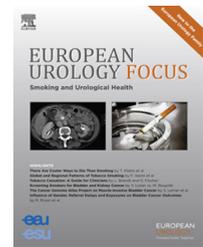


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Gray Zone – Infections

## Gray Zones in the Field of Urinary Tract Infections

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Bacterial resistance to antimicrobial agents is an imminent threat to contemporary medicine and a global health problem showing rapid progress. Resistance patterns vary widely in Europe, whereas in some Asian regions, resistance of urinary tract pathogens has already brought medicine into the “postantibiotic era” [1]. Microbial resistance is directly linked to the use and misuse of antimicrobials in humans and animals. The average prevalence of health care-associated urinary tract infections (UTIs) is 10–12% with a trend toward more severe infections like urosepsis and with a profile of causative microorganism that is changing in an unfavorable direction [2,3].

### 1. Biology of urinary tract infections

Symptoms of urogenital infection are caused by the immune reaction of the host to a urinary pathogen. The severity of UTIs ranges from local irritation in simple cystitis to physiologic collapse in urosepsis [4]. The host reaction is mediated by virulence factors expressed by the pathogen (eg, P or type 1 fimbriae) and the response of the receptors located on the uroepithelial cells. Toll-like receptor 4 recognizes gram-negative uropathogens and activates the uroepithelial cells, which release inflammatory mediators (eg, interleukin [IL] 6 and IL-8) [5]. Despite this knowledge, the complete cascade of events during UTI is still largely unknown.

Not all pathogens are killed when symptoms resolve after antimicrobial treatment. Some withdraw into “trenches” within the uroepithelium or the perineal skin and may protect themselves with intracellular biofilms.

Some microorganisms residing in the intestine also are not killed by antimicrobial treatment of UTI and may develop resistance. Most studies on uropathogens are made in rich media, and we have little understanding of how bacteria behave and adapt in urine. Finally, there is increasing evidence of carriage of resistant microorganisms between geographical regions. Consequently, the biology of UTI has gray zones at molecular, microbiological, individual, and international levels (Table 1).

### 2. Diagnosing urinary tract infections

Classification of UTI is based on evidence of the presence of living pathogens. The most common definition is 10<sup>5</sup> colony-forming units per milliliter of urine, although lower counts are accepted in certain situations [4]. Recently, metagenomic sequencing has provided new knowledge about the organisms that are or have been present in the urinary microbiota. A broad range of noncultivable bacteria can now be detected in what was thought to be “sterile” bladder urine or expressed prostate secretions in patients with urologic disorders as well as in healthy persons [6]. Their impact on the immune system and the development of diseases is poorly understood.

Presently it takes at least 24 h to identify a causative pathogen and its sensitivity pattern. Meanwhile, wide-spectrum antimicrobials are used on an empirical basis, putting pressure on the local microflora by the collateral damage phenomenon. However, recent research has shown that the time to microbiological characterization of the pathogen can be reduced to a few hours [7]. Research on

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**Table 1 – Gray zones, clinical relevance, and directions for future research in urinary tract infection**

Gray zones	Clinical relevance	Directions for future research
Molecular, microbiological, and epidemiological aspects of UTI	Understand the biology of UTI	<ul style="list-style-type: none"> <li>• Cascade of immunologic events during UTI</li> <li>• Effect of antibiotics on the microbiota of urine and feces</li> <li>• Carriage of resistant urinary tract pathogens between geographical regions</li> </ul>
	Improve diagnosis of UTI	<ul style="list-style-type: none"> <li>• Significance of noncultivable and low-virulence bacteria in urine or EPS on the immune system and the development of diseases</li> <li>• New technologies for instant identification of causative pathogens and their sensitivity patterns</li> </ul>
Prerequisites for antimicrobial stewardship	Improve treatment and prevention of UTI and postoperative infective complications	<ul style="list-style-type: none"> <li>• Development of nonantimicrobial treatments for UTI of low-grade severity</li> <li>• Identification of risk factors for progression to severe sepsis and septic shock</li> <li>• Identification of patient-related risk factors for postoperative infections</li> <li>• Importance of local prevalence and resistance of pathogens for postoperative infections</li> <li>• Value of rectal swab culture versus culture of feces before prostate biopsies</li> <li>• Importance of biopsy route for infective complications in prostate biopsies</li> <li>• Benefits of individualized, tailored antibiotic prophylaxis</li> <li>• Benefits of guideline adherence</li> </ul>

EPS = expressed prostatic secretion; UTI = urinary tract infection.

diagnostics of UTI addresses the role of both living and dead microorganisms (Table 1).

### 3. Recurrent lower urinary tract infection

Diagnostic principles in UTI are challenged in patients with recurrent lower UTI, a disabling condition affecting millions of women worldwide. Many risk factors are known such as sexual habits, hormonal status, asymptomatic bacteriuria, cold, and vaginal flora, but the common pathogenic mechanism is not known. With the best of intentions, far too many antimicrobials are prescribed to these patients. Unfortunately, the harms induced by antimicrobial treatment for patients with asymptomatic bacteriuria outweigh the benefits. The spectrum of causative pathogens changes in an undesirable way, and the resistance pattern worsens [8]. These are arguments for urgent development of nonantimicrobial treatments such as probiotics, lysins, immune stimulation, vaccines, antibodies that inactivate pathogens, and various peptides [9]. In addition, the “protective” role of low-virulence bacteria needs to be further explored, as does the role of the prostate in recurrent UTI in men (Table 1).

### 4. Perioperative antimicrobial prophylaxis

Periprocedural/operative antimicrobial prophylaxis is widely used to prevent infective complications; however, robust evidence for a benefit exists only for a limited number of procedures (eg, transurethral resection of the prostate and transrectal prostate biopsy). For other procedures, study results are contradictory or the interpretations are controversial. Consequently, many prophylactic regimens are used without underlying evidence. This practice also deviates from the principles of antimicrobial stewardship.

To reduce the amount of antimicrobials used for prophylaxis, we need intelligence about the local prevalence of infective complications, resistance of the most common pathogens, and patient-related risk factors. This will enable

us to prescribe tailored prophylaxis to patients at risk. A recent study showed that adherence to European Association of Urology (EAU) guidelines on antimicrobial prophylaxis reduced antimicrobial usage without increasing postoperative infection rates, lowered the prevalence of resistant uropathogens, and reduced costs [10].

According to the EAU guidelines, the contamination category of a procedure is regarded as the most prominent risk factor for infectious complications [4]; however, there is a trend toward subdividing contamination categories according to the degree of invasiveness, such as mucosa breakage and duration and complexity of the procedure. There is great need for more evidence related to antimicrobial prophylaxis; currently, the search for risk factors seems more important than finding the best antimicrobial. Because of regional variations in antimicrobial resistance, such studies require meticulous study designs to capture accurate information that can provide generalizable outcomes.

Urosepsis is the most feared infective complication in urology, and prostate biopsies and kidney stone surgery are the most common causes [2]. Preoperative screening for bacteriuria and resistant strains in feces are currently the most important preventive measures, and detection of fluoroquinolone- and cephalosporin-resistant *Escherichia coli* is key for safer targeted prophylaxis in urologic procedures. The increasing rate of urosepsis is an urgent call for better prevention and for identification of patients at risk of progression to severe sepsis and septic shock (Table 1).

### 5. Conclusions

There is an urgent need for better understanding, prevention, and treatment options for patients with UTI. The field is vast and intriguing, with research topics that cover molecular biology, microbiology, infectiology, pharmacology, and epidemiology. With fewer and less effective antimicrobial substances at hand, urologists must weigh the balance of benefits and harms in high-risk procedures while adhering to the highest standards of hygiene and surgical technique.

**Conflicts of interest:** The authors have nothing to disclose.

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