Current Anti-Infective Treatment of Bacterial Urinary Tract Infections

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Abstract: Antibiotic resistance nowadays plays an important role in the treatment of uncomplicated and complicated urinary tract infections (UTIs). In uncomplicated UTI efforts are made to use antibiotic substances exclusively for this indication. In complicated UTI substances with activity against bacteria harbouring common resistance mechanisms are investigated. Additionally pharmacokinetic/ pharmacodynamic parameters are used to improve dosing strategies.

Key Words: Urinary tract infections, uncomplicated UTI, complicated UTI, antibiotic resistance, pharmacokinetics, pharmacodynamics.

1. INTRODUCTION

Urinary tract infections (UTIs) are among the most prevalent microbial diseases, and their financial burden on society is substantial. UTIs account for more than 100,000 hospital admissions annually, most often for pyelonephritis [1, 2], and they also account for at least 40% of all hospital-acquired infections which are in the majority of cases catheter-associated [3-5].

2. UNCOMPLICATED, COMMUNITY ACQUIRED UTI

In uncomplicated UTI *E. coli* is the most common pathogen, typically being isolated from over 80% of outpatients with acute uncomplicated cystitis across the various regions of the world [2, 6-8]. In clinical practice urine culture is usually not performed in the setting of community acquired, uncomplicated cystitis. Antibiotic therapy therefore is mostly empiric and more or less based upon knowledge of national or international surveillance studies. The local resistance level of *E. coli* therefore determines the empiric antibiotic treatment. The range of pathogens associated with acute uncomplicated pyelonephritis is similar to that seen in acute uncomplicated cystitis [9].

In a surveillance study of urinary *E. coli* isolates from outpatient women in the United States, collected during the year 2000, the rates of ampicillin and TMP/SMX susceptibility (60% and 76%, respectively) were far lower than the incidence of susceptibility to ciprofloxacin (96%) [10, 11]. Similar findings were reported in the analysis of 16,745 *E. coli* isolates from female outpatients with UTI collected in the Pacific region of the United States in 2001 (ampicillin resistance: 38%; TMP/SMX resistance: 20%; ciprofloxacin resistance: 2%) [10, 11].

The ARESC Project, an international surveillance study involving 9 countries in Europe and Brasil, has monitored the antimicrobial susceptibility of uropathogens during September 2003 and June 2006. The aim of the study was to rank the present usefulness of drugs employed in the therapy of this condition [12]. 3018 uropathogens including 2315 *E. coli* (76.7%; range 75-85% in the different countries). 316 other Gram-negatives (10.5%) and 387 Gram-positives (12.8%) were collected. Susceptibility of *E. coli* was least common towards ampicillin (mean 45.1%; range 33-66%), cotrimoxazole (71%; 55-88%), cefuroxime (81%; 75-91%) and amoxicillin/clavulanic acid (81.8%; 52-94%). Ciprofloxacin susceptibility was 91.3% (87-98%) with the lowest figures for Italy, Spain and Russia (87-88%). Fosfomycin, mecillinam and nitrofurantoin were the most active agents (98.1%; 95.8% and 95.2% of susceptible *E. coli*) with no significant difference between the countries.

The results of these studies show that antibiotic substances classically used for the treatment of uncomplicated UTI, such as cotrimoxazole, fluoroquinolones or aminopenicillines, loose their effectiveness due to increasing resistance. Ideal substances are those with low resistance rates, exclusively used for this indication, such as fosfomycin tromethamine, nitrofurantoin or pivmecillinam (Table **1**).

i. Fosfomycin

Fosfomycin tromethamine is the oral applicable salt of fosfomycin. Fosfomycin (cis-(1R,2S)-epoxypropylphosphonic acid) is an oxirane antibiotic unrelated to other substances [13] and is produced as a secondary metabolite by *Streptomyces* and *Pseudomonas* spp. (S)-2-Hydroxypropylphosphonic acid epoxidase catalyzes the epoxide ring closure of (S)-2-Hydroxypropylphosphonic acid to form fosfomcyin in an iron-redox mechanism [14]. Interestingly hydroxypropylphosphonic acid epoxidase represents a new subfamily of non-haem mononuclear iron enzymes that respond to its substrates with a conformational change that protects the radical-based intermediates formed during catalysis [15]. Fosfomycin is active against Gram-positive and Gram-negative bacteria, but shows decreased activity against *M. morganii*, *P. vulgaris*, *P. aeruginosa* and *E. faecium*. Despite many years of usage, fosfomycin continues to be characterized by a low incidence of *E. coli* resistant strains (1% to 3%) worldwide [16]. Fosfomycin trometamol has retained its activity against quinolone-resistant strains of *E. coli* and cross-

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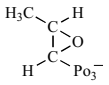
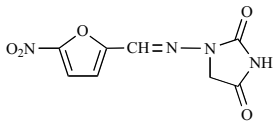
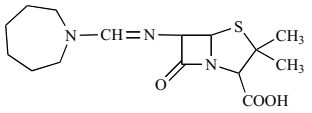
1389-5575/08 $55.00+.00

Table 1. Selected Compounds for the Treatment of Uncomplicated UTI.

Group	Substance	Chemical structure
---	---	
Fosfomycines	Fosfomycin	
Nitrofuranes	Nitrofurantoin	
Amidinopenicillin	Mecillinam	

resistance with other classes of antimicrobial agents is presently not a problem [17]. It is less active against coagulase-negative staphylococci. However, in a metaanalysis including 2,048 patients it has been shown that overall single dose therapy with fosfomycin trometamol exhibits equivalent results as short term therapy with comparative agents [18]. Fosfomycin tromethamine has approximately 40% oral bioavailability [19], urine recovery is approximately 40% [20].

ii. Nitrofurantoin

Nitrofurantoin belongs to the nitroheterocyclic compounds. The nitrogroup coupled onto the heterocyclic furan ring represents the proper site of effect. The nitrogroup is inactive and has to be activated by microbial nitroreductases after penetration into the microbial cell [21]. Nitrofurantoin interferes with the carbohydrate metabolism. The antibacterial activity is generally weak, but in the urine the activity against *E. coli* and some other enterobacteria like *Klebsiella* spp., *Enterobacter* spp. is sufficient in the treatment of uncomplicated UTI. There is no activity against *Proteus* spp. or *P. aeruginosa*. Low levels of resistance to nitrofurantoin among uropathogens (*E. coli* < 2%) has revived interest in this agent. In a multicenter clinical trial single-dose fosfomycin tromethamine was compared with a 7-day course of nitrofurantoin for the treatment of acute uncomplicated cystitis in female patients. Both treatment groups had an 80% overall clinical success rate (cure and improvement) and an approximately 5% adverse effect related to study medication [22]. Therefore in women with risk factors for infection with resistant bacteria, or in the setting of a high prevalence of TMP-SMX-resistant uropathogens, nitrofurantoin can also be used. It´s use for the empiric treatment of uncomplicated cystitis is supportable from a public health perspective in an attempt to decrease uropathogen resistance because it does not share cross-resistance with more commonly prescribed antimicrobials [7], but short term therapy is not well established with nitrofurantoin [2]. It is also less active against Gram-negative pathogens other than *E. coli*. The urinary excretion is 40%, most of the rest is converted to inactive metabolites [20].

In a multicenter clinical trial single-dose 3-gramms fosfomycin tromethamine was compared with a 7-day course of 100 mg nitrofurantoin monohydrate/ macrocrystal for the treatment of acute uncomplicated lower urinary tract infection (UTI) in female patients [22]. 749 patients were enrolled in the study (375 received fosfomycin and 374 received nitrofurantoin). Overall, 94% of pretreatment isolates were susceptible to fosfomycin and 83% were susceptible to nitrofurantoin. Bacteriologic cure rates at 5 to 11 days after initiation of treatment were 78% and 86% for fosfomycin and nitrofurantoin, respectively (P = 0.02). One week posttreatment they were 87% and 81% for fosfomycin and nitrofurantoin, respectively (P = 0.17). Clinical success rate (cure and improvement) was higher than 80% in both treatment groups. Therefore bacteriologic and clinical cure rates were comparable in both treatment groups [22].

iii. Pivmecillinam

Pivmecillinam is a unique beta-lactam antimicrobial that has been used for the treatment of acute uncomplicated urinary tract infection for more than 20 years. Pivmecillinam is the pro-drug (ester) of mecillinam with specific and high activity against Gram-negative organisms such as *E. coli* and other Enterobacteriaceae. Mecillinam is an amidine derivative of the penicillin group. Pivmecillinam is also well absorbed orally [23].

Since its introduction, it has been widely used for the treatment of acute uncomplicated cystitis, primarily in the Nordic countries. The level of resistance has remained low, approximately less than 2% of *E. coli* community isolates are resistant to mecillinam [24]. A comparative study (pivmecillinam versus norfloxacin) has shown similar outcomes with 7 days of pivmecillinam 200 mg bd or 3 days of norfloxacin 400 mg bd, when pooling bacteriological outcomes from two studies [25]. The *in vitro* MIC for *S. saprophyticus* is 8-64 mg/L, so these bacteria are considered resistant. However the cure rates for this organism were reported between 73% and 92%. Pivmecillinam therefore can be considered effective also for treatment of cystitis caused by *S. saprophyticus* [25].

Nicolle *et al.* evaluated the efficacy of a three day regimen of pivmecillinam 400 mg b.i.d. versus norfloxacin 400 mg b.i.d. in 954 premenopausal women with symptoms of acute cystitis [26]. Bacteriologic cure at early post-therapy follow-up was achieved in 75% pivmecillinam patients and

91% norfloxacin patients (P < 0.001). Clinical cure/improvement four days following initiation of therapy was observed in 95% women who received pivmecillinam and 96% who received norfloxacin (P = 0.39). In women younger than 50 years, early clinical cure rates were 84% for pivmecillinam and 88% for norfloxacin (P = 0.11). Adverse effects were similar for both regimens, and there was no evidence of the emergence of increasing resistance with therapy. The authors concluded that short-course therapy with norfloxacin was superior to that with pivmecillinam in terms of bacteriologic outcome, however clinical outcome in young women was comparable [26].

3. COMPLICATED AND NOSOCOMIALLY ACQUIRED UTI

Gram-negative species account for approximately 60 to 80% of the bacterial spectrum of complicated and nosocomially acquired UTI and comprise *E. coli*, followed by *Klebsiella* spp., *Pseudomonas* spp., *Proteus* spp., *Enterobacter* spp. and *Citrobacter* spp.. The Gram-positive pathogens account for about 15 to 30% of the spectrum and comprise enterococci and staphylococci [27-32].

Nosocomial uropathogens are frequently subject to antibiotic pressure and cross-infection. Different species of uropathogens show distinct abilities to develop antibiotic resistance.

Surveillance studies such as the SENTRY-, ESGNI- or PEP study, or a local urological surveillance study revealed that, considering the total bacterial spectrum investigated, in general the aminopenicillins (with beta-lactamase inhibitors) showed resistance rates of approximately 60% (respectively 30%). TMP/SMZ showed resistance rates between 22 to 45%. Resistance to ciprofloxacin was approximately 20 to 40%, to gentamicin 18 to 34%, to ceftazidime 13 to 28%, to piperacillin/ tazobactam 8 to 15%, to imipenem 7 to 14%. Resistance in enterococci to vancomycin was between 0 to 5% [27-32]. It has convincingly been shown that severe infections have lower mortality rates, when the empiric therapy has initially covered all causative bacteria [33, 34]. This has been confirmed in a small study for bacteremic UTIs as well [35]. As a result, broad spectrum antimicrobial agents are increasingly launched in clinical studies.

In all the studies increasing rates of antibiotic resistance were found with specific species like *E.coli, P. aeruginosa*, *Klebsiella spp., Enterobacter spp.*, enterococci and coagulase negative staphylococci. Extended-spectrum β-lactamase producing *E. coli* and *K. pneumoniae* rapidly increase and may cause significant clinical problems in the treatment of UTI [36, 37]. Species producing chromosomally encoded β-lactamases, although from the hygienic point of view regarded not as dangerous as plasmid encoded β-lactamases, also pose significant clinical problems for empiric antibiotic therapy. Carbapenems still retained their activity in most of these uropathogens (Table **2**).

i. Carbapenems

Carbapenems however are mainly available only intravenously up to now, because they are unstable, especially in gastric juice or intestinal juice. The available carbapenems are currently classified by different criteria. The classification by groups can follow the bacterial spectrum as in other antibiotic classes (Table **2**) [38]. According to that ertapenem is the sole representative of the first group and imipenem and meropenem are the representatives of the second group, which are currently licensed in Europe. Carbapenems are active against Gram-positive and Gram-negative pathogens, as well as anaerobic pathogens. Carbapenems maintain antibacterial efficacy against the vast majority of β-lactamase-producing organisms. This stability against serine-β-lactamases is due to the trans-1-hydroxyethyl substituent and its unique juxtaposition to the β-lactam carbonyl group [39]. The stability encompasses extended spectrum-β-lactamases and AmpC β-lactamases, however it does not extend to metallo-β-lactamases.

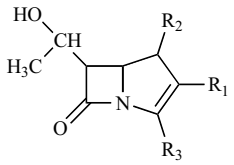
The group one parenteral carbapenem ertapenem has good Gram-negative activity, excluding *P. aeruginosa*. It is also not active against MRSA and enterococci. It contains a 1β-methyl substituent which reduces hydrolysis of the β-lactam group by the renal dihydropeptidase I. It further contains a meta-substituted benzoic acid substituent, which increases the molecular weight and lipophilicity of the substance, and a carboxylic acid moiety resulting in a net negative charge. This results in a high protein binding, which leads to a longer serum half-life [39]. Urinary excretion is approximately 80% [20].

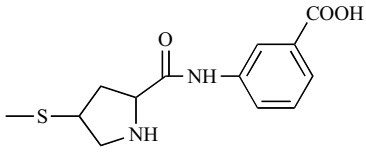
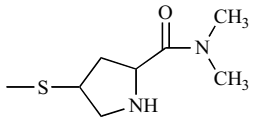
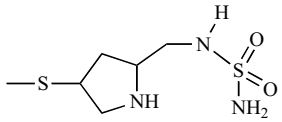
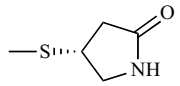
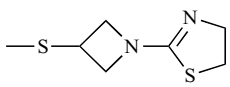
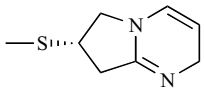
Group two parenteral carbapenems include imipenem and meropenem. They are active against many Gram-positive and Gram-negative uropathogens excluding MRSA, *E. faecium* and VRE. Imipenem is hydrolysed by the renal dihydropeptidase I and is therefore combined with the specific inhibitor cilastatin. Urinary excretion of the active imipenem is about 70%, if combined with cilastatin. Meropenem contains the 1β-methyl-substituent and is therefore stable against the renal dihydropeptidase I. Compared with imipenem, it is somewhat more active against *P. aeruginosa*, but less active against Gram-positive uropathogens. The urinary excretion of the active substance is 70% [20].

Doripenem is a new parenteral carbapenem and offers slightly more activity than meropenem against selected pathogens including some but not all strains of *P. aeruginosa* not susceptible to imipenem or meropenem. Doripenem is also active against Gram-positive pathogens except MRSA, *E. faecium* and VRE. Urinary excretion is 75% and therefore it is of potential interest for the treatment of complicated UTI [40]. A large, multinational phase 3 study evaluated the efficacy and safety of doripenem for the treatment of complicated lower UTIs and pyelonephritis (complicated and uncomplicated) and compared it to levofloxacin [41]. A total of 753 patients were randomized. The microbiologic cure rate in the test of cure population was 82.1% for doripenem and 83.4% for levofloxacin. The clinical cure rate in the test of cure population was 95.1% for doripenem and 90.2% for levofloxacin. Doripenem was microbiologically and clinically effective and therapeutically non-inferior to levofloxacin in this study for the treatment of complicated UTIs and was generally safe and well-tolerated [41].

Orally active 1β-methylcarbapenems are undergoing preclinical or clinical trials since some years [42]. Faropenem is currently the only oral carbapenem in clinical use in Japan.

Table 2. Pharmacophore and Structures of Carbapenems in Clinical use and Development for the Treatment of UTI



Group	Substance	R1	R2	R3
Carbapenem group 1	Ertapenem		CH_3	COOH
Carbapenems group 2	Imipenem	$-S-CH_2-CH_2-NH-CH=NH$	H	COOH
	Meropenem		CH_3	COOH
Intravenuous carbapenems in clinical trials	Doripenem		CH_3	COOH
Oral carbapenems in preclinical-clinical trials	CS-834		CH_3	$CO_2CH_2OCOC(CH3)_3$
	L-084		CH_3	$CO_2CH_2OCOC(CH3)_3$
	DZ-2640		CH_3	$CO_2CH_2OCOC(CH3)_3$

Other drugs, especially the substances CS-834, L-084 and DZ-2640 have been selected for further investigation [42].

CS-834 from Sankyo is the orally active prodrug of the substance R-95867. The substance is active against Gram-positive and Gram-negative species, such as *S. aureus*, *E. coli* and *K. pneumoniae*, but is less active against *Pseudomonas* spp. and *Enterococcus* spp. [43]. The 24h cumulative renal excretion into the urine in healthy volunteers ranged from 27 to 34% [42].

L-084 was developed by Wyeth and is the orally active prodrug of L-036. This substance exhibits excellent antibacterial activity against gram-positive and gram-negative species with the exception of *P. aeruginosa*. The cumulative urinary recoveries in volunteers within 24h ranged from 54 to 73% [42].

DZ-2640 from Dai-ichi group exhibits broad antibacterial activity except for *P. aeruginosa*. The cumulative renal recoveries in volunteers ranged between 32 to 45% [42].

Urinary excretions of the oral carbapenems are certainly not optimal, however still in the intermediate range. Nevertheless exaggerated consumption of carbapenems in the future most certainly will also lead to the emergence of antibiotic resistance and multiresistant pathogens.

7. FUTURE STRATEGIES IN THE TREATMENT OF BACTERIAL UTI

Bacteria exhibit an enormous repertoire of different resistance mechanisms. Unspecific mechanisms such as reduced permeability or efflux alter the tolerance to antibiotic substances less than specific mechanisms, such as inactivation of the antibiotic for example. However the antibiotic spectrum targeted is much more extensive. On the other hand unspecific mechanisms can also be induced by non antibiotic substances such as salicylates. Low-level resistance can thus be confered and give bacteria a selection-advantage [44]. To counteract these factors anti-infective substances are continuously evaluated and investigated. The current research goals in medicinal chemistry comprise the following targets:

- known substances are improved in terms of higher bioavailability, longer half life, better PK/PD performance, other formulations (i.e. extended/ gastric release formulation; liposomal formulation).
- new derivatives of known substance classes are developed in order to enlarge the bacterial spectrum, improve bioavailability, improve antimicrobial action (i.e. younger generation substances).
- new strategies to improve susceptibility of bacteria are developed (i.e. efflux-pump inhibitors) and to slow down the emergence of antimicrobial resistance are developed.
- alternative strategies such as bacteriophages, bacteriophage enzymes or vaccination are investigated. Bacteriophages or bacteriophagal enzymes [45, 46] have shown very interesting *in vitro* results. The further development might be promising, because these strategies involve highly conserved evolutionary mechanisms that have proven to be efficacious in nature over millions of years. However clinical application still seems to be far away.

What parameters should be assessed for new drugs to become included in the treatment of UTI? Although there are no exact quantitative prerequesites, the following qualities should be considered:

- coverage of the respective bacterial spectrum (uncomplicated versus complicated UTIs)
- antimicrobial activity in urine in an acidic as well as alkaline environment
- sufficient urinary excretion of the drug

CONCLUSION

The most important draw-back in the treatment of UTIs is the development of antimicrobial resistance. Therefore the action of current available antimicrobial substances and the structure-property relationships have to be understood for the prudent use of antibiotics. Pharmacokinetic and pharmacodynamic parameters are increasingly used to improve dosing strategies of the current anti-infective agents and guide the development of new derivatives and new agents for treatment of UTIs. Models that are able to predict efficacy in patients and the degree of emergence of resistance are needed in that respect. New treatment strategies are needed in order to maintain effective treatment of UTIs. There are a number of new derivatives of classes in use. In most cases these derivatives are subject to cross resistance inherent to the whole substance class. Therefore new classes of antibiotics with unrelated mode of action are a more valuable development. The indications for treatment of such novel substances should be selected very carefully, in order to conserve new substance classes as long as possible. For a variety of reasons however new substance classes will be increasingly difficult to launche. Therefore new derivatives of classes in use should be thoroughly screened for their potential to induce resistance. Substances with a low potential will be highly welcome. Very important in that respect will be combinatory agents that impede general widespread mechanisms of resistance, such as efflux pump inhibitors.

The ongoing process in the treatment of infectious diseases is highly dynamic. The substantial difference to non-infectious diseases is that the management of an infection in a single patient allways has an effect on the environment. Considering this, the management of infectious diseases must be highly responsible.

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Received: 10 July, 2007 **Revised: 31 December, 2007** **Accepted: 01 January, 2008**