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НЕОБХОДИМОСТЬ НОВЫХ АНТИБИОТИКОВ В УРОЛОГИИ

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Инфекция мочевыводящих путей (ИМП) одна из самых распространенных бактериальных инфекций в обществе, а также во всей системе здравоохранения. Для лечения осложненной инфекции мочевыводящих путей обязательно необходимы антибиотики «нового» спектра действия. В связи с этим были предложены различные стратегии и новые антибактериальные препараты для лечения инфекции мочевыводящих путей. Однако, необходимо тщательнее изучить возможности терапии без использования антибиотиков, чтобы сократить их потребление, по крайней мере при доброкачественных, нетяжелых инфекциях, таких как неосложненный цистит.

Ключевые слова: инфекция мочевыводящих путей, осложненные инфекции мочевыводящих путей, новые антибактериальные средства, стратегии лечения без антибиотиков, нетяжелые инфекции.

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Background. 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 gen 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) may not account for the most frequent uropathogens, but they also play an important role in health care associated UTI (HAUTI) [4].

Needs for new treatment strategies in different cohorts of UTI. From a clinical point of view UTIs can be best classified into uncomplicated and complicated UTI [5]. Uncomplicated UTIs comprise uncomplicated cystitis and uncomplicated pyelonephritis. An uncomplicated UTI

is defined as an UTI without relevant structural and functional abnormalities within the urinary tract, without relevant kidney diseases, and without relevant comorbidities. Complicated UTIs on the other hand are very heterogenous entities, characterized by a common pattern of complicating factors such as anatomical, structural or functional alterations of the urinary tract (e.g. stents, obstruction, instrumentation of the urinary tract, stones, tumors, neurological disorders), impaired renal function, by parenchymal diseases, or pre,-intra,-or post renal nephropathies (e.g. acute, chronic renal insufficiencies, heart insufficiency), accompanying diseases or conditions that impair the patients immune status (e.g. diabetes mellitus, liver insufficiency, immunosuppression, cancer, AIDS, hypothermia) [5].

Surveillance studies on antimicrobial resistance should consider the different entities of UTI. In an international surveillance study on women with uncomplicated cystitis performed in nine European countries and in Brazil frequently used antibiotics such as ampicillin, cotrimoxazole, amoxicillin combined with clavulanic acid and cefuroxime showed resistance levels of 20 % or higher. Only fosfomycin, mecillinam, nitrofurantoin and ciprofloxacin had resistance rates below 10 %, although resistance to fluoroquinolones in some parts of the world is higher than 10 % already [6].

Sureveillance studies in complicated UTI/HAUTI are scarce. An ongoing, world-wide one day prevalence study monitoring infections explicitly in urological patiens is the Global Prevalence Study of Infections in Urology (GPIU) performed by the European Section of Infections in Urology (ESIU) [7]. From the period of 2003 to 2010, 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 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 % [7].

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

I) In more 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 and phytotherapeutics. Approximately 40 to 60 % of patients will profit of non-antibiotic treatment and therefore do not need antibiotics.

II) 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 [8, 9]. Antibiotics with exclusive indication for this very frequent entity are also warranted in the future to be explored [8, 9].

For the treatment of complicated UTI and HAUTI however, «new» antibiotics are urgently needed. Different strategies are followed in this respect [10]:

I) Substances of known antibiotic classes, such as fluoroquinolones, 3rd gen cephalosporins, betalactamase-inhibitors, monobactams, aminoglycosides, tetracyclines analogues are developed further.

II) Compounds directed against novel bacterial targets, such as aminoacyl-tRNA synthetase (aaRS) inhibitors, e.g. mupirocin, LpxC inhibitors, oligonucleotide therapeutics, peptidomimetics are investigated.

However, new antibiotic substances can only become successful therapeutics for UTI, if they are largely eliminated by the kidneys in 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 I studies for better profiling new substances selected for clinical development [11].

Novel antibacterial agents for the treatment of UTI

Aminoglycosides. ACHN-490 is the lead in a series of next-generation broad-spectrum aminoglycosides, known as neoglycosides for the treatment of infections caused by resistant Gram-negative bacterial pathogens and MRSA. In preclinical studies, ACHN-490 displayed efficacy against resistant strains of K. pneumoniae and E. coli and showed a high degree of activity against carbapenemase-expressing strains as well as against MRSA, including the VRSA, VISA and h-VISA subtypes. Phase 1 and phase 2 trials in bacterial infections are currently performed.

Beta-lactamase inhibitors. NXL-104 is a novel non-β-lactam class-A and -C β-lactamase inhibitor for use in combination with different β-lactam antibiotics developed in the treatment of nosocomial Gram-negative infections caused by pathogens including P. aeruginosa. In preclinical models NXL-104 and ceftazidime showed efficacy against enterobacteriaceae bearing CTX-M β-lactamases compared to ceftazidime alone. Combinations of NXL-104 with cephalosporins in general reduced the MICs of resistant Enterobacter and Klebsiella spp. more than 4-fold. Phase 2 and 3 trials are performed also in the indication of complicated UTI.

Cephalosporins. CXA-101 is a novel cephalosporin for the treatment of P. aeruginosa infections. In vitro, CXA-101 was 8-fold more stable against AmpC β-lactamase from P. aeruginosa than ceftazidime. Phase 2 and 3 trials are performed in the indication of complicated UTI.

CXA-201 is a combination of CXA-101, with a β-lactamase inhibitor, for the treatment of serious Gram-negative infections in hospitalized patients, also tested in the indication complicated UTI.

Carbapenem antibiotics. Sulopenem is a penem antibiotic for the treatment of hospital- and community-acquired pneumonia, complicated skin, intra-abdominal infections and complicated UTIs. It has activity against extended-spectrum β-lactamase Gram-negative strains and is tested in trials for different bacterial infections.

Fluoroquinolones. Finafloxacin is an oral fluoroquinolone more active in an acidic environment, while classical fluoroquinolones are more active in an alkaline milieu. A phase 2 trial is currently performed in complicated UTI.

Monobactams. BAL30072 is a novel siderophore dihydroxypyridone monobactam. Siderophores sequester iron from the surrounding medium and siderophore antibiotic conjugates are used to deliver antimicrobial agents into bacterial cells. BAL30072 is stable to beta-lactamases and metallo-carbapenemases and therefore shows potent in vitro activity against Gram-negative fermenters and non fermenters, including carbapenem-resistant Acinetobacter baumanii, P. aeruginosa, multiresistant Burkholderia spp., Stenotrophomonas spp., and multiresistant Enterobacteriaceae, including Klebsiella oxytoca, Proteus spp., Providencia spp. Serratia

marcescens, and E. aerogenes.Clinical phase 2 and 3 studies in the indication of complicated UTI are planned.

Conclusion. 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 [12].

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DO WE NEED NEW ANTIBIOTICS IN UROLOGY?

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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. For the treatment of complicated UTI and HAUTI however, «new» antibiotics are urgently needed. Different strategies and novel antibacterial agents for the treatment of UTI are suggested with this respect. However 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.

Keywords: Urinary tract infections, complicated infections of urinary tract, «new» antibiotics, non-antibiotic treatment strategies, non-severe infections

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