical guidelines. Given these challenges, there is a risk of misapplication of guidelines and treatment recommendations, with potential for impacting patient care. This emphasizes the need for simpler definitions that allowing practitioners to categorize UTIs in the relevant treatment group at the point of care that is appropriate for the individual patient.

In response to this need, we propose a modified classification scheme for UTIs aimed at enhancing consistency in clinical practice and providing a comprehensive framework for understanding diverse presentations. This scheme retains the terms "uncomplicated" and "complicated" while emphasizing the clinical signs and symptoms of systemic infection to categorize UTIs. It also recommends consideration of sex-specific factors, reflecting emerging knowledge regarding genetic and microbiome distinctions between males and females.

We propose the following approach. The urinary tract is composed of urine-producing organs (kidneys), a urine-storing organ (bladder), and a urine-draining system (ureter and urethra). To simplify our approach, infection of the urethra (urethritis) is discussed separately because of its association with sexually transmitted diseases. Ureteritis refers to inflammation of the ureter; it is rare and mostly associated with cystitis and pyelonephritis and therefore it is not considered as its own condition. The resulting definitions are as follows.

1. An uncomplicated UTI is a localized urinary tract infection (ie, cystitis) without any signs of systemic infection in either sex. Risk factors predisposing to a severe clinical course or treatment failure might be present and should be considered and addressed.
2. A complicated UTI is a systemic urinary tract infection with or without localized symptoms originating from any site in the urinary tract in either sex. Risk factors predisposing to a severe clinical course or treatment failure might be present and should be considered and addressed.

According to these new definitions, UTIs can manifest as either uncomplicated (localized) or complicated (systemic). Both uncomplicated and complicated UTIs may be accompanied by risk factors that increase the likelihood of a challenging clinical course and jeopardize treatment success. Clinicians must be aware of these risk factors, particularly urinary tract abnormalities included in the original UTI definitions, and keep them at the forefront of their considerations (Fig. 1). Building on this clear classification, clinicians can promptly differentiate between a predominantly outpatient-manageable UTI and a more complex UTI presenting with systemic signs. Accompanying risk factors, such as urinary catheters (catheter-associated UTIs), UTIs in neurological patients, urinary tract obstruction, and UTIs in renal transplant patients, warrant individual attention.

An important point is that differentiation between infections in biological males and females is imperative. Consideration of male sex as a risk factor per se is antiquated and

lacks support from contemporary literature. Instead, current evidence highlights the significant influence of biological sex, whether female or male, on various immune phenotypes, particularly immune responses to diseases affecting mucosal surfaces including the urothelium. Factors such as sex hormones, sex chromosomes, sexual dimorphism, and sex disparities collectively shape responses to urinary tract diseases, including bladder infections [9,10].

Our aim in proposing this new classification is to stimulate scientific discourse and provide clinicians with a robust framework for classifying UTIs. The proposed classification would provide clarity and facilitate effective clinical management of UTIs, and acknowledges the importance of addressing clinical and sex-specific nuances in the care of individual patients.

Conflicts of interest: Gernot Bonkat has received consultancy fees from Janssen-Cilag AG, OM Pharma, IBSA, Zambon SpA, and Sun Pharma; company speaker honoraria from Zambon SpA, OM Pharma, IBSA, Bionorica SE, Hoechst Marion Roussel, and Sun Pharma; and fellowship and travel grants from Sun Pharma, OM Pharma, IBSA. and Bionorica SE. Jennifer Kranz has received consultancy fees from Bionorica, GSK, and Shionogi; has received speaker honoraria from Bionorica, GSK, Janssen-Cilag GmbH, MSD, and Apogepha Arzneimittel GmbH; has received research grants from DFG; and has participated in trials run by Janssen-Cilag GmbH. Florian Wagenlehner has received consultancy fees from Achaogen, Bionorica, GSK, Janssen, Klosterfrau, Pfizer, MIP Pharma, Shionogi, Spero, VenatorRX, and OM Pharma; has received speaker honoraria from Astellas, AstraZeneca, Bionorica, GSK, Janssen, Klosterfrau, MSD, Pfizer, MIP Pharma, and OM Pharma; has received research grants from DFG and DZIF; and has participated in trials run by GSK, Klosterfrau, Select Immune, Janssen, and VenatoRx.

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