Review - Infections

Treatment of Bacterial Urinary Tract Infections: Presence and Future

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1. Background

Urinary tract infections (UTIs) are among the most prevalent microbial diseases, and their financial burden on society is substantial.

In the United States of America, UTIs are responsible for over 7 million physician visits annually, including more than 2 million visits for cystitis [1,2]. Approximately 15% of all community-prescribed antibiotics in the United States are dispensed for
UTI, at an estimated annual cost of over $1 billion [3]. Furthermore, the direct and indirect costs associated with community-acquired UTIs in the United States alone exceed an estimated $1.6 billion [2].

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 and are in the majority of cases catheter-associated [4–6]. Nosocomial bacteriuria develops in up to 25% of patients requiring a urinary catheter for ≥7 days, with a daily risk of 5% [6]. It has been estimated that an episode of nosocomial bacteriuria adds $500 to $1,000 [7,8] to the direct cost of acute-care hospitalization. In addition the pathogens are fully exposed to the nosocomial environment, including selective pressure by antibiotic or antiseptic substances. Therefore nosocomial UTIs comprise perhaps the largest institutional reservoir of nosocomial antibiotic-resistant pathogens [6].

Whereas community acquired UTIs are often uncomplicated, almost all nosocomial UTIs are complicated infections. Complicated UTI is a very heterogenous entity, with a common pattern of the following complicating factors:

- anatomical, structural or functional alterations of the urinary tract (e.g. stents, urine transport disturbances, 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, that impair the patients immune status (e.g. diabetes mellitus, liver insufficiency, immunosuppression, cancer, AIDS, hypothermia).

For antimicrobial chemotherapy the bacterial spectrum, it's antimicrobial resistance patterns and the development of both over the time is critical for an effective chemotherapy.

The prevalence of uropathogens is different comparing uncomplicated and complicated UTI.

### 2. Aims in the treatment of UTI

There are two predominant aims in the treatment of both uncomplicated and complicated UTIs:

(i) rapid and effective response to therapy and prevention of recurrence in the individual patient treated.

(ii) prevention of emergence of resistance to chemotherapy in the microbial environment or at least prevention of further increase of resistance.

#### 2.1. Current treatment and prophylaxis of UTI

Two major strategies currently exist in the pharmacological treatment and prophylaxis of UTIs:

(i) Antimicrobial chemotherapy and

(ii) Vaccines.

#### 2.1.1. Chemotherapy

The currently recommended chemotherapeutic classes and dosages of antimicrobics for the treatment of bacterial UTI are listed in Table 1. The target and mechanism of actions of chemotherapeutic drugs is shown in Fig. 1.

Antimicrobial susceptibility levels are often gauged relative to what antibiotic concentration is achievable in the blood. However tissue levels in renal parenchyma, the deeper layer of the urinary bladder wall or in the prostate may be more relevant in the treatment of UTI. Because these concentrations are difficult to assess in humans, urinary concentrations or antimicrobial activity levels in the urine are frequently consulted to evaluate the activity of an antibiotic substance in the treatment of UTI [9]. The urinary excretion and the determination of the activity of a substance in urine is therefore important to assess if a substance is suitable for treatment of UTI. The urinary excretion of fluoroquinolones for example differs widely between substances. A high urinary excretion...
(≥75%) can be observed with gatifloxacin (80%), levofloxacin (84%), lomefloxacin (75%) and ofloxacin (81%). An intermediate excretion rate (40–74%) is seen with ciprofloxacin (43%), enoxacin (53%), fleroxacin (67%), and a low excretion rate (<40%) is seen with gemifloxacin (28%), moxifloxacin (20%), norfloxacin (20%), pefloxacin (14%) and sparfloxacin (10%) [9]. Whereas most of the drugs with high or intermediate excretion achieved the clinical indication for the treatment of UTI, of the drugs with low excretion only the older substance norfloxacin achieved this indication, possibly because of the lack of comparator substances at these days. The newer fluoroquinolone substances gemifloxacin and moxifloxacin both have passed phase III UTI studies with the comparator agents ciprofloxacin, ofloxacin or levofloxacin with generally unsatisfying results (data on file Bayer Healthcare, SmithKline Beecham). As a result of these studies the indication for the treatment of UTI in both substances was not achieved up to date. Therefore both pharmacokinetic parameters, serum concentration and urinary excretion are currently used to evaluate if an antibiotic substance might be suitable for the treatment of UTI.

## Table 1 – Groups and dosages of current chemotherapeutics for the treatment of UTI in adults

<table>
<thead>
<tr>
<th>Antibiotic groups</th>
<th>Antimicrobial substance</th>
<th>Daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-lactams</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mecillinam</td>
<td>Pivmecillinam</td>
<td>2 × 200−400 mg</td>
</tr>
<tr>
<td>Aminopenicillin + BLI</td>
<td>Ampicillin/Sulbactam</td>
<td>2 × 200 mg</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid</td>
<td></td>
<td>3 × 250−500 mg</td>
</tr>
<tr>
<td>Acylureidopenicillin + BLI</td>
<td>Piperacillin/Tazobactam</td>
<td>3 × 2.5−4.5 g</td>
</tr>
<tr>
<td>Cephalosporin Gr. 1</td>
<td>Cephalexin</td>
<td>for prophylaxis only</td>
</tr>
<tr>
<td>Cephalosporin Gr. 2</td>
<td>Cefuroxime axetil</td>
<td>2 × 0.75−1.5 g</td>
</tr>
<tr>
<td>Cephalosporin Gr. 3</td>
<td>Cefuroxime</td>
<td>2 × 3−1.2 g</td>
</tr>
<tr>
<td>Cefotiam</td>
<td></td>
<td>3 × 0.75−1.5 g</td>
</tr>
<tr>
<td>Cephalosporin Gr. 3a</td>
<td>Cefotaxime</td>
<td>2 × 3−1.2 g</td>
</tr>
<tr>
<td>Cephalexin</td>
<td></td>
<td>1 × 1 g</td>
</tr>
<tr>
<td>Cefixime</td>
<td>1 × 0.5−1 g</td>
<td></td>
</tr>
<tr>
<td>Ceftibuten</td>
<td>1 × 0.5−1 g</td>
<td></td>
</tr>
<tr>
<td>Cephalosporin Gr. 3</td>
<td>Cefpodoxim proxetile</td>
<td>2 × 200 mg</td>
</tr>
<tr>
<td>Carbenem Gr. 1</td>
<td>Cefixime</td>
<td>2 × 500−750 mg</td>
</tr>
<tr>
<td>Carbenem Gr. 2</td>
<td>Ceftizidime</td>
<td>1 × 2.2 g</td>
</tr>
<tr>
<td>Carbenem Gr. 4</td>
<td>Cefepime</td>
<td>2 × 2 g</td>
</tr>
<tr>
<td>Carbapenem Gr. 1</td>
<td>Ertapenem</td>
<td>1 × 1 g</td>
</tr>
<tr>
<td>Carbapenem Gr. 2</td>
<td>Imipenem</td>
<td>3 × 4.0 mg</td>
</tr>
<tr>
<td>Carbapenem Gr. 3</td>
<td>Meropenem</td>
<td>3 × 0.5−1 g</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Norfloxacin</td>
<td>2 × 0.5−1 g</td>
</tr>
<tr>
<td>Fluoroquinolone Gr. 1</td>
<td>Ciprofloxacin</td>
<td>2 × 400 mg</td>
</tr>
<tr>
<td>Fluoroquinolone Gr. 2</td>
<td>Levofloxacin</td>
<td>1 × 0.75−1.5 g</td>
</tr>
<tr>
<td>Fluoroquinolone Gr. 3</td>
<td>Gatifloxacin</td>
<td>1 × 0.5−1 g</td>
</tr>
<tr>
<td>Fluoroquinolone Gr. 4</td>
<td></td>
<td>1 × 0.5−1 g</td>
</tr>
<tr>
<td>Pyrimethamines</td>
<td>Trimethoprim</td>
<td>2 × 200 mg</td>
</tr>
<tr>
<td>Trimethoprim + Sulfamethoxazole</td>
<td>2 × 160 mg + 2 × 800 mg</td>
<td></td>
</tr>
<tr>
<td>Fosfomycines</td>
<td>Fosfomycin</td>
<td>1 × 3 g</td>
</tr>
<tr>
<td>Nitrofurans</td>
<td>Nitrofurantoin</td>
<td>3 × 100 mg</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Gentamicin</td>
<td>1 × 5−7 mg/BW</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>Tobramycin</td>
<td>1 × 5−7 mg/BW</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Linezolid</td>
<td>2 × 600 mg</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Vancomycin</td>
<td>2 × 1000 mg</td>
</tr>
<tr>
<td>Glycopeptide</td>
<td>Teicoplanin</td>
<td>1 × 400 mg</td>
</tr>
</tbody>
</table>

BLI – beta-lactamase inhibitor; Gr. – group according to PEG [31]; BW – body weight (kg); ‘recommended for uncomplicated UTI.
The main drawback of current antibiotic therapies is the emergence and rapid increase of antibiotic resistance [10]. Since antibiotics have been introduced into clinical medicine, antibiotic resistant bacteria have evolved [11]. Antibiotic resistance mechanisms have recently been alluded to in the European Urology Update Series 2, 2004, page 125–135 [10]. The overall cause of increasing antibiotic resistance is selective pressure by antimicrobial substances in various environmental settings causing antibiotic resistant bacterial clones, followed by the distribution of such clones facilitated by modern medico-social circumstances [10]. The development of new antimicrobial substances in the past has counterbalanced this trend. However we are currently approaching a resistance level that might pose a risk to loose effectiveness of antibiotic treatment in the future. The epidemiology of antibiotic resistant bacteria varies with type of infection, with medical speciality, with region, and with time.

2.1.2. Vaccines
There are two different agents for immunisation currently available: Uro-vaxom* and Strovac*. Both preparations are recommended for patients with recurrent uncomplicated UTIs.

Uro-vaxom* is an orally administered bacterial extract consisting of immunostimulating components derived from 18 uropathogenic E. coli strains [12]. A metaanalysis on five placebo controlled, double-blind studies comprising 601 women resulted in a pooled odds ratio of 2.28. UTIs per year were reduced from 1 to a rate of 0.15–0.82 [13]. In a multicenter, double-blind study 453 female patients were enrolled and Uro-vaxom* resulted in a 34% reduction of UTIs in patients compared to placebo [14]. Therefore the oral immunotherapy with Uro-vaxom is effective in the prevention of recurrent UTI. Nevertheless a metaanalysis showed that if antibiotic prophylaxis was compared with placebo the reduction of recurrent UTIs was 81% with antibiotics compared to placebo [15]. Unfortunately there are no data comparing Uro-vaxom* with antibiotics in the prevention of recurrent UTI.

Strovac* is a whole cell bacterial extract derived from uropathogenic E. coli strains, P. mirabilis, M. morganii, K. pneumoniae and E. faecalis. The preparation is administered intramuscularly also for prevention of recurrent UTI. In an prospective, comparing study 41 patients with recurrent uncomplicated UTI were evaluated. The rate of reinfecions within 6 months was 41% in patients treated with SulcoUrovac* versus 96% in patients receiving placebo [16]. Follow-up studies, however should be carried out.

2.1.3. Probiotics
The use of probiotics entails prophylaxis and treatment of UTI and is mainly concentrated on Lactobacilli. Conflicting results have been observed in clinical trials and animal studies mostly because unspecific strains of Lactobacilli have been used. Positive results have only been obtained using well characterized strains [17]. Application for prophylaxis can be intravaginal or oral. For treatment probiotics were mainly installed into the bladder.

Clinical studies using vaginally administered Lactobacillus rhamnosus GR1 in combination with either L. reuteri B 54 or RC 14 resulted in reduced UTI recurrences. In one study of 52 women, UTI recurrences were reduced from an average of 6 per year to 1.6 with once weekly vaginal suppositories of GR-1/B-54 [18].

A clinical randomized, placebo controlled study of 64 women using daily oral intake of L. rhamnosus GR-1 and L. reuteri RC-14 led to a significant reduction in uropathogens and yeast in the vagina [19]. It can possibly be concluded from such findings that UTI might also be preventable by oral intake of specific lactobacilli.

Few studies have shown positive results in the treatment of UTI by probiotics. One such animal study showed that after therapeutic application of Lactobacillus murinus bladder counts of treated mice were significantly lower although no significant differences were detected in P. mirabilis kidney colonisation of treated and non-treated animals [20].

3. Future strategies in the treatment of bacterial UTI
The current research goals 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).
- known substances are evaluated for other indications (i.e. UTI).
- 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 substance classes which should have new molecular targets are developed.
- new strategies to improve susceptibility of bacteria are developed (i.e. efflux-pump inhibitors).
- new strategies to slow down the emergence of antimicrobial resistance are developed.
- alternative antimicrobial substances are under discovery (e.g. bacteriophages, bacteriophage enzymes).
- new compounds for vaccination in uncomplicated, and possibly as well as in complicated UTI are developed.

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 conferred and give bacteria a selection-advantage [10].

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

3.1. Emerging chemotherapeutics

Emerging compounds are discussed in Table 2 regarding the following parameters: Substance, class, mode of action, bacterial spectrum, pharmacokinetics with emphasis on urinary excretion, opinion about success. The target and mechanism of actions of future chemotherapeutic drugs are shown in Fig. 1.

3.2. Emerging novel strategies

Bacteriophage lytic enzymes are highly evolved molecules produced by bacterial viruses to digest the bacterial cell wall for bacteriophage progeny release [21]. These enzymes have been used successfully in animal models to treat bacterial infections in blood and mucosal surfaces. Phages or their enzymes are very specific for the pathogen without disturbing the normal flora. These novel antimicrobial strategies have shown very interesting in vitro results [22,23]. The further development might be promising, because this strategy involves highly conserved evolutionary mechanisms that have proven to be efficacious in nature over millions of years.

3.3. Emerging vaccines

Vaccination theoretically is the best strategy to prevent bacterial infections. There are however some pitfalls in the vaccination against UTIs: Complicated UTIs show a highly heterogenous bacterial spectrum. In uncomplicated UTIs E. coli is the predominant pathogen. However infections and recurrent infections are usually caused by a variety of E. coli strains.

All uropathogenic E. coli as a common feature have a FimH-chaperone-adhesin on the tip of their type 1 fimbrae. A FimH adhesion-based vaccine, which showed promising results in animal and in vitro studies [24,25], so far could not enter larger vaccination trials in humans.

A somewhat different approach is made by using a vaginal vaccine containing 10 heat killed uropathogenic bacteria. A placebo-controlled phase II clinical trial was performed in 54 women. Women receiving immunisation experienced an infection in 45%, whereas the placebo treated women experienced an infection in 89% [26]. Based on this result vaginal mucosal vaccine seem to be effective.

P. mirabilis is a difficult to treat pathogen causing complicated UTIs especially in patients with permanent catheters or stents. The urease produced by this organism leads to stone formation and catheter blockage. The primary surface antigen is the MR/P fimbra is a good candidate for vaccination. In vitro studies with a MrpH vaccine showed promising results [27].

4. Prevention of emergence of antibiotic resistance

The most important draw-back in the treatment of UTIs is the development of antimicrobial resistance. The prevention of emergence of resistance in human medicine entails several strategies:

- decrease of antibiotic consumption
- antibiotic cycling
- new dosing strategies for antibiotics
- combination of two classes of antibiotics

All strategies not specifically designed for antimicrobial therapy of UTI may have to be adjusted accordingly.

4.1. Decrease of antibiotic consumption

To lower antibiotic consumption in UTI three strategies are developed and are evidence based by several good clinical studies: (i) asymptomatic
Table 2 - Emerging compounds are discussed regarding substance-name, antibiotic class and characteristics (mode of action, bacterial spectrum, pharmacokinetics with emphasis on urinary excretion, opinion about success)

<table>
<thead>
<tr>
<th>Antibiotic substance</th>
<th>Antibiotic class</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daptomycin (intravenous)</td>
<td>Lipopetide-antibiotic</td>
<td>Exerts its antibacterial activity by disrupting multiple aspects of the bacterial membrane function. Specific activity against Gram-positive pathogens including MRSA and VRE, not active against Gram-negative bacteria. Urinary excretion is 78%. Clinically relevant toxicities are limited to skeletal muscle effects, at higher dose levels, peripheral nerve effects. The high urinary excretion promises activity in UTI, however the large molecule might hinder distribution into urinary tract tissues. The specific Gram-positive activity restricts the substance to treatment of a relative small proportion of UTIs [32–37].</td>
</tr>
<tr>
<td>Tigecycline (intravenous)</td>
<td>Glycycline</td>
<td>Exerts its antibacterial activity by inhibiting protein synthesis. Good activity against Gram-positive pathogens including MRSA and VRE, and against E. coli, Klebsiella spp., Enterobacter spp. and C. freundii, including ESBL producing organisms. Less active against P. aeruginosa, Proteus spp., M. morganii and S. marcescens because of efflux-mechanisms. Urinary excretion is approximately 14%. Side effects observed in general were mild. The substance covers an interesting bacterial spectrum for the treatment of UTI, although difficult to treat organisms, such a P. aeruginosa or Proteus spp. are more resistant because of efflux pump activity. The relatively low urinary excretion might be a potential drawback in the treatment of UTI [38].</td>
</tr>
<tr>
<td>Cefozopran (intravenous)</td>
<td>Cephalosporin</td>
<td>Strong activity against P. aeruginosa. Because of the specific activity against P. aeruginosa this compound is of potential interest for the treatment of complicated UTI [39].</td>
</tr>
<tr>
<td>Ceftobiprole (intravenous)</td>
<td>Cephalosporin</td>
<td>Anti-MRSA cephalosporin. Against Gram-negative bacteria comparable activity to group 3 and 4 cephalosporins. The spectrum of activity towards P. aeruginosa resembles that of cefazidime. Limited activity against putative ESBL producers but good activity against putative high-level AmpC producers. Urinary excretion is about 90%. Because of the wide range of activity against most uropathogens and the high urinary excretion, the substance is of potential interest in the treatment of UTI [40].</td>
</tr>
<tr>
<td>Doripenem (intravenous)</td>
<td>Carbapenem</td>
<td>Exerts activity against Gram-positive bacteria except MRSA and enterococci and Gram-negative bacteria including imipenen resistant P. aeruginosa. Urinary excretion is 75%. Doripenem is highly excreted in urine and shows excellent activity against P. aeruginosa. Therefore it is of potential interest for treatment of complicated UTI [41].</td>
</tr>
<tr>
<td>Not indicated</td>
<td>β-lactamase inhibitors</td>
<td>Novel β-lactamase inhibitors are under development for the potential treatment of UTI. Because of the increasing prevalence of ESBL-producing enterobacteria in UTIs, novel β-lactamase inhibitors might be promising.</td>
</tr>
<tr>
<td>Ciprofloxacin XR (extended release) (oral)</td>
<td>Fluoroquinolone</td>
<td>Exerts identical antibacterial activity as ciprofloxacin targeting predominantly Gram-negative pathogens with good activity against P. aeruginosa. Urinary excretion is 40%. Ciprofloxacin XR is a once daily formulation, overall comparable to twice daily ciprofloxacin [42–44].</td>
</tr>
<tr>
<td>Balofloxacin (oral)</td>
<td>Fluoroquinolone</td>
<td>Exerts good antibacterial activity against Gram-positive pathogens, but in comparison to other fluoroquinolones decreased activity against Gram-negative pathogens. Urinary excretion is 86%. Balofloxacin is in the treatment of UTI probably not superior to other fluoroquinolones [45].</td>
</tr>
</tbody>
</table>
bacteriuria must not be treated in general (there are some exceptions), (ii) short-term therapy of uncomplicated UTI by suitable antimicrobial agents, and iii) low dose prophylaxis in uncomplicated recurrent UTI, respectively development of effective vaccines.

4.2 Antibiotic cycling

For antibiotic cycling there are practically no reliable studies available concerning treatment of UTI. There is, however, a more or less general agreement that the overuse of one group of antibiotics selecting for similar resistance genes should be avoided especially in a hospital of institutional setting. Therefore good guidelines recommend in general alternative substances as well, to allow antibiotic cycling.

4.3 Antibiotic dosing

The key idea of the third strategy, however yet clinically untested, is based on the use of antibiotic concentrations that require bacterial cells to obtain two concurrent resistance mutations for growth. That concentration has been called mutant prevention concentration (MPC) because no resistant bacterial colony is recovered even when high numbers of bacterial cells are plated. Resistant mutants are selected exclusively within a vulnerable concentration range (mutant selection window) that extends from the point where growth inhibition begins, approximately by the minimal inhibitory concentration, up to the mutant prevention concentration [28]. If the antibiotic dose given is high enough also to kill the mutant population, the selection of clinically resistant mutants could be restricted [29]. A further idea in this respect is to narrow the mutant selection window by developing appropriate substances, for example those which lower the MPC, or those that lower these concentrations of other drugs (e.g. efflux pump inhibitors). Therefore drugs with the most favourable pharmacokinetic/pharmacodynamic characteristics should be used as first-line

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**Table 2 (Continued)**

<table>
<thead>
<tr>
<th>Antibiotic substance</th>
<th>Antibiotic class</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garenoxacin (oral and intravenous)</td>
<td>Des-F(6)-quinolone</td>
<td>Exerts good antibacterial activity against Gram positive pathogens. Activity against Gram-negative pathogens is comparable to fluoroquinolones, such as ciprofloxacin or levofloxacin, activity against <em>P. aeruginosa</em> is poor. It seems that garenoxacin exerts also activity against fluoroquinolone resistant strains. The ability to induce resistance in vitro is apparently less than with fluoroquinolones such as levofloxacin. Urinary excretion is 30 to 40%. In view of the increasing quinoline resistance, substances of this class with decreased cross resistance and less susceptibility to resistance emergence are needed. Des-F(6)-quinolone derivatives like garenoxacin are promising substances for the treatment of UTI [46].</td>
</tr>
<tr>
<td>Not indicated</td>
<td>Dihydrofolate reductase inhibitors</td>
<td>Novel dihydrofolate reductase inhibitors are under discovery. The novel compounds are more active against Gram-positive pathogens. Because of the long lasting activity of trimethoprim, novel dihydrofolate reductase inhibitors are generally of interest in the treatment of UTI.</td>
</tr>
<tr>
<td>Not indicated</td>
<td>MurA inhibitors</td>
<td>Exert activity against Gram-positive and Gram-negative organisms to a variable degree. They target the bacterial enzyme MurA and thus inhibit cell wall synthesis. In view of the increasing antimicrobial resistance novel acting antibiotics are of interest for all kinds of bacterial infections [47].</td>
</tr>
<tr>
<td>Not indicated</td>
<td>Bacterial efflux pump inhibitors</td>
<td>Exert activity in combination with other antimicrobials against bacterial species that overexpress efflux pumps, such as <em>P. aeruginosa</em>. Efflux pump inhibitor agents have provided proof-of-principle of potentiation of other aninimicrobials both in vitro and in vivo. The initial practical application of improving activity against <em>P. aeruginosa</em> confirms that existing antibiotics can be potentiated by inhibition of efflux pumps, and suggests that efflux pump inhibitors may be a possible future treatment option that would address an unmet medical need. In addition efflux pumps contribute to a large extent to the emergence of resistance against different antibiotic classes. Efflux pump inhibitors can narrow the mutant selection window and thus slow down emergence of antibiotic resistance [48].</td>
</tr>
<tr>
<td>Not indicated</td>
<td>Siderophore-β-lactam conjugates</td>
<td>Novel strategy for the potential treatment of Gram-negative bacterial infections, including <em>P. aeruginosa</em>. Siderophore substances are covalently bound to aminopenicillins. Because of the bacterial spectrum covered, siderophore-β-lactam conjugation is a novel strategy of interest for the treatment of UTIs [49].</td>
</tr>
</tbody>
</table>
agents in order to preserve the potential of a specific drug class and, most importantly, to provide the patient with an optimally effective regimen. On the other hand the dosing of an antibiotic should be aimed high enough to reach the MPC.

4.4. Combination of two classes of antibiotics

For some organisms or in some infections it is difficult to find antibiotics that can be dosed high enough to prevent emergence of antibiotic resistance. A typical example is antibiotic treatment of M. tuberculosis where combination therapy with two or more antibiotic substances of different classes is recommended. In order to become resistant against two antibiotic substances, two concurrent mutations are required for bacterial growth, which has a very low probability to occur [28]. Clinical studies in UTIs however are very scarce. In one study combination therapy with a macrolide and ciprofloxacin showed higher efficacy in eliminating uropathogens than the single therapy with ciprofloxacin [30]. The success of the macrolide in this study however was more attributed to the specific biofilm inhibiting effect of the macrolide [30].

5. Conclusion

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 launch. Therefore new derivatives of classes in use should be thoroughly screened for their potential to induce resistance. Substances with a low potential to select resistant strains will be highly welcome. Very important in that respect will be combinatorial agents that impede general widespread mechanisms of resistance, such as efflux pump inhibitors. Novel antimicrobial strategies, such as the use of bacteriophagal enzymes urgently need to be evaluated further.

The best strategy in infection in general is the prevention of the disease. In UTI there is a variety of concepts involved:

- Hygienic issues and catheter materials are predominantly important in complicated, health-care associated UTIs.
- The low dose antibiotic prophylaxis in recurrent UTIs is effective, however the emergence of antibiotic resistant pathogens might be underestimated, although the idea of antibiotic prophylaxis is to use low dosages that do not fall within the mutant selection window and thus theoretically should not cause emergence of resistance.
- Vaccination will be an important issue in the future. The most experience has been made with vaccines in recurrent uncomplicated cystitis, because a single species E. coli causes more than 90% of episodes. Desirable would be more attempts for vaccination in complicated UTIs, especially with difficult to treat organisms like P. aeruginosa.

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 always has an effect on the environment. Considering this, the management of infectious diseases must be highly responsible.

References

[41] Jones RN, Sader HS, Fritsche TR. Comparative activity of doripenem and three other carbapenems tested against


