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How the microbiome is influenced by the therapy of urological diseases: standard versus alternative approaches

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Abstract

Until recently the generally accepted paradigm implied that urine of healthy people is sterile. In the meantime several studies have established also a microbiome in the bladder with many different species. Whether bacteria cause damage in the bladder depends not only on their virulence, but also on the inflammatory response of the host. Under certain circumstances asymptomatic bacteriuria can even protect from recurrent urinary tract infections (UTI). Some bacteria in the gut microbiome, such as *Oxalobacter formigenes*, are protective for calcium oxalate stone formation. The rapid rise of bacterial antibiotic resistance also among uropathogens due to wrong and often unreflected use of antibiotics has become a great concern. Instead of combating the pathogens, it appears to be more useful in many cases to treat the inflammatory host reaction - and to preserve the protective bacterial flora. Due to its antiphlogistic, spasmolytic and antinociceptive properties in a pilot study the herbal triad combination - centaury, lovage, and rosmary leaves (CLR (Canephron® N (Bionorica SE, Neumarkt, Germany))) – showed very good results in the treatment of acute uncomplicated cystitis. In the meantime a phase 3 study with CLR in comparison with fosfomycin trometamol has started. Analysing microbiome profiles in mice showed that even a single dose of fosfomycin as well as daily application of nitrofurantoin resulted in massive microbiome shifts, whereas phytotherapy with CLR largely preserved the gut microbiota.

Keywords: Microbiome, Cystitis, Urinary tract infection, Phytotherapy

The urinary microbiome in healthy individuals

Based on enhanced urine culture techniques and sequencing of 16S rDNA amplicons it was found that urine of healthy sexually active men and women is not sterile under normal conditions, which is in contrast to the generally accepted paradigm [1–3]. In the study of Kogan et al. [1] it was shown that in men and women, the group of facultative aerobic bacteria (FAB) is dominated by clusters of coagulase-negative staphylococci and *Corynebacterium* sp., and the group of nonclostridial anaerobic bacteria (NCAB) in women is dominated by clusters of *Lactobacillus* sp. and *Peptococcus* sp., and among men by *Eubacterium* sp. This knowledge of normal microbial communities in urine may alter the standard diagnostic and therapeutic approaches to infectious and inflammatory diseases of the urogenital tract.

Review

Asymptomatic bacteriuria is normal

Since a high proportion of people are hosting bacteria in their urinary tracts, asymptomatic bacteriuria (ABU) is surprisingly common, which clearly should be differentiated from symptomatic urinary tract infection (UTI). Whether bacteria cause damage in the bladder depends not only on their virulence, but also on the inflammatory response of the host. The host and pathogens had developed a kind of peaceful coexistence in which both the virulence of the bacterial strain and the host response were downregulated. Colonization with specific strains of *E. coli* may even protect against symptomatic UTI episodes: In a placebo-controlled study, patients' bladder prone to recurrent UTI were instilled with the strain *E. coli* 83972 originally cultured from

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a patient with ABU. The study not only demonstrated how effective this treatment is, it also suggested that similar *E. coli* strains may also prevent virulent and antibiotic-resistant bacteria from infecting the urinary tract [4].

Pro or Con antibiotic treatment of asymptomatic bacteriuria?

To test this theory, Cai et al. [5, 6] compared two different approaches to treating women prone to recurrent UTI and showing ABU between symptomatic episodes. Patients were split into two groups: ABU of those in group A ($n = 257$) was not treated with antibiotics, while that of those in group B ($n = 293$) was. Group A showed a significant lower frequency of symptomatic UTI episodes than group B. Moreover *E. coli* strains from patients in group B showed significantly higher resistance rates to a range of antibiotics – including amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole and ciprofloxacin. Thus, treating ABU with antibiotics might even be harmful [7].

Siener et al. [8] investigated the role of Oxalobacter formigenes, an oxalate-degrading bacterium that colonizes the intestinal tract, in calcium oxalate stone formation. The study revealed that patients with O. formigenes in their gut microbiome had a significantly lower rate of stone recurrence. Furthermore, it showed that the absence of O. formigenes in patients prone to kidney stones is likely due to the use of antibiotics, implying that antibiotic treatment may increase the risk of calcium oxalate stone formation.

Antibiotic usage in acute urinary tract infections

Every second woman has an acute UTI at least once during her life, 30% of women suffer from recurrent cystitis. Main pathogens are uropathogenic *E. coli* from the adjacent intestinal tract. Thus, the acute uncomplicated cystitis (AUC) in the outpatient area is the most frequent reason for prescribing an antibiotic and urology is one of the specialties with the highest outpatient antibiotic prescriptions (Table 1).

Table 1 Antibiotic prescriptions for Outpatients in Germany in the Year 2014 [13]

Medical specialist	DDD[a] per medical specialist
ENT specialist	5563
Paediatrician	5533
Urologist	5309
Dermatologist	5243
General practitioner	5003
All medical specialists	2186

[a]defined daily dose

How widespread is antibiotic resistance?

The World Health Organization considers the rapid rise of bacterial antibiotic resistance among the three largest health problems worldwide. Wagenlehner [9] conducted a study in 2014 on antibiotic resistance in uropathogens like *E. coli*. It found that in Germany, 10–25% of *E. coli* was resistant to 3rd generation cephalosporin antibiotics, and 1–5% of *Klebsiella pneumoniae* showed even resistance to carbapenem antibiotics. The latter is particularly worrying, as carbapenem-resistant strains tend to be superbugs – i.e. they are often resistant to all available antibiotics.

The study concluded that:

- Antibiotic resistance is widespread in patients with UTI
- Many strains have developed multi-drug resistance
- The more severe the infection, the higher the level of resistance

The wrong and often unreflected use of antibiotics may be responsible for that. These findings raise the question whether routine antibiotic therapy for AUC can still be considered useful - notleast because of the high spontaneous cure rates, the low complication risk and the increasing bacterial resistance development.

Anti-inflammatory instead antimicrobial therapy

The better understanding of the host-pathogen interaction leads to completely new therapeutic approaches. For example, in the case of uncomplicated UTI, broad-spectrum antibiotics can be avoided and antiinflammatory drugs can be used. Instead of combating the pathogens, it appears to be more useful in many cases to treat the inflammatory host reaction - and to preserve the protective bacterial flora. This concept of "host tolerance" aims at a tolerance development of the host on the pathogen.

That antibiotics are not absolutely necessary to treat AUC in woman is demonstrated by a recent study comparing the symptom relief in AUC by an antiphlogistic drug, ibuprofen, with an antibiotic, fosfomycin. If the symptoms persisted or worsened, the patients of the ibuprofen arm could also switch to an antibiotic therapy. Nevertheless, two-thirds of women were able to be treated satisfactorily with anti-inflammatory therapy, only one in three women needed an antibiotic. On day seven, most patients were symptom-free. However, the symptoms in the fosfomycin group receded faster [10]. This study can be taken as proof of principles, but to search for better symptom-reducing drugs is still warranted.

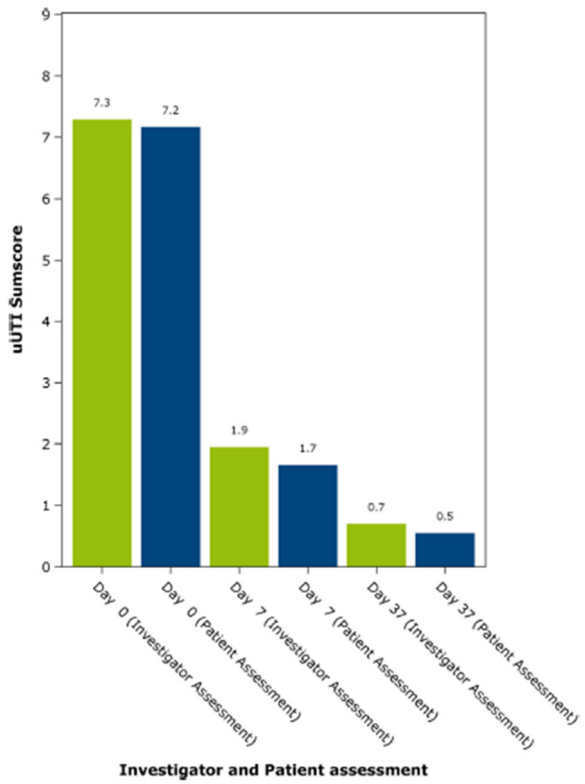

Fig. 1 Reduction of symptoms in female patients with acute uncomplicated cystitis (uUTI) treated with the phytodrug CLR for 7 days as assessed by patients and investigators [11]. The uUTI Sumscore includes the symptoms dysuria, frequency and urgency; uUTI Sumscore was assessed on Day 0, Day 7 and Day 37 (full analysis set, $N = 125$)

Multitarget phytotherapy

Multitarget phytotherapy may become relevant in the treatment of uncomplicated UTI. The herbal triad combination - centaury, lovage, and rosmary leaves (CLR[1]) - has been used for decades for the supportive treatment of acute and recurrent UTI. CLR shows a broad spectrum of pharmacological activity. In addition to antiphlogistic effects, acute spasmolytic and antinociceptive properties also play an important role in acute therapy. Burning during micturition and spasms in the lower abdomen diminish. Additional anti-adhesive effects can prevent adherence and penetration of bacteria into the bladder mucosa. All these findings support the faster elimination of the pathogens and protect against recurrent infection.

Promising pilot study

In an open pilot study of 125 women with AUC were treated with the phytodrug CLR for 7 days [11]. Also in this study a switch to an antibiotic therapy was possible if the symptoms persisted or increased. Under this therapy, the severity of symptoms dropped sharply. Cystitis-specific symptoms such as dysuria, pollakisuria, and urinary urgency were only mild or decreased completely on day seven in 71% of the patients. On average, herbal therapy reduced the symptom score by 74% from 7.3 to 1.9 points (Fig. 1). Almost all women (98%) did not need any antibiotic therapy. None of the successfully treated patients developed an early recurrence upto day 37. The therapy was very well tolerated by the study participants; no adverse events were registered. Currently CLR is being tested in a Phase III study comparing the herbal triad combination with the antibiotic fosfomycin in women with AUC.

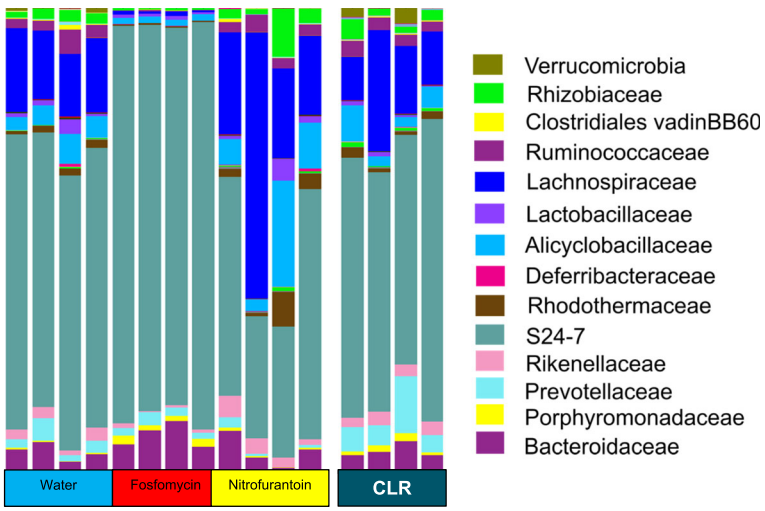

Fig. 2 Protection of microbiome with CLR in comparison to fosfomycin and nitrofurantoin after daily administration of CLR and antibiotics, respectively, by gavage in mice [12]

Microbiome preserving therapy

A further advantage of the symptomatic therapy with the herbal triple combination is the low collateral damage compared to the antibiotic therapy. Many side effects of the antibiotics are caused by shifts in the body's bacterial colonization, e.g. gastrointestinal complaints, allergies or fungal infections in the vaginal area. Detailed knowledge about this has only been possible using modern DNA sequencing methods, since many bacteria cannot be detected with conventional cultivation methods at all.

Gessner et al. [12] investigated the intestinal microbiome of mice that received either a single dose of fosfomycin, 7 days of nitrofurantoin, water as a substance-free vehicle, or two different doses of the phytocombination. While the therapy with fosfomycin or nitrofurantoin showed massive microbiomic shifts, the intestinal bacterial flora remained largely unaffected by the phytocombination. The alpha-diversity, a measure of the biodiversity of the bacteria, was found in the faeces of the phytotherapeutically treated mice on a level with the faeces of the mice, which had only received water (Fig. 2). This was even the case when the plant combination was administered in a tenfold higher human equivalent dosage - a finding consistent with the very good tolerability of CLR in the pilot study. The faeces of the nitrofurantoin-treated mice, on the other hand, were clearly outside the normal range. This difference was even more pronounced in the mice who received single dose therapy with fosfomycin. Some bacterial families had even completely disappeared.

Conclusion

As shown by clinical studies the paradigm of antibiotic therapy for treatment of AUC is obviously changing. Instead of combating the pathogens, it may be more useful to treat the inflammatory host reaction to avoid collateral damage by the antibiotic treatment on the healthy microbiome. In this regard phythotherapeutic options could play a more important role and should be investigated further in prospective randomized clinical studies.

Endnotes

[1]Canephron® N (Bionorica SE, Neumarkt, Germany)

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Author's contributions

KGN drafted the manuscript and all authors read and approved the manuscript.

Competing interests

The authors declare that they have no competing interest.

Disclosure

Kurt G. Naber: Investigator: Enteris Biopharma. Scientific Advisor (Review Panel or Advisory Committee): Bionorica, Enteris Biopharma, Helperby Therapeutics, Leo Pharma, MerLion, MSD Sharp&Dohme, OM Pharma, Paratek, Rosen Pharma, Zambon. Speaker's Bureau: Bionorica, DaiichiSankyo, Leo Pharma,OM Pharma, Rosen Pharma, Zambon.
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