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Antibiotic Resistance and Novel Antibiotics for the Treatment of Urinary Tract Infections

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Surveillance data on antibiotic resistance need to be considered with respect to the origin of isolates, types of surveillance studies, and types of types of registered infections. Antibiotic resistance in gram-negative uropathogens has been investigated in both local and multinational studies. A compilation of worldwide studies for example showed resistance rates of gram-negative uropathogens against fluoroquinolones in 10% to 80%, against cephalosporines in 5% to 70% and against carbapenems in 0% to 35%. A specific surveillance study in the field of urology—the global prevalence of infections in urology (GPIU) study—is a point prevalence study with a global effort to create surveillance data in patients at various urological departments with health-care associated urogenital infections (HAUTIs). The GPIU study has been performed annually since 2003, with a total inclusion of 27,542 patients, thus far. Resistance rates of most uropathogens against all tested antibiotics were high, especially with multidrug resistance. A concerning finding was that the severity of HAUTI is also increasing—25% being urosepsis in recent years. In order to keep up with this alarming trend, novel antibiotics for the treatment of urinary tract infections need to be developed. Several strategies are currently employed: Beta-lactam/beta-lactamase inhibitor combinations are extended to cephalosporines and carbapenems. Novel fluroroquinolones have been developed, and so called siderophore antibiotics are being tested. Novel aminoglycosides and novel tetracyclines are also in the clinical development phases. Thus, several antibiotic substances are currently being developed, or in the late clinical phases of development.

Keywords: Urinary tract infections; Surveillance studies; Drug resistance, microbial; Novel antibiotics

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INTRODUCTION

Urinary tract infections (UTIs) are amongst the most frequent infections in the outpatient clinic as well as in the general healthcare setting. Healthcare-associated urogenital tract infections (HAUTIs) are one of the most frequently occurring healthcare-associated infections [1].

They are also amongst the most frequent infections treated with antibiotics.

Surveillance data on antibiotic resistance are therefore necessary. These data, however, may vary significantly in different infections and different clinical cohorts. In particular, clinical cohorts with interventions in the urogenital tract are more prone to acquire HAUTI, such

as urology [2,3]. It is, therefore, important that specific surveillance data are generated for uropathogens, and in addition to specific cohorts—i.e., urological patients—these data could also serve for specific recommendations if they can be interpreted correctly.

SURVEILLANCE STUDIES ON URINARY TRACT INFECTIONS

Worldwide antibiotic resistance data on uropathogens have been compiled by Zowawi et al. [4].

In this study, quinolone resistance in *Escherichia coli* from China, India, and Vietnam has been reported to be as high as 70%, with approximately 60% of strains also expressing extended spectrum β-lactamases (ESBLs). Different findings are seen in Australia and in some northern European countries, where resistance rates are significantly lower. Resistance to third-generation cephalosporines ranged from 4.2% to 70%. In Greece, carbapenem resistance in some regions is as high as 59.4% in *Klebsiella pneumoniae*, yet carbapenem resistance in *K. pneumoniae* is only 0.2% in the Netherlands.

Specific data on HAUTI in urology patients are continuously being collected in the point prevalence study on infections of urological patients, that started in 2003 with the aim to deliver surveillance data on a world-wide basis and was named the global prevalence of infections in urology (GPIU) study [5]. The GPIU study is a multi-national, multicenter study, performed as a one-day prevalence study in November of every year. A total of 27,542 urological patients are currently in this study database from a worldwide setting. The prevalence of HAUTI in this study was 11% and the most frequent forms of HAUTI

was asymptomatic bacteriuria in 29%, followed by cystitis in 26%, pyelonephritis in 21%, and urosepsis in 20% [3]. A comparison between the different HAUTIs showed that severe infections, such as pyelonephritis and urosepsis, are becoming more prevalent in recent years, and especially the frequency of urosepsis increased significantly over the past few years, with a rate of 25% [6].

Resistance rates of all antibiotics tested other than carbapenems against the total bacterial spectrum were higher than 10% in all geographic regions (Table 1) [7]. Resistance to almost all pathogens was lowest in North Europe and highest in Asia [7]. In up to 50% of uropathogens also had multi-drug resistance [7]. The data on resistance also showed that the resistance was even higher in more severe infections, such as urosepsis [6].

The combination of bacterial antibiotic resistance, plus fewer and fewer effective antibiotics, suggests that the prevention and treatment of infections in urology have become a major challenge to overcome. Urologists must deal with sicker and more elderly patients who expect better and better outcomes. Patients presented with persistent recurrent UTIs, complicating factors, and complex medical problems pose significant clinical problems.

NOVEL ANTIBIOTIC SUBSTANCES

Novel antibiotics for the treatment of gram-negative bacteria are almost always also tested in the indication of UTIs. In this development programme, several strategies are currently employed: Beta-lactam/beta-lactamase inhibitor combinations are extended to cephalosporines and carbapenems [8-14]. Novel fluroroquinolones have been developed and so called siderophore antibiotics are being

Table 1. Percent antibiotic resistance in healthcare-associated urinary tract infections in the global prevalence of infections in urology study between the years 2003 and 2010

Uropathogen	Aminopenicillin +BLI	Piperacillin tazobactam	Trimethoprim/ sulfamethoxazole	Ciprofloxacin	Cefuroxime	Cefotaxime	Ceftazidime	Imipenem	Gentamicin
Escherichia coli	50	25	48	45	33	28	29	3	30
Klebsiella spp.	64	40	62	57	63	57	51	2	46
Proteus spp.	42	15	55	30	26	27	30	2	31
Enterobacter spp.	63	40	52	42	66	47	48	4	48
Pseudomonas aeruginosa	Not tested	27	96	64	Not tested	Not tested	28	20	54
Enterococcus spp.	23	23	62	69	Not tested	Not tested	Not tested	25	73
CoNS	52	33	55	60	66	46	66	29	46
Staphylococcus aureus	57	46	26	54	35	35	22	41	18

Data from the article of Tandogdu et al. World J Urol 2014;32:790-801 [7].
BLI: beta-lactamase inhibitor, Spp.: species, CoNS: coagulase negative staphylococci.

Table 2. Novel antibiotic substances for the treatment of complicated urinary tract infections and pyelonephritis

Antibiotic substance	Phase of development	Comparator agent in study	Antibacterial spectrum	Reference
Ceftolozane-tazobactam	Marketed	Levofloxacin	Gram-negatives *Pseudomonas aeruginosa* Class A, some Class C BL producing bacteria	[9]
Ceftazidime-avibactam	Marketed	Doripenem	Gram-negatives *P. aeruginosa* Class C, some Class D BL (ESBLs, KPCs, AmpC) producing bacteria	[11,12]
Imipenem relebactam	Phase three	Colistin	Gram-negatives *P. aeruginosa* Class C, some Class D BL (ESBLs, KPCs, AmpC) producing bacteria	[14]
Meropenem-vaborbactam	Phase three	Peperacillin tazobactam	Gram-negatives *P. aeruginosa* Class C, some Class D BL (ESBLs, KPCs, AmpC) producing bacteria	[14]
S-649266	Phase two	Imipenem	Gram-negatives *P. aeruginosa* *Acinetobacter baumanii* Class C, some Class D BL (ESBLs, KPCs, NDM) producing bacteria	[14]
BAL30072	Phase one	No comparator	Not tested clinically	[15]
Finafloxacin	Phase two	Ciprofloxacin	Gram-positives Gram-negatives *P. aeruginosa* Anaerobes Atypical bacteria	[14]
Plazomicin	Phase three	Meropenem	Selected gram-positives Gram-negatives (including aminoglycoside resistant) *P. aeruginosa* KPC, VIM, OXA BL producing bacteria	[14]
Eravacycline	Phase three	Levofloxacin	Gram-positives Gram-negatives *A. baumanii*	[14]

BL: beta-lactamases, ESBLs: extended spectrum β-lactamases, KPCs: *Klebsiella pneumoniae* carbapenemases, AmpC: Class C β-lactamase, NDM: New Delhi metallo-β-lactamase, VIM: Verona integron-encoded β-lactamase, OXA: oxacillinase group β-lactamase.

tested. Novel aminoglycosides and novel tetracyclines are also in the clinical development phases (Table 2) [9,11,12,14,15].

Amongst the cephalosporine/beta-lactamase inhibitor combinations, two combinations have passed the clinical phase three development: Ceftolozane is a novel antibacterial with gram-negative and anti-pseudomonal activity that is combined with tazobactam. Ceftolozane-tazobactam also exhibits activity against Class A extended-spectrum β-lactamases, as well as some Class C β-lactamases [8].

In the study with complicated UTI or pyelonephritis, 1.5 g of ceftolozane-tazobactam every eight hours was tested against 750 mg of levofloxacin once daily (ASPECT trial) [9]. The primary endpoint was a composite of microbiological eradication and clinical cure five to nine days after the treatment. One thousand eighty-three patients were enrolled; among then, 82% had pyelonephritis. Ceftolozane-tazobactam was non-inferior to levofloxacin for composite cure and was superior to levofloxacin in the microbiological eradication rate. Adverse event profiles were similar in the two treatment groups and were mainly not serious. Thus, in this study, treatment with ceftolozane-tazobactam led to better responses than high-dose levofloxacin in patients with complicated UTI or pyelonephritis [9]. Although this treatment effect was due to a higher fluoroquinolone resistance rate, to date, fluoroquinolones were the primary recommended treatment substances in complicated UTI and pyelonephritis [10].

Ceftazidime-avibactam is the second cephalosporine/beta-lactamase inhibitor combination, whereby avibactam is a novel non-beta-lactam beta-lactamase inhibitor with a unique mode of action. It exhibits high binding affinity for Class A, C, and some Class D β-lactamases (ESBLs, *K. pneumoniae* carbapenemases [KPCs] and Class C-β-lactamase [AmpC]), some of which (e.g., KPCs) are unaffected by current beta-lactamase inhibitors. The efficacy, safety, and tolerability of ceftazidime-avibactam were compared with doripenem in complicated UTI and pyelonephritis (RECAPTURE trial) [11]. For this comparison, 2,000 mg of ceftazidime and 500 mg of avibactam was administered

every eight hours; contrastingly, 500 mg of doripenem was administered every eight hours with a possible switch to oral antibiotic after the fifth day. One thousand thirty-three patients were randomized. Ceftazidime-avibactam met the primary objective of statistical non-inferiority compared with doripenem for both the microbiological eradication endpoint and the composite of microbiological eradication and clinical cure. For the microbiological eradication endpoint at test of cure, ceftazidime-avibactam was statistically superior to doripenem. No significant adverse events or safety concerns were identified. Ceftazidime-nonsusceptible baseline pathogens were observed in 19.6% of patients, and both treatment arms showed a similar efficacy against ceftazidime- nonsusceptible pathogens.

The specific cohort of patients with ceftazidime-resistant bacteria was also studied in the REPRISE trial, where patients with ceftazidime resistant bacteria suffering from complicated UTI and pyelonephritis and complicated intraabdominal infections were exclusively studied and compared with the best available therapy [12]. More than 90% of patients suffered from complicated UTI and 97% of the best available therapy treatments were treated with carbapenems. The primary endpoint was clinical response at the test-of-cure visit, seven to ten days after last infusion of the study therapy. This was analyzed in all patients who had at least one ceftazidime-resistant gram-negative pathogen, as confirmed by the central laboratory, and who received at least one dose of the study drug. The overall proportions of patients with a clinical cure at the test-of-cure visit were similar with ceftazidime-avibactam (91%) and best available therapy (91%). Therefore, ceftazidime-avibactam was also confirmed to be effective in treating patients with complicated UTI and pyelonephritis with ceftazidime-resistant bacteria [13]. Gastrointestinal disorders were the most frequently reported treatment-emergent adverse events, but no new safety concerns were identified for ceftazidime-avibactam. Therefore, ceftazidime-avibactam might serve as a potential alternative to carbapenems in patients with ceftazidime-resistant enterobacteria and *Pseudomonas aeruginosa* [13].

Carbapenems are also combined with beta-lactamase inhibitors and tested against several infection entities. Imipenem is combined with relebactam, a novel beta-lactamase inhibitor and compared with colistin. This is currently tested in a phase three study in patients with complicated UTI and pyelonephritis, as well as intraabdominal infections and pneumonia in imipenem resistant pathogens (RESTORE-IMI 1 study [NCT02452047]) [14].

Additionally, the efficacy, safety, and tolerability of meropenem, combined with vaborbactam—another novel beta-lactamase inhibitor—is compared with piperacillin-tazobactam for complicated UTI and acute pyelonephritis, which is also in a phase three study (Tango 1 study [NCT02166476]) [14]. There is also a trial of meropenem-vaborbactam versus best available therapy in serious infections amongst carbapenem resistant enterobacteria, which also involves complicated UTI or acute pyelonephritis [14].

In a phase two, multicenter, double-blind, randomized, clinical study, the efficacy and safety of 2 g of intravenous S-649266 three times daily in complicated UTI or pyelonephritis caused by Gram-negative pathogens is assessed in hospitalized adults compared with 1 g of intravenous imipenem three times daily [14]. S-649266—a siderophore antibiotic cepahlosporine—is taken up by the bacterial cells via siderophore channels, which are then upregulated in uropathogens during an infection in the urinary tract.

Another siderophore antibiotic in preclinical development is BAL30072, which is a novel siderophore monosulfactam. BAL30072 was studied in a phase one study aimed to make a correlation between urinary concentrations and urinary bactericidal titers (UBTs) of BAL30072 in healthy subjects for dose finding [15]. Subjects received either 1 g intravenously once a day on day one and 1 g thrice daily on day two, or 2 g once daily (one hour) on day one and 2 g thrice daily on day two, or 1 g once daily (4 hours infusion) on day eight. UBTs were determined for seven *E. coli* isolates (three wild type, CTX-M-15, TEM-3, TEM-5, and New Delhi metallo-b-lactamase-1 [NDM-1]), two *K. pneumoniae* isolates (wild type and KPC), one *Proteus mirabilis* isolate (wild type), and two *P. aeruginosa* isolates (wild type and Verona integron-encoded β-lactamase [VLM-1] plus AmpC). BAL30072 exhibited positive UBTs for 24 hours of 1 g intravenously administered once daily for five of seven *Enterobacteriaceae* strains and after 2 g intravenously administered thrice daily for all strains, except one *P. aeruginosa* strain. Given this dose finding study, the clinical efficacy in the treatment of complicated UTI or pyelonephritis should be evaluated with a dosage regimen of 2 g of BAL30072 intravenously administered thrice daily [15].

Furthermore, finafloxacin—a novel eight-cyano-fluoro-quinolone—is under investigation as a potential treatment for UTI or pyelonephritis [16]. Finafloxacin is a fluoroquinolone also exhibiting activity in acidic urine, in contrast to all other marketed fluoroquinolones, that show markedly decreased antibacterial activity in an acidic environment. Finafloxacin was studied in a study where UBTs were determined for a reference strain and nine selected clinical uropathogens at the pH of native, acidified (pH 5.5) and alkalinized (pH 8.0) urine. UBTs in alkaline urine were significantly lower than those in native or acidic urine, except for *Enterococcus faecalis*. Finafloxacin also exhibited significant bactericidal activity against susceptible uropathogens. The urinary bactericidal activity of finafloxacin, therefore, was enhanced in acidic urine and significantly lower in alkaline urine [16]. The safety and efficacy of finafloxacin were further studied in comparison with ciprofloxacin as the treatment of hospitalized patients with complicated UTI and pyelonephritis in a double-blinded, double-dummied, randomized phase two study in patients with complicated UTI and acute pyelonephritis [17]. Patients were randomized to receive finafloxacin (800 mg intravenously and orally once daily) either for a total of five or ten days or ciprofloxacin (400 mg intravenously twice daily and 500 mg orally twice daily) for ten days. Two hundred twenty-six patients were enrolled in the study. Finafloxacin activity was not influenced by the urine pH. Patients treated with a high-dose, short course regimen of just five days with finafloxacin had higher, more rapid and more sustainable levels of microbiological eradication and showed improved clinical outcomes than those treated with ciprofloxacin taken twice daily for ten days. In contrast to ciprofloxacin, the activity of finafloxacin was not reduced by acidic urine pH [17].

Another antibiotic tested is plazomicin—a novel aminoglycoside. Plazomicin exhibits activity against gram-negative and selected gram positive bacteria and overcomes aminoglycoside modifying enzymes that inactivate the existing aminoglycosides. Aminoglycoside modifying enzymes often co-travel with other resistance mechanisms, including beta-lactamases and carbapenemases. Plazomicin is active against broadly susceptible and resistant *Enterobacteriaceae*, including broad spectrum beta-lactamases, such as KPC, VIM, imipenem, and oxacillinase type enzymes. It is not active against NDM-1 producing bacteria [18]. Plazomicin was tested in a phase two study at 10 mg/kg and 15 mg/kg once daily versus levofloxacin 750 mg once daily [19]. Microbiological eradiaction rates with plazomicin were higher in the 5 mg/kg arm (89%) compared with the 10 mg/kg arm (86%), and the rates were also higher than in the levofloxacin arm (81%) [19]. Fifteen mg/kg of plazomicin once daily is currently tested in a phase three randomized, multi-center, double-blinded study versus meropenem one gram thrice daily followed by optional appropriate oral therapy for the treatment of complicated UTI or acute pyelonephritis [14].

Lastly, a novel tetracycline, eravacycline was also tested in a phase three, randomized, multi-center, double-blinded study to evaluate the efficacy and safety of eravacycline with a dose of 1.5 mg/kg versus 750 mg of levofloxacin for the treatment of complicated UTI or acute pyelonephritis (IGNITE2 study). Eravacycline, however, did not achieve non-inferiority to the preset primary efficacy variables in this study [14].

CONCLUSIONS

Surveillance studies in patients with complicated UTI have been uniformly shown high rates of antibiotic resistance in complicated UTI and pyelonephritis with more and more multiresistant organisms playing a significant role. Specific surveillance studies in healthcare-associated complicated UTI or pyelonephritis have corroborated this finding and shown that severe infections—i.e., urosepsis—have also been increasing over past year.

In order to be able to compete with this development, novel antibiotices on the one hand need to be developed and tested in appropriate clinical trials, and on the other hand, antibiotic stewardship strategies need to be set in place to slow down the emergence of antibiotic resistance. Several novel antibiotics or antibiotic combinations are currently being marketed or tested in clinical trials, reflecting development strategies of combining beta-lactam antibiotics with beta-lactamase inhibitors, siderophore antibiotics, novel fluoroquinolone, novel aminoglycoside, and novel tetracycline. In all these antibiotic developments, however, the implementation of antibiotic stewardship practices is paramount, as misuse and overuse of antibiotics are the significant driving factors for the emergence of antibiotic resistance.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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