

Advances in the Management of Acute and Recurrent Urinary Tract Infections Caused by Resistant Pathogens – What's Next?

This GSK Industry Symposium took place at the European Association of Urology (EAU) Conference on 1st July 2022, Amsterdam, the Netherlands



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Disclosure:	Fromer is a legal consultant for Johnson & Johnson, and a speaker and advisor for GSK. Khullar is a consultant and researcher for AbbVie, and consultant and speaker for GSK. Wagenlehner has worked as a consultant for Achaogen, Astellas, Eumedica, Janssen, Klosterfrau, Leo-Pharma, Merlion, Shionogi, Quiagen, Sysmex, and VenatoRX. As a consultant and speaker for Bionorica, GSK, MSD, Rosen Pharma, and OM/Vifor-Pharma. As a speaker for AstraZeneca and Pfizer, and as a researcher for Helperby, Phagomed and Saxonia R&D. The speakers have no conflicts of interest relating to this presentation.
Acknowledgements:	This symposium review article was proposed by EMJ and was written by Caroline E. Cross, Reading, UK. All speakers were given the opportunity to review the article.
Support:	The symposium and publication of this article was funded by GSK.
Disclaimer:	The opinions expressed in this article belong solely to the named speakers and do not necessarily reflect those of GSK. GSK was provided with the opportunity to review this publication prior to submission to EMJ, for the sole purpose of ensuring its data is accurately stated herein. Not all medicines and/or indications presented in this webinar may be approved for use in all countries. This medical education activity is intended for healthcare professionals only.
Citation:	EMJ. 2022;7[3]:23-29. DOI/10.33590/emj/10081330. https://doi.org/10.33590/emj/10081330



Meeting Summary

Uncomplicated urinary tract infections (uUTI) are one of the most common infections in the community, affecting >150 million people each year worldwide, and being responsible for large amounts of antibiotic prescribing.^{1,2} Up to 80% of females will experience at least one uUTI in their lifetime, and 45% will have recurrent uUTI.³ The debilitating symptoms that accompany urinary tract infections (UTI), including

pain and urinary urgency, coupled with the unpredictability of recurrence, negatively impact quality of life (QoL).^{1,3}

The GSK Industry Symposium took place on 1st July 2022 as part of the European Association of Urology (EAU) Conference in Amsterdam, the Netherlands, and focused on the challenges surrounding the diagnosis and management of uUTIs and recurrent UTIs in the context of increasing antimicrobial resistance.

During the presentations, speakers Debra Fromer, Vik Khullar, and Florian Wagenlehner, all specialists in urology, outlined the challenges facing clinicians and patients in treating UTIs effectively whilst maintaining good antibiotic stewardship. The wide-ranging discussions included questions around differential diagnosis, personalised approaches to treatment, and the challenges of treating recurrent UTIs.

The panel also discussed the need for new strategies to manage such infections, and highlighted alternatives to antibiotics that are under development and could help to slow the rise in antimicrobial resistance. The symposium finished on a positive note with discussions around new and emerging therapies, such as immune stimulation, vaccination, and fulguration, that could help many females to break the debilitating cycle of recurrent UTIs.

INTRODUCTION

At least 60% of females worldwide will experience at least one UTI in their lifetime.⁴ An array of pathogenic bacteria, both gram-negative and gram-positive, can cause the infections, although in uUTIs, *Escherichia coli* (*E. coli*) is the predominant pathogen.⁵

Symptoms are debilitating, and include urinary urgency, dysuria, and frequency. More than 25% of females who experience a UTI will go on to have further infections, often within 3 months, increasing anxiety levels with feelings of helplessness and dread, and reducing QoL.^{6,7}

Oral antibiotics are the mainstay of treatment, and medications to treat UTIs currently account for 15% of all antibiotic prescriptions in the USA and Europe.² Increasingly, patients are experiencing UTIs that are resistant to first line antibiotics,⁸ contributing to the global threat of antimicrobial resistance. Clinical guidelines for the treatment of UTIs recommend that first line antibiotics be chosen based on local antimicrobial resistance patterns.⁹

During this symposium, the speakers highlighted the complexities of both uncomplicated and recurrent UTIs that mean a more personalised approach to treatment could be beneficial. They also discussed the increasing prevalence

of antibiotic resistant uropathogens, and what clinicians should consider when prescribing antimicrobial medications. Discussions also covered recent clinical studies that demonstrate the value of a more clinically informed approach to treatments, and show the potential of novel treatment approaches with antibiotics and other alternatives.

This article captures the main questions discussed during the symposium and draws attention to novel therapeutic strategies that can help clinicians apply appropriate antibiotic prescribing when treating patients with uncomplicated and recurrent UTIs.

How is the Differential Diagnosis of Urinary Tract Infection Done in Female Patients Presenting at Clinic, and What Is the Impact of These Infections on the Patient?

Most young females (>90%) who present at clinic with urinary urgency and pain whilst passing urine (dysuria) will have a UTI,¹⁰ explained Fromer, who sees hundreds of females with uncomplicated and recurrent UTIs in her clinics. She commonly sees females in their mid-thirties with previous history of culture-proven uUTIs who present with dysuria, frequency, urgency,

and suprapubic pain. "However, it's also possible that patients presenting with UTI symptoms could instead have overactive bladder or bladder pain syndrome."¹¹

Wagenlehner concurred, saying: "Diagnosis is not always straightforward. For a long time the gold standard has been lab culture of the urinary bacteria. However, in more than a third of cases, we do not get a positive culture, sometimes because the culture test is not sufficiently sensitive, and in others, the bacteria is not culturable in the lab." It has also become increasingly clear that bacteria can be present in the healthy bladder.⁵

The panel members agreed that the impact of UTIs on females can be pervasive. Some females have as many as six recurrent infections in a year, and the impact on individuals are significant. As Fromer outlined: "The infections are sudden, unforeseeable and distressing, taking a toll on mental health and sense of wellbeing."¹² Fromer drew attention to a study of 575 patients with recurrent UTIs, in which 61.9% of patients with a UTI suffered some degree of depression, and almost three quarters of females experienced anxiety. A reduction in UTIs correlated with improvements in QoL.¹²

Khullar added that other impacts of recurrent UTIs on patients' lives include sleep disruption, persistent fatigue, negative impacts on intimate relationships, and the financial consequences of taking time off work.¹³

Referring to one of his own studies, Wagenlehner said: "Using a self-administered anonymous web-based survey across five countries, we demonstrated that recurrent UTIs had a significant impact on QoL and are associated with mental stress for a high proportion of women."¹⁴ Other studies also report negative QoL impacts associated with treatment failure, often caused by antimicrobial resistant strains.^{15,16}

Antibiotic Resistance in Common Bacteria Has Reached Alarming Levels in Many Parts of the World Indicating that Many of the Available Treatment Options for Common Infections in Some Settings are Becoming Ineffective.⁸ How

does this Impact the Management of Patients with Urinary Tract Infections?

Uropathogens such as *E. coli* and *Klebsiella pneumoniae* (*K. pneumoniae*) feature prominently in the World Health Organization (WHO)'s 2014 report on emerging resistant pathogens.⁸ As Fromer explained: "There is now a high frequency of resistance to third generation cephalosporins commonly used to treat UTIs. This can lead to a reliance on carbapenems to treat severe infections, which really should be used only as a last resort."

The speakers emphasised the need for clinicians to consider antimicrobial resistance when treating patients for UTIs. "Often, when taking a patient's recent history we find that the patient has had multiple courses of antibiotics, for example for dental work. It is important to understand the resistance patterns for the individual at the time of symptom onset and prior to treatment,"¹⁷ Fromer said.

Fromer reinforced the point by describing data from a retrospective study of 908 female patients with UTIs from an outpatient clinic in the USA, which identified *E. coli* as the most common organism causing UTIs (complicated UTI [cUTI] and uncomplicated UTI [uUTI]). More than a third of patients had experienced three or more UTIs in the previous year (2015–2016), and rates of resistance to three or more oral antibiotics were as high as 30%.¹⁸ Antibiotic resistant infections were more prevalent in females with recurrent UTIs, and who were older.¹⁹

The speakers outlined how clinicians can support good antimicrobial stewardship and reduce inappropriate use of antibiotics. Strategies include not treating asymptomatic bacteriuria,¹⁷ avoiding use of broad-spectrum fluoroquinolones,⁹ using the shortest possible effective course of antibiotics,¹⁷ and raising awareness among patients of the dangers of 'self-starting' antibiotics, and not adhering to recommended dosage.^{11,17,20}

Wagenlehner also emphasised the complexities of diagnosing UTIs and the need for clinicians to rule out other underlying causes where possible, and to consider alternative strategies before prescribing antibiotics. Non-antibiotic interventions include behavioural changes, antiadhesive treatments, local antiseptics, topical

oestrogens, and immunomodulation.²¹ “We use symptom questionnaires that are also used in other conditions and can provide quantitative information to help clinicians to rule out complicated UTI and assess risk factors such as treatment failure and risk of recurrence.”

What can be Done in Clinical Practice to Assess the Risk of Antimicrobial Resistance In Patients with Urinary Tract Infection?

Wagenlehner believes we need a more personalised approach to the treatment of UTI patients, to identify patients who are more likely to have resistant pathogens. His team studied antibiotic sensitivity in 386 females with uUTIs and found that two-thirds (n=259) had infections that were susceptible to all antibiotics, but almost one-third (n=112) had infections that were resistant to one or two antibiotics, and 15 patients had infections that were resistant to multiple antibiotics.²² The patients with multiple drug resistant infections were generally older, and with history of recurrent infections.

Physical examination and history taking are important in supporting UTI diagnosis. “If resistance is suspected and the patient can tolerate the symptoms until a positive culture is returned, that is preferable. But for many the symptoms are unbearable, even with increased fluids and pain medication, and sometimes there is concern over more serious infection. In these cases, empiric antibiotics are necessary,” stated Fromer. “At this point we must rely on knowledge of local uropathogen resistance patterns and any history of antibiotic allergy or intolerance when deciding which antibiotic to prescribe.^{9,17} It is also important to consider the patient’s prior antibiotic use and previous culture results to clarify any history of antimicrobial resistance,”^{17,23} she reiterated. Avoiding use of broad-spectrum antibiotics and fluoroquinolones, and keeping the duration of therapy to a minimum also help to reduce the chances of further resistance developing.^{9,17}

Khullar reiterated the importance of checking for local uropathogen resistance patterns as they can vary considerably between regions and countries, with fluoroquinolone

resistance common in southern Europe,²⁴ and penicillin resistance common in the UK.²⁵ The speakers unanimously referred the audience to international clinical practice guidelines for the treatment of acute uncomplicated cystitis in the context of local resistance patterns.⁹

What are the Potential Roles of the Urinary Microbiota in Homeostasis of the Urinary Tract, and How does that Influence the Host Bacterial and Inflammatory Interactions in Patients with Urinary Tract Infections?

The human microbiome consists of trillions of bacteria, viruses, and fungi that are found in the human body, and outnumber human cells by 10:1.²⁶ The intimate and complex relationships that exist between the microbiome and human cells are vital for homeostasis.²⁶ The symbiotic ecosystem which results, influences both health and disease. For example, as Khullar explained, in the bladder, ‘beneficial bacteria’ such as some *Lactobacilli sp*, can attack pathogenic organisms, communicate with the bladder, control neurological function, and destroy chemicals in the urine.²⁶

Patients who experience recurrent UTIs often have repeated courses of antibiotics which can change the balance of microbiota in the gut and bladder. Older, post-menopausal females with low oestrogen levels had lower levels of beneficial *Lactobacilli* in their urinary tract compared to younger females.²⁷ When the DNA of bacteria in urine was analysed in both females with urgency urinary incontinence (UUI) and those without, females with UUI had more *Gardnerella* and *Enterobacteriaceae*, and fewer *Lactobacilli*.⁵ The differences were confirmed when bacteria were cultured from bladder biopsies.⁵ Khullar also highlighted a study that suggests *Lactobacillus crispatus*, one of the beneficial *Lactobacilli*, when given as a probiotic intravaginally, may help to reduce recurrent UTIs (rUTI).²⁸

Khullar also drew attention to experimental models of bladder infection that demonstrate that *E. coli* can invade superficial bladder epithelium, mature into biofilms, and create pod-like bulges on the bladder surface.²⁹ These

'pods' allow bacteria to evade the host's immune system defences, and can be a source of rUTI. In translational work, a study of urine sediments, prepared from females with acute episodes of rUTI caused by uropathogenic *E. coli*, found evidence of intracellular bacterial colonies in almost a fifth of cases.³⁰

"Some people get an infection and it is cleared by the immune system, or they may have asymptomatic infection. Others have frequent painful infections and have an abnormal response to infection causing inflammation with bacteria entering the bladder wall," Khullar explained. When epithelial cells collected from the bladder lining of females without active UTI were lysed, bacteria were found inside cells. Further analysis from both cultures of the samples showed *Staphylococcus* and *Enterococci* in both groups, with more *E. coli*, *Proteus sp*, and *Micrococcus sp* in the bladder walls,³¹ reinforcing the likelihood that bacteria in the bladder wall that are not killed by antibiotics are a source of recurrent UTIs.

With increasing evidence that microbial biofilms play a role in causing recurrent UTIs, cystoscopic electrofulguration as an experimental treatment has been used as a way to clear resistant bacteria from the bladder lining by cauterising inflammatory lesions. Fromer described a study of 95 females who received the treatment. Five-year follow up showed an 88% cure rate.³²

What are the Risk Factors Associated with Uncomplicated Urinary Tract Infection Recurrence?

The risk of recurrent uUTIs is higher for females over 55 years old.³³ These females have diminishing levels of oestrogen as they enter the menopause. Other risk factors include diabetes, particularly more advanced Type 2 diabetes when the patient is receiving insulin,³⁴ vaginal atrophy, urinary incontinence, vaginal wall prolapse, and increased post-void residual volume.³⁵

Khullar shared his clinical experience and practice, reiterating that in older, post-menopausal patients, it is important to

attempt urine culture while the patient has symptoms, while taking account of patient's history and previous antibiotic use. Additional assessments, such as urinary flow rate and post-void residual volume, will help the clinician to assess risk of recurrence. Also, if haematuria is present, cystoscopy should be carried out, and if needed, a CT urogram to examine the upper urinary tract. Additional factors that increase the risk of UTI recurrence include constipation rather than diarrhoea, and recent antibiotic use.³⁶

What is the Current Guidance in the Management of Recurrent Urinary Tract Infections in Female Patients?

Based on clinical experience and practice, Khullar recommends antimicrobial prophylaxis for up to 6 months for patients with recurrent UTIs. "We tend to use nitrofurantoin or fosfomycin in line with EAU guidelines,"²⁶ he outlined. Also, postcoital prophylaxis can be used, or the antiseptic methenamine hippurate, 1 g twice daily for 6 months, which has been shown to reduce recurrent infections.³⁷ Fromer emphasised that there are currently no evidence-based guidelines for the use of antibiotic prophylaxis for recurrent UTIs, and that it should be seen as a last resort option.

There is also evidence that non-antimicrobial prophylactics are effective. For example, an oestrogen-releasing vaginal ring,³⁸ intravaginal probiotics (*L. rhamnosus*, *L. reuteri*),³⁹ or immunoactive prophylaxis.^{40,41} *L. crispatus* given intravaginally as a probiotic, shows promise at reducing recurrent UTIs.²⁸ Topical oestrogens can help to decrease vaginal pH, while increasing glycogen production and *Lactobacillus* concentrations⁴² and antibacterial peptide secretions.⁴³

What are the Emerging Targets and Therapies In Urinary Tract Infections?

For the millions of females worldwide who live with the uncertainty of when their next debilitating UTI will strike, there is some hope. "Vaccine therapy is showing promise, although

as yet, the mechanism of action is not clearly understood," enthused Wagenlehner. Recent data is strong, said Fromer, who presented data from a trial of a sublingual vaccine of whole-cell inactivated bacteria (*E. coli*, *K. pneumoniae*, *E. faecalis*, and *P. vulgaris*).⁴¹ The study showed vaccination reduced the recurrence of UTIs at 9-months post-vaccination. Also encouraging, was that the time to first UTI post-vaccine was 275 days in the vaccine group, versus 48 days in the placebo group. Females also reported improved QoL.⁴¹ Fromer added: "Interestingly, all women had similar microbiota in their bladder, despite the reduction in UTIs, and the study authors suggest that the vaccine boosts local innate immune mechanisms that might be deficient in women who experience recurrent UTIs." Wagenlehner supported this viewpoint, suggesting that the host response to the bacteria might be more important in causing disease, rather than the bacteria themselves. "Sublingual vaccines help to boost the innate immune system and this might help to prevent severe disease," he surmised.

The panel also discussed the potential of bacteriophages to target and kill specific bacterial species, such as specific *E. coli* isolates and *Klebsiella*.⁴⁴ Wagenlehner explained that these are already available in Georgia as a 'cocktail' of bacteriophages, but are not sufficiently tested clinically. He suggested that there is still a lot of preclinical and clinical work to be done until bacteriophages might in future provide an alternative to antibiotics. Novel β -lactam and β -lactamase inhibitors are also currently being tested in clinical phases as oral treatments for patients with UTIs.⁴⁵

The panel also discussed novel antibiotics that are in the pipeline, such as Gepotidacin, which is currently in Phase III clinical development.^{46,47} New oral carbapenems, Tebipenem⁴⁸ and sulopenem,⁴⁹ are also under development for complicated UTIs and uUTIs, respectively. The speakers emphasised that these new antibiotics could be very helpful to patients who have uropathogens that are resistant to orally administered antibiotics. However, it will be important to ensure they are only used under appropriate antibiotic prescribing stewardship.

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NX-GBL-UTI-ADVR-220002
July 2022