New Treatment Strategies in Urinary Tract Infections

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Urinary Tract Infections (UTIs) are amongst the most prevalent bacterial infections, in the community as well as in the whole health-care system. Antimicrobial resistance of uropathogens is increasing worldwide [1-3]. Especially resistance of E. coli and other Enterobacteriaceae against trimethoprim/sulfamethoxazole, fluoroquinolones, 3rd generation cephalosporin, and even against carbapenems are of great concern. In addition the rates of resistance of non-fermentative Gram-negative bacteria, such as Pseudomonas spp. against fluoroquinolones and carbapenems have also increased [1-3]. Methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus spp. (VRE) are less frequent uropathogens, but they play an important role in hygiene issues in patients with health care associated UTI (HAUTI) [4]. Surveillance studies in complicated UTI/HAUTI are scarce. An ongoing, world-wide one day prevalence study monitoring infections explicitly in urological patients is the Global Prevalence Study of Infections in Urology (GPIU) performed by the European Section of Infections in Urology (ESIU) [5]. Since 2003 19,756 hospitalized patients were analyzed and in 1,866 of them HAUTI was reported. The resistance rates of most of the uropathogens against the antibiotics tested fluctuated usually around high average values without any significant trends of increase or decrease with Asia exhibiting the highest rates in general. The only antibiotic tested with an overall resistance rate below 10% was imipenem, representing the carbapenems. All other antibiotics had much higher overall resistance rates including so called broad-spectrum antibiotics like piperacillin/tazobactam, ciprofloxacin and gentamicin approaching 30 to 40% [6].

As the total antibiotic consumption in the community drives the selection pressure of antibiotic resistance, different strategies should be applied:

In benign, but very frequent infections, such as uncomplicated cystitis, strategies to avoid antibiotics either to treat acute episodes or to prevent recurrent episodes are currently investigated. Such strategies comprise antiinflammatory drugs, phytotherapeutics and immunostimulation. Approximately 40 to 60% of patients will profit of non-antibiotic treatment and therefore do not need antibiotics.

For antibiotic treatment of uncomplicated cystitis older antibiotics, such as fosfomycin, pivmecillinam and nitrofurantoin, have experienced a revival and are now included in many national and international guidelines [6,7]. Antibiotics with exclusive indication for this very frequent entity are also warranted in the future to be explored [6,7].

For the treatment of complicated UTI and HAUTI however, new antibiotics are urgently needed [8]. Analogues of substances of known antibiotic classes (fluoroquinolones, 3rd gen cephalosporins, beta lactamase-inhibitors, monobactams, aminoglycosides, and tetracyclines) are developed further. Compounds directed against novel bacterial targets, such as aminocycl-tRNA synthetase inhibitors, e.g. mupirocin, LpxC inhibitors, oligonucleotide therapeutics, peptidomimetics are currently investigated. However, new antibiotic substances can only become successful therapeutics for UTI, if they are largely eliminated by the kidneys in its active form.

Since bacterial growth and also antibacterial activity are very much depending on the milieu, pharmacokinetic/pharmacodynamics considerations directed to the urinary tract should be investigated already in phase one studies for better profiling new substances selected for clinical development [9].

There are some new analogues of known antibiotic classes evaluated also for the treatment especially of complicated UTI. However, given the high administration rate of antibiotics for treatment of UTI, several non-antibiotic treatment strategies should be further explored, in order to reduce antibiotic consumption at least in benign, non-severe infections, such as uncomplicated cystitis [10].

References

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