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Q1 Urinary tract infections (UTI) remain one of the most common bacterial infections. How have recent trends in incidence and pathogen profiles changed the way clinicians should approach diagnosis and initial management?

UTIs cover a very broad area; there isn't just one type. Therefore, we try to better classify them. Traditionally, UTIs are divided into uncomplicated and complicated infections, but this is now evolving. The Infectious Diseases Society of America (IDSA), similarly to the European Association of Urology (EAU), has moved towards classifying UTIs in a new way. The EAU classifies UTI as either localised or systemic. Both can have or not have risk factors or complicating factors. This approach is more encompassing and allows for comparable cohorts in studies.

Using this newer classification, we can still observe trends in incidence and prevalence. These correlate with morbidity and age. As the population ages, we see a higher prevalence of UTIs. Severe infections, such as urosepsis, are also increasing, and primarily affect those over 65 years of age.

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Changes in the pathogen spectrum are less pronounced. In infections without risk factors, *Escherichia coli* predominates. In patients with risk factors, other *Enterobacteria* and Gram-positive cocci, such as *Enterococcus*, are more frequent. Now, with microbiome research, we have more patient data, but we still do not know exactly what the urobiome means for pathophysiology and disease course.

The most important trend is the rise in resistance, especially in complicated UTIs. This trend is endemic and has persisted for many years. Resistance started with co-trimoxazole, about 2 decades ago, followed by fluoroquinolones, then cephalosporins. Even in Central Europe, including Germany, low levels of carbapenem-resistant bacteria are now observed. In other countries, such as Greece, Italy, and parts of Asia, these bacteria are already common. This significantly influences how clinicians manage these patients.

Q2 Antibiotic resistance in uropathogens is rising globally. Which resistance patterns are most concerning, and how should empiric therapy adapt to this evolving landscape?

Resistance to key antibiotics is the main concern, including fluoroquinolones, third-generation cephalosporins, and emerging carbapenem resistance. Carbapenem is particularly concerning as it drives mortality in severe UTIs.

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The problem with empiric therapy is that it creates a vicious cycle: there is a tendency to use broad-spectrum antibiotics to cover potentially resistant pathogens. In Germany, resistance rates are around 25% for fluoroquinolones, 15% for cephalosporins, and less than 5% for carbapenems. This means that the majority of pathogens remain susceptible, yet broad-spectrum antibiotics are often used unnecessarily, which drives collateral damage and further resistance. Breaking this cycle is essential.

Q3 Chronic prostatitis and recurrent UTIs are notoriously difficult to treat. How has your research improved our understanding of their pathophysiology, and what strategies are proving most effective for long-term management?

These are two distinct entities, so I'll address them separately.

Chronic prostatitis is classified, using the National Institutes of Health (NIH) system, into acute bacterial prostatitis, chronic bacterial prostatitis, and chronic pelvic pain syndrome. Less than 10% of patients with these symptoms have bacterial prostatitis at diagnosis, which means that 90% have a non-bacterial form. These patients do not need antibiotics at that stage, even if bacterial prostatitis was previously causative.

Diagnosis in these patients is often incomplete. At least a two-glass test is needed to rule out contamination, though a three-glass or four-glass test is better. True chronic bacterial prostatitis is rare outside acute inflammation. Treatment is difficult because antibiotic penetration into the prostate is limited. Only lipophilic drugs, mainly fluoroquinolones, reach adequate concentrations. Most studies use fluoroquinolones, and increasing resistance poses a major challenge. Alternative antibiotics, such as fosfomycin, are often used off-label, but evidence is variable. Patients with chronic pelvic pain syndrome are even more difficult to treat due to varying phenotypes.

Recurrent UTIs are usually more common in females. In males, they are often catheter-associated. For recurrent cystitis in females, we try to avoid antibiotics where possible. Non-antibiotic strategies are evolving, though evidence is limited, and vaccines are not yet available. We have immune-modulating strategies and fimbrial-blocking agents, but the evidence is low. Treatments like cranberry or d-mannose are not entirely convincing, so recommendations differ.

Other strategies include urine disinfection, e.g., methenamine hippurate, where evidence is increasing. In postmenopausal women, local oestrogen therapy is recommended. Antibiotics are reserved for failure of these strategies, either as long-term therapy or for each infection episode.

Q4 Your work on host–pathogen interactions in pyelonephritis and complicated UTIs has revealed new insights. How can these findings inform more personalised approaches to patient care?

We are currently investigating this in depth in a Deutsche Forschungsgemeinschaft (DFG)-funded consortium called Bacterial Renal Infection and Defence (BARICADE). We are using proteomics, metabolomics, metagenomics, microbiome analysis, and immune phenotyping to study the activation of different immune cell populations. I think we will be able to identify signals that can help predict which patients are at higher risk of pyelonephritis, severe disease courses, or recurrent infections. For the time being, though, results have not yet fully unravelled.

This consortium involves a lot of basic research, and we already have findings from mouse models that we are now translating into the clinic. Currently, I cannot pinpoint individual pathophysiological pathways, but I am confident that, in the next 2–3 years, we will have validated markers that can be applied in routine clinical practice.

Q5 Diagnostic tools, like the Acute Cystitis Symptom Score (ACSS), aim to streamline clinical decisions. How do you see symptom-based assessment and microbiology-driven diagnostics complementing each other in everyday practice?

We developed the ACSS for two reasons. One was to provide a low-threshold, diagnostically accurate tool for acute bacterial cystitis in everyday clinical practice. The other was to create a tool suitable for clinical and regulatory studies, because regulatory authorities, including the FDA and EMA, now include symptoms as a primary endpoint. We needed a way to objectively assess these symptoms.

We have shown that asking about individual symptoms alone is not accurate enough, and that graded symptom scoring is better. This tool can be used both in everyday practice and as a patient-related outcome measurement in clinical studies. It can be used for follow-up to assess the success or failure of different treatments, and to compare treatment arms.

The ACSS is currently translated and validated in almost 20 languages. It complements microbiology-driven diagnostics; it does not replace them. Additionally, point-of-care microbiological testing is developing rapidly, and I think this will be extremely important in the future for combining both approaches.

Q6 Developing novel antibiotics for UTIs faces challenges, including resistance, safety, and regulatory hurdles. From your experience, what strategies are most effective in bringing new therapies to patients?

The hurdles start even before the antibiotics come to market. Developing novel antibiotics is expensive, and for pharmaceutical companies, the reimbursement is relatively low. That's because once these antibiotics are available, we intentionally restrict their clinical use to avoid overuse, which is important to prolong their effectiveness and prevent resistance.

A key strategy in the past 10 years has been to develop novel β-lactam antibiotics combined with new β-lactamase inhibitors. In the future, it would be helpful to develop entirely new classes of antibiotics, ideally not broad-spectrum, but selective antibiotics, to protect the microbiome and reduce collateral damage.

The next important point is market access. Even if these novel antibiotics are developed, not all countries have equal access. For example, only about half of the new antibiotics are available on the European market. Political and regulatory measures are needed to incentivise pharmaceutical companies to make these drugs widely available.

Finally, once these novel antibiotics are on the market, we need strategies to avoid overuse, particularly in outpatient populations, where stewardship is more challenging than in hospitals. Prudently managing their use is critical to maintaining their effectiveness.

Q7 Looking ahead, how do you envision molecular diagnostics, host immune profiling, and personalised medicine transforming the diagnosis and treatment of urogenital infections over the next decade?

We need a lot more diagnostics in general. Culture takes 48–72 hours, which is usually after antibiotics have already started, or sometimes even stopped. We need to know within the first 2–4 hours if bacteria are present, their classification, and their susceptibility. Point-of-care testing, including phenotypic investigations, is rapidly evolving and is one of the most important diagnostic strategies. They allow appropriate first treatment and support antimicrobial or diagnostic stewardship, helping to avoid unnecessary use of last-resort or broad-spectrum antibiotics.

The second important area is host immune profiling. Currently, we often only know if leukocytes are present or not. Ideally, we would know which immune cell populations are present and whether they are activated. This is feasible; we already do it routinely for haematological patients. For more severe UTIs, detecting such signatures during the acute phase would allow stratification of patients by higher or lower risk. This drives personalised medicine.

Other techniques, such as metabolomics and proteomics, will likely develop in parallel. Proteomics at the point of care may be more difficult, but omics data overall will enhance our understanding and enable a more personalised view of the patient, guiding management.

This is the challenge for the next decade. These methods may become available, but we need to translate them from the bench to the bedside and incorporate them into routine clinical practice. Yes, they will cost more initially, but in the end, they will be cost-effective.

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