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Current Therapies for *Pseudomonas Aeruginosa*

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In the 1970s, *Pseudomonas aeruginosa* was recognized as the micro-organism associated with lethal bacteremia in the neutropenic host. Currently, *P aeruginosa* is a highly virulent micro-organism recognized as a major cause of nosocomial bacteremia and infections associated with invasive devices, mechanical ventilation, burn wounds, or surgery in the immunocompromised and the immunocompetent host [1,2]. The worldwide emergence of multidrug-resistant (MDR) nosocomial clones has added significantly to the ominous prognosis of *P aeruginosa* infections. It has been reported that MDR strains are associated with a threefold higher rate of mortality, a ninefold higher rate of secondary bacteremia, a twofold increase in the length of hospital stay, and a considerable increase in cost [3]. The high virulent potential of MDR *P aeruginosa* strains were also shown in current US data in which greater mortality (30.7%) was observed in hospitalized patients who received inadequate empiric therapy for bacteremia compared with those who were given appropriate therapy (17.8%) [4].

Based on the worldwide prevalence of MDR strains of *P aeruginosa* and the fact that no newer antipseudomonal agents are available, this article aims to investigate therapeutic solutions for combating infections caused by *P aeruginosa,* including MDR strains. The article focuses mainly on colistin, the re-emerging old antibiotic that possesses prominent antipseudomonal activity in vitro and on doripenem, a newer carbapenem that seems to

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be close to its global marketing [5,6]. Regarding older antipseudomonal antibiotics that have been reviewed extensively, only newer aspects on their use are considered in this article [7].

Newer aspects on the efficacy of traditional antipseudomonal antibiotics

Currently available older antipseudomonal antibiotics include ticarcillin/clavulanate, ceftazidime, aztreonam, cefepime, imipenem, meropenem, piperacillin-tazobactam, the aminoglycosides, and ciprofloxacin. Because of the versatility and the large size of *P aeruginosa* genome, various resistance mechanisms can be present simultaneously, causing cross-resistance to several antipseudomonal agents [8]. Specifically the production of penicillinases, cephalosporinases, and carbapenemases represent the most common underlying resistance mechanisms against β-lactams. The production of the metallo–β-lactamases, which number 36, is particularly harmful because they hydrolyze—with the exception of aztreonam—all β-lactams, including carbapenems [9]. Various efflux pumps, which remove several β-lactams from the intracellular milieu, and the reduction in the number of porin channels at the bacterial cell wall represent other important mechanisms of resistance that are also responsible for collateral damage to the fluoroquinolones. On the other hand, five plasmid–mediated acetylaces and adenylaces plus ribosomal methylation are capable of modifying the aminoglycosides and neutralizing their activity [10].

The increasing resistance rates of *P aeruginosa* strains to several antibiotics are expanding globally. In the United States, according to the NNIS system, 33% of the isolates were found resistant to ciprofloxacin, 22% to imipenem, and 30% to ceftazidime, which increased the period from 1997 to 2001 to 37%, 32%, and 22%, respectively [11]. Relevant figures for intensive care unit (ICU) isolates derived from Europe are even worse, because from 1990 to 1999, resistance to aminoglycosides reached 37% to 70%, resistance to ceftazidime reached 57%, resistance to piperacillin-tazobactam reached 53%, resistance to ciprofloxacin reached 56%, and resistance to imipenem reached 52% [12]. Current resistance patterns of *P aeruginosa* strains collected by the global surveillance study MYSTIC are shown in Table 1 (http://www.mystic-data.org). It should be pointed out that Greece, Brazil, the Czech-Republic, and Bulgaria possess the highest individual resistance rates to carbapenems, probably indicating high consumption rates of the latter antibiotics. Compared to imipenem, however, meropenem is more potent and is active against up to one third of imipenem-resistant strains, which indicates that a considerable percent of the strains should have lost the OprD porin, which is influential mainly against imipenem [13]. On the other hand, piperacillin and tazobactam seem to be less vulnerable to resistance development in most countries and regions. Based on the reported resistance surveillance data, it is evident that the current therapeutic approach for *P aeruginosa* infections is limited [14].

Table 1
Global resistance surveillance of *Pseudomonas aeruginosa* isolated in the MYSTIC program: resistance rates to the indicated antimicrobial agent

Region	Gentamicin 2000–2006	Tobramycin 2000–2006	Pip/Tazo 2000–2006	Ceftazidime 2000–2006	Cefepime 2000–2006	Imipenem 2000–2006	Meropenem 2000–2006	Ciprofloxacin 2000–2006
Northern Europe[a]	31.5–28.3	9.7–17.6	11.1–10.5	23.4–23.6	26.6–37.5	27.8–31.3	16.4–15.3	24.9–28.2
Southern Europe[b]	45.5–24.2	26.9–42.1	10.6–8.6	29.7–31.9	26.9–26.3	35.4–27.6	13–18	50–26.7
Eastern Europe[c]	39.5–39.8	54.4–46.0	25.7–24.2	47.4–26.4	52.8–40.8	48–35.8	45.7–35.6	48.4–41.7
United States	18.4–15.8	8.1–10.1	13.7–11.4	17.4–18	29.8–25.8	19.1–19	13.3–13.5	26.4–26.1
Canada	NA–30[d]	NA–16.8	NA–16.2	NA–38.2	NA–31.3	NA–30.8	NA–22.5	NA–22.5
South America[e]	65.2–49.2	65.2–49.3	23.9–34.5	49–44	31.2–55	38.1–54.8	11.9–49.5	63–56
Mexico	25–33.2	38.9–53.5	11.1–25.3	11.1–53.5	20–0	6.5–32.4	56–24	58.3–29.6
Hong–Kong[d]	NA–13.2	NA–5.6	NA–1.6	NA–18.5	NA–29.4	NA–11.6	0.0	NA–15.8
Australia[f]	NA–13.2	NA–NA	NA–7.9	NA–15.8	NA–9.1	NA–18.4	NA–7.9	NA–7.8

Susceptibility breakpoints (μg/mL): Amikacin $\leq$16, gentamicin $\leq$4, todramycin $\leq$4, piperacillin/tazobactam $\leq$64, ceftazidine $\leq$8, cefepime $\leq$8, imipenem $\leq$4, meropenem $\leq$4, ciprofloxacin $\leq$1.

Abbreviations: NA, nonavailable; MYSTIC, Meropenem Early Susceptibility Test Information Collection Program.

[a] Belgium, Finland, Germany, Sweden, United Kingdom.

[b] Greece, Italy, Malta, Portugal, Spain, Switzerland.

[c] Bulgaria, Croatia, Czech Republic, Israel, Poland, Romania, Russia, Slovenia, Turkey.

[d] Refers to year 2005.

[e] Argentina, Brazil, Columbia, Peru, Venezuela.

[f] Year 2000 not included because of low numbers of strains.

In numerous studies, the application of pharmacokinetics/pharmacodynamics (PK/PD) has enabled the enhancement of the antipseudomonal activity of antimicrobials with in vitro activity at the susceptibility cut-off points. For concentration-dependent antibiotics like the aminoglycosides and the quinolones, the estimation of the maximum serum concentration divided by the minimum inhibitory concentration (MIC) and the area under the serum concentration-time curve divided by the MIC predict a successful therapy. For time-dependent agents, such as the β-lactams, the percentage of time that the drug concentration remains two to four times above the MIC has helped to predict the probability of a successful clinical outcome, whereas for both types of antibiotics, the PK/PD applications decreased resistance development during therapy [15]. It seems that the dosages of antipseudomonal antibiotics should be adapted to meet PK/PD criteria of efficacy. In Table 2, some PK/PD target values for optimizing therapy against *P aeruginosa* are described. Source models are mostly represented

Table 2
Pharmacodynamic targets for successful treatment of *Pseudomonas aeruginosa* infections

	PD Target	Effect
Type of antimicrobial		
Penicillins		
Ticarcillin	% t > MIC 100%	Maximum
Piperacillin	% t > MIC 40%	Static
Cephalosporins		
Ceftazidime	% t > MIC 60%–70%	Cidal
	Serum levels 6.6 × MIC	Maximum
Cefepime	83%–95% of the dosing interval > 4.3 × MIC	Maximum
Carbapenems		
Imipenem	% t > MIC 22%	Static
and Meropenem	% t > MIC 100%	Cidal
Meropenem	C_{min}/MIC > 6.2 (> 1.7 in combination with tobramycin)	Resistance prevention
Aminoglycosides		
Tobramycin and Gentamicin	C_{max}:MIC ≥ 8; C_{max} ≥ 6 μg/mL	
Amikacin	C_{max}:MIC ≥ 8; C_{max} ≥ 24 μg/mL	
Netilmicin	C_{max}:MIC ≥ 8	
Fluoroquinolones		
Ciprofloxacin	AUC:MIC ≥ 125	Maximum
	AUC:MIC ≥ 100–157	Resistance prevention

% t > MIC: percentage of the dosing interval that the drug concentration remains greater than the MIC.

AUC, area under the serum concentration curve; C_{max}, maximum serum concentration; C_{min}, minimum serum concentration.

Data from Burgess DS. Use of pharmacokinetics and pharmacodynamics to optimize antimicrobial treatment of *Pseudomonas aeruginosa* infections. Clin Infect Dis 2005;40(S2): 99–104.

by neutropenic mouse thigh and lung infections, mathematical modeling, and in vitro time-kill curves, whereas relevant studies in humans are scarce [15]. Recently, in patients with *P aeruginosa* ventilator-associated pneumonia (VAP) and an APACHE-2 score of more than 17, an extended (4-hour) infusion of piperacillin-tazobactam ($n = 41$) versus intermittent infusion ($n = 38$) produced significantly less 14-day mortality rates (12.25% versus 31.6%; $P = .04$) and fewer days of stay in the ICU (21versus 38 days; $P = .02$) [16]. On the other hand, meropenem, 2 g, every 8 hours with a 3-hour infusion (in combination with an aminoglycoside) provided the greatest likelihood of *P aeruginosa* coverage, probably also preventing resistance development [17]. For the aminoglycosides, once-daily administration, by maximizing peak levels, allows optimal efficacy and possibly minimizes toxicity. For the fluoroquinolones, it seems that the total daily dosage is more important, whereas with current therapeutic schedules, MICs more than 0.5 μg/mL increase the risk of failure and resistance development [15].

The need to maintain the traditional antibiotic combination of a broad-spectrum antipseudomonal β-lactam plus an aminoglycoside is still controversial. Two recent meta-analyses on infections caused by susceptible strains showed that there was no advantage over monotherapy in terms of mortality, clinical efficacy, or prevention of resistance, whereas more adverse effects—especially nephrotoxicity—were observed in the combinations [18,19]. The analysis of *P aeruginosa* bacteremia subgroups showed a significant survival benefit for the combination [19].

Colistin

The emergence of MDR gram-negative bacilli, mainly of *P aeruginosa* and *Acinetobacter baumannii*, in parallel with the lack of new antibiotics, led to the revival of polymyxins, an old class of cyclic polypeptide antibiotics that was discovered in 1947 and since 1950 has been on the market [14,20]. Colistin, which is produced by *Bacillus colistinus*, is identical to polymyxin E and is available in two forms: colistin sulphate (tablets or syrup for bowel decontamination and powder for topically treating skin infections) and colistin methanesulfonate (CMS). It also appears under the names of colistimethate sodium, pentasodium colistimethanesulphate, and colistin sulfonylmethate. Throughout the world, various brand names of CMS are used by different pharmaceutical industries (eg, Coli-mycin M in the United States, Colomycin and Promixin in the United Kingdom). It should be pointed out, however, that compared with colistin sulphate, CMS is less potent but also less toxic [14,20].

Mode of action: resistance mechanisms

The target of antimicrobial action of colistin in gram-negative bacteria is the bacterial cell membrane, in which an electrostatic interaction between

the cationic polypeptide (colistin) and the anionic lipopolysaccharide (LPS) of the outer membrane is observed [21]. This leads to the displacement of magnesium and calcium, which normally stabilize LPS, from the negatively charged LPS, leading finally to an increase in the permeability of the cell envelope, leakage of cell contents, and eventually cell death [21]. The bactericidal efficacy of colistin is rapid in vitro. Studies with colistin-resistant *P aeruginosa* have reported alterations at the outer membrane of the cell, such as reduction in cell envelope Mg^{2+} and Ca^{2+} contents, lipid alteration, and substitution of protein OprH for magnesium in the outer membrane [22]. Despite the slow development of resistance, in Greece in 2005, among MDR *Klebsiella pneumonia* strains (ESBL and VIM producers) derived from ICU patients and belonging to six different clones, 16% were found to be resistant to colistin, whereas after 2005 resistance mounted to 37% [23,24]. Colistin has potent antiendotoxin activity; however, the significance of the latter mechanism in humans is not clear [14].

Antibacterial activity

Colistin is active in vitro against *P aeruginosa, Aeromonas* spp, *Acinetobacter* spp, *Stenotrophomonas maltophilia, Escherichia coli, and Klebsiella* spp, including ESBL producers, *Enterobacter, Citrobacter* spp, *Salmonella* and *Shigella* spp, *Haemophilus influenzae, Legionella pneumophila, Bordetella pertussis,* and several mycobacteria, including *Mycobacterium tuberculosis* [25]. Colistin is not active against gram-positive cocci or Proteus, *Providencia* spp, *Morganella morganii, Serratia* spp, *Vibrios, Burkholderia cepacia complex, Burkholderia pseudomallei,* and *Edwardsiella* spp. The pathogenic *Neisseria* spp, *Moraxella catarrhalis*, *Helicobacter pylori,* and *Brucella* spp and all anaerobic species are intrinsically resistant [14]. Compared with colistin sulphate, CMS has inferior antibacterial activity. Currently it is not clear whether in vitro testing results with the sulphate compound are suitable for predicting the in vivo activity of CMS [26]. The heterogeneity and variability in the composition of CMS and its instability in solution complicate studies of its antibacterial activity [26]. After administration, CMS is converted, at least partially, to colistin base.

In 2007, the Clinical and Laboratory Standards Institute reported interpretation of MIC for *P aeruginosa* susceptible strains indicated by MICs 2 μg/mL or less and resistant ones by MICs of 8 μg/mL or more with relevant zones of inhibition of 11 mm or more and 10 mm or less for colistin sulfate disks of 10 μg (Oxoid, Hampshire, UK) [26]. According to the Societé Française de Microbiologie, a concentration of 2 μg/mL or less has been selected as the susceptibility break point, whereas the British Society for Antimicrobial Chemotherapy has selected a break point of 4 μg/mL or less [27]. It should be pointed out that correlation of agar dilution MICs, which is considered the gold standard, with disk diffusion susceptibility testing showed that the latter classical method is unreliable for detecting colistin

resistance. Interestingly, 81%, 79%, and 89% of resistant to colistin gram-negative strains were falsely reported as susceptible when tested either by the product insert guidelines or the British Society for Antimicrobial Chemotherapy and the Societé Francaise de Microbiologie suggested disk diffusion methods, respectively [28]. MICs obtained by the Vitek-2 system are not reliable, with only agar dilution or E-test being highly recommended [29].

The in vitro interaction of CMS with rifampin has been evaluated against pan–drug-resistant *P aeruginosa* strains, including colistin. Synergy was reported in 11.8% to 41.7% of strains, depending on exposure time [30].

Dosage schedules: pharmacokinetics and pharmacodynamics

CMS is administered intravenously, intramuscularly, intrathecally, or inhalationally [14,20]. Parenterally and in patients with normal renal function, CMS is given in the United States at a dose of 2.5 to 5 mg/kg/d (31,250–62,500 IU/kg) divided into two to four equal doses (1 mg of colistin equals 12,500 IU). In the United Kingdom, it is given at a dose of 4 to 6 mg/kg/d (50,000–75,000 IU/kg) in three divided doses for adults and children with body weights of less than or equal to 60 kg and at a dose of 80 to 160 mg (1–2 million IU) every 8 hours for body weights of more than 60 kg. The Greek experience has proved that a higher dose of 3 million IU (2.4 mg/kg) every 8 hours is safe [20]. The intrathecal and the intraventricular doses are equal to 125,000 to 500,000 IU per day. By the inhalation route, the recommended dosage ranges from 500,000 IU every 12 hours to 2 million IU every 8 hours [31]. In case of renal dysfunction, the dosage adjustment recommended by the manufacturers is as follows: for serum creatinine levels of 1.3 to 1.5, 1.6 to 2.5, or more than or equal to 2.6 mg/dL, the recommended dosage of colistin administered intravenously is 160 mg (2 million IU) every 12, 24, or 36 hours, respectively. During hemodialysis treatment, the recommended dose is 80 mg (2 million IU) after each session, whereas in continuous venovenous hemodiafiltration patients, a dosage of 2 to 3 mg/kg every 12 hours has been recommended [5,14,26].

Because microbiologic assays are not accurate, recently two different high performance liquid chromatography assays were developed that permit the accurate estimation of colistin base or sulphate and CMS values in human plasma and biologic fluids, respectively [5,32]. CMS is poorly absorbed by the gastrointestinal tract. After the intravenous administration of 1.63 to 3.11 mg/kg every 8 hours of CMS to patients with cystic fibrosis (CF) at steady state, levels in plasma at 1 hour ranged from 2.6 to 9.8 μg/mL, whereas at 6 hours they were between 0.36 and 2.5 μg/mg [32]. In 12 patients who had CF who received intravenous CMS at a dose of 160 mg (2 million IU) every 8 hours (for patients with body weight of < 50 kg) or 80 mg (1 million IU) every 8 hours (for patients with body weight of < 50 kg), the mean ($\pm$ SD) half-life of CMS was estimated as 125 ± 5.2 min, whereas the level of colistin sulphate as 251 ± 79 min [32]. Mean ($\pm$ SD) total body

clearance, mean (± SD) volume of distribution (Vd), and area under the curve (AUC) of CMS were 2.0 ± 0.5 mL/min/kg, 340 ± 95 mL/kg, and 23.43 μg/h/mL, respectively [32]. In case of meningitis, the intravenous administration of 1 million IU of CMS every 6 hours resulted in cerebrospinal fluid levels that were equal to 25% of the simultaneous serum concentration [31]. In patients with CF, CMS plus several of its metabolites are excreted primarily by the kidney through glomerular filtration. Approximately 62.5% is excreted as unchanged drug in urine, whereas no biliary excretion is reported in humans [26].

Colistin sulphate and CMS express their bactericidal activity as concentration-dependent antibiotics; the latter effect seems to be related to the AUC/MIC. Further PK/PD investigations are essential for this unknown antibiotic [5,26,32].

Clinical experience

In total from 1999 until August 2005, eight retrospective studies involved 335 patients without CF, among whom 264 (78%) represented ICU patients and 186 (55%) suffered from pneumonia (50% as VAP), who were given (with the exception of one study where polymyxin B was given) intravenous CMS at a dose of 1 million to 3 million IU every 8 hours for 12 to 22 days [14,33–35]. In almost all patients at a rate close to 50% either MDR *P aeruginosa* or MDR *A baumannii* were isolated in relevant cultures. Colistin as a rule was given in combination with other antibiotics, mostly with a carbapenem. Clinical cure rates ranged between 57% and 73% with mortality rates of 20% to 61.9% and 0% to 37% incidence of nephrotoxicity. Clinical efficacy in pneumonia exceeding 50% was comparable to previously reported rates of outcome with piperacillin, imipenem, and ciprofloxacin.

In 2007, three retrospective studies were published, two of which referred exclusively to monotherapy with colistin in the treatment of VAP due to colistin susceptible only *P aeruginosa* or *A baumannii* [36–38]. In a small sample size study, Rios and colleagues [36] did not find any difference in mortality rate (51.6% versus 45.1%) of 31 patients with VAP caused by isolates susceptible only to colistin who were treated with colistin monotherapy compared to 30 patients with VAP caused by carbapenem-susceptible strains who were treated with imipenem or meropenem. Appropriate empiric antimicrobial therapy in the carbapenem-susceptible group should have contributed to the lower mortality rate observed in this group when compared to patients who had not received appropriate therapy with underlying strains susceptible only to colistin (36.6% versus 70%, respectively, $P = .014$). It was concluded that VAP episodes susceptible only to colistin can be treated effectively using colistin, whereas the MDR susceptibility pattern of pathogens should be suspected in patients with previous VAP or prior antibiotic use for more than 10 days preceding the current VAP episode.

In the largest retrospective matched case-control study thus far to assess the efficacy of monotherapy with colistin, the latter was compared with imipenem in VAP caused by colistin-susceptible ($n = 60$) and carbapenem-susceptible ($n = 60$) *A baumannii* (51.6% versus 61.7%) or *P aeruginosa* (48.4% versus 38.3%). A favorable clinical response was observed in 75% of the group susceptible only to colistin versus 71.7% in the carbapenem-susceptible group ($P = .68$) without difference in the time to resolution of infectious parameters between the two groups. None of the patients developed renal failure [37].

The effectiveness of colistin was studied retrospectively in 95 cancer patients diagnosed with infections caused by MDR *P aeruginosa* treated either with colistin ($n = 31$) or with at least one active antipseudomonal agent (a β-lactam antibiotic or a quinolone) ($n = 64$) [38]. In 13 patients, colistin was given in combination with other antipseudomonal antibiotics; in 18 patients it was given as monotherapy. Compared with the control group, patients in the colistin group were more likely to have had nosocomial infections (87% and 64%, respectively; $P = .02$). Among all patients 45% and 37%, respectively, were neutropenic, 68% versus 58% had an ICU stay during therapy, and Pseudomonas infection or colonization within the previous year was reported in 42% versus 48%. No difference in the incidence of clinical and microbiologic response (52% versus 31% and 48% versus 41%), relapse rate (10% versus 11%), infection-related mortality (26% versus 17%), or overall mortality (61% versus 47%) and nephrotoxicity (23% versus 22%) was observed. Multiple logistic regression analysis showed that patients treated with colistin were 2.9 times more likely than patients in the control group to experience a clinical response to therapy, however ($P = .026$). Particularly in patients treated with colistin monotherapy, higher clinical and microbiologic responses were observed, which rendered colistin a useful or preferred alternative therapy for MDR infections in cancer-neutropenic patients. A major limitation of the study is the lack of evaluation of the time to initiate adequate therapy, however.

Recently, the efficacy of inhaled polymyxin B was studied in 19 patients with MDR gram-negative infections of the respiratory tract, 14 patients with pneumonia, 13 of whom experienced failure with previous therapy with intravenous polymyxin-B, and 5 patients with purulent tracheobronchitis [39]. Inhaled polymyxin B (after an aerosolized β_2-agonist) was given at a dose of 500,000/IU twice a day in combination with the parenteral drug for 4 to 25 days. Cure was recorded in 10 (53%) patients, with improvement in 8 (42%) and failure in 1. All 5 patients with *P aeruginosa* tracheobronchitis were successfully treated with monotherapy of inhaled polymyxin-B. Although aerosolized delivery seems promising as a therapeutic adjunct, it requires prospective evaluation and careful monitoring for side effects, resistance development, and superinfections [39].

Most of the reported studies share common drawbacks, however. They are mostly small and retrospective without definite designed protocols.

Other antibiotics—irrespective of the susceptibilities of the isolated pathogens—were mostly given simultaneously with CMS, which confounded its therapeutic efficacy. Deterioration of renal function could not be attributed exclusively to CMS. Neurotoxicity could not be evaluated because most patients were mechanically ventilated. Variable dosing of colistin and treatment duration were applied. Resistance development during and at the end of the studies was not monitored. No study among the reported ones referred to a large number of patients with pure *P aeruginosa* infections. Usually the reported studies also include *A baumannii* as a pathogen, the virulent capacity of which greatly differs from that of *P aeruginosa*.

Although experience with CMS in *P aeruginosa* CNS infections is lacking, the results reported in MDR *A baumannii* central nervous system infections in 14 patients were successful. Thirteen patients were cured after the administration of CMS intravenously or intrathecally or both [40].

Toxicity and adverse reactions

The most common and important adverse effects of colistin reported in the literature are nephrotoxicity and neurotoxicity [14,20]. Early experience with CMS revealed an incidence of nephrotoxicity mounting to 20.2% that was attributed mainly to acute tubular necrosis. Colistin nephrotoxic effect is closely related to its mechanism of action because it increases the tubular epithelial cell membrane permeability, which results in increased influx of cations, anions, and water and leads to cell swelling and lysis. In contrast to older information, recent data indicated that nephrotoxicity in ICU patients after CMS administration is lower—ranging from 0% to 36% [14,20]. Safety data from 19 courses of prolonged intravenous CMS administration (mean duration 43.4 days, mean daily dosage 4.4 million IU, mean cumulative dosage 190.4 million IU) indicated that the median creatinine value increased only by 0.25 mg/dL, which returned close to baseline at the end of therapy [41]. The reported discrepancies should be attributed to the improvement in supportive care offered to seriously ill patients, the possible avoidance of coadministering other nephrotoxic drugs such as aminoglycosides, the different definitions of nephrotoxicity, and different formulations of colistin lacking colistin sulphate impurities that are more nephrotoxic.

The incidence of neurotoxicity in earlier studies of colistin reached approximately 7%, with paresthesias being the main adverse events that mounted for unknown reasons to almost 29% in patients who had CF [14,20]. In addition to facial paresthesias, dizziness, weakness, vertigo, visual disturbances, confusion, ataxia, neuromuscular blockade leading to respiratory failure and apnea have been reported. Only one study included prospective electrophysiologic testing of 12 colistin recipients that showed evidence of neuromuscular junction blockade, although findings consistent with critical polyneuropathy were seen in 6 of the tested patients [33].

Intraventricular high-dose administration also may cause convulsions. It is hoped that nephro- and neurotoxicity are dose dependent and reversible [14,20].

In the case of aerosolized CMS, bronchoconstriction has been reported, which is an adverse effect that can be prevented by the inhalation of β_2-agonists before CMS administration [20].

Resistance development

None among the reported studies monitored resistance development to colistin during and at the end of therapy. Three recent studies investigated the possibility of resistance development to colistin [24,42,43]. In a study by Landman and colleagues [42] in a New York Hospital after 4 years of increasing purchases of colistin, *P aeruginosa* expressed 5% resistance rate. In a Greek ICU, the emergence of colonization in 37% of patients with colistin-resistant *K pneumonia* in bronchial and bowel floras (among those colonized with *K pneumonia* strains) is of concern. The simultaneous occurrence of various infections with colistin-resistant gram-negatives and breakthrough bacteremias with intrinsically resistant to colistin *Proteus* and *Serratia* spp in patients on treatment with colistin for more than 12 days, is certainly worrying [24]. On the other hand, the emergence of *K pneumoniae* strains producing metallo-β-lactamases in Greek ICUs since 2001 resulted in excessive empirical use of colistin, which led to a cluster of multiclonal pan–drug-resistant *Klebsiella* strains implicated in bacteremias, VAP, and soft tissue infections, mostly in patients with prolonged administration of colistin (median 27 days) [43]. Horizontal transmission through hands also was proved by repetitive extragenic palindromic-polymerase chain reaction. The analysis of risk factors after a Greek ICU outbreak with pan–drug-resistant *P aeruginosa* causing VAP revealed that the sole independent predictors were the administration of colistin for 13 days or more or the combined use of a carbapenem for more than 20 days [44]. The outbreak resolved after reduction in the days of therapy with colistin plus reinforcement of infection control measures.

Conclusions

It is evident that future studies with colistin necessitate (1) large prospective trials in MDR infections of ICU patients under well-designed protocols and reliable susceptibility testing, (2) clarification in vivo of the possible benefits of coadministering colistin with other antimicrobials, (3) evaluation in VAP of nebulized colistin as single therapy or in combination with parenteral colistin to establish the optimal dosing regimen in ICU patients, (4) better monitoring and elucidation of resistance mechanisms, and (5) larger experience in the febrile neutropenic host. There is no doubt that we must explore ways for maintaining the survival of colistin. It is evident that to escape resistance, duration of therapy should be limited to less than 12 days,

coadministration with a carbapenem should be better avoided, PK/PDs should be exploited, and hand hygiene should be strictly applied. Colistin is not an ICU panacea to be prescribed casually but only under certain strict indications, as in severe ICU infections with pathogens susceptible only to colistin or empirically in ICU nosocomial sepsis of late onset in settings with high prevalence of MDR isolates. Even then, de-escalation should be prompt whenever culture results permit replacement with another antibiotic. It is probable that these policies may keep colistin as a real frontier against MDR gram-negative micro-organisms.

Doripenem

Doripenem (S-4661) is a novel parenteral carbapenem with a research history in international meetings since 1994. It was developed by Shionogi & Co, Ltd. (Osaka, Japan), approved in Japan in July 2005, and launched in September 2005 [6]. Outside Japan, the rights were licensed to Peninsula Pharmaceuticals, Inc. (Alameda, California) and acquired subsequently by Ortho-McNeil Pharmaceutical, Inc. (New Brunswick, New Jersey). Doripenem is not listed on the European Medicines Agency Web site (http://www.emea.eu.int).

The chemical structure of doripenem is almost identical to that of meropenem. Doripenem, like meropenem and ertapenem and unlike imipenem, has a 1-β-methyl side chain, whereas in doripenem the dimethylcarbamoyl side of meropenem has been substituted by a sulfamoylaminomethyl group. This structure confers β-lactamase stability and resistance to inactivation by renal dehydropeptidases. The new agent shares the bactericidal mechanism of action of other β-lactams, particularly carbapenems, by targeting PBP_{1-3} [6].

Antimicrobial activity

Doripenem is characterized in vitro by spectrum and potency against gram-positive cocci similar to imipenem and ertapenem, whereas against gram-negatives it is mostly similar to meropenem and is two- to fourfold superior to imipenem. Against wild-type *P aeruginosa* isolates, doripenem was found to be two- and fourfold more potent than meropenem and imipenem, respectively (MIC_{90} 0.5 μg/mL versus 1 μg/mL and 2 μg/mL, respectively) [45]. After testing 2137 bacterial isolates in vitro, among which were 150 *P aeruginosa* strains, the range of MICs, MIC_{50}, and MIC_{90} for doripenem, imipenem, and meropenem was determined as follows: 0.03 to 16 μg/mL, 0.25 μg/mL, and 1 μg/mL, 0.06 to 32 μg/mL, 1 μg/mL, and 2 μg/mL, 0.03 to 32 μg/mL, 0.25 μg/mL, and 4 μg/mL [46]. The results of the latter study permitted the characterization of a "susceptible" category as 2 μg/mL or less, "intermediate" as 4 μg/mL, and "resistant" as 8 μg/mL or more, with disc diffusion breakpoints of 21 mm or more for susceptible, 18 to 20 mm for intermediate, and 17 mm or less for resistant isolates.

Similar results were obtained against MDR *P aeruginosa* strains isolated from patients who had CF with no difference between mucoid (No 200) strains and nonmucoid (No 200) strains. Doripenem also was active against 15% to 20% of the strains resistant to imipenem and almost 40% of the strains characterized as resistant to ceftazidime, cefepime, and aztreonam [47]. Similarly among 34 carbapenem-resistant and MDR *P aeruginosa* strains, the lowest rate of resistance (approximately 30%) was found for doripenem, which indicated the possibility that infections caused by carbapenem-resistant strains may be treatable with doripenem [48].

Doripenem did not show antagonism and demonstrated either addictive effects or mild synergy when tested in vitro with daptomycin, levofloxacin, linezolid, and vancomycin against gram-positives and with amikacin, levofloxacin, and trimethoprim-sulfamethoxazole against fermenting and nonfermenting gram-negative bacteria [6].

Regarding the in vitro resistance selection potential of doripenem, mutants seemed to be harder to select in vitro than with other carbapenems, and the increases in MICs were smaller for the resistant mutants [49]. Single-step doripenem mutants were resistant only to carbapenems and had lost Opr D, whereas multistep mutants had broader resistance, putatively including upregulated efflux mechanisms. Like other carbapenems, doripenem, loses its activity against *P aeruginosa* isolates with metallo-β-lactamases enzymes (IMP and VIM).

Pharmacokinetics and pharmacodynamics

In a phase I, double-blind trial, 24 healthy volunteers received one of three dosing regimens of doripenem: a 4-hour infusion of 500 mg every 8 hours for 10 days (cohort A); a 6-hour infusion of 1000 mg every 12 hours for 10 days (cohort B); or a 4-hour infusion of 1000 mg every 8 hours for 10 days (cohort C) [50]. In each cohort, six subjects received doripenem and two received placebo. Steady state was achieved in all cohorts after administration of doripenem for 7 consecutive days. Doripenem serum half life was in the range of 0.65 to 1.65 hours (mean, approximately 1 hour), AUC was 40.2 μg/h/mL, creatinine clearance was in the range of 15 to 36 L/h with Vd_{ss} in the range of 19 to 56 L. The mean doripenem concentration at steady state (C_{ss}) was approximately 3.3 μg/mL in cohorts A and B and approximately 4.5 μg/mL in cohort C. Doripenem was excreted mainly by the renal route (70%) [50]. As renal function decreased, serum half life increased from 1 to 5 hours (severe renal impairment) to up to 9 hours (end-stage renal failure). Dialysis reduced systemic doripenem levels by 48% to 62% [51]. Regarding the use of PK/PD target attainment analysis and the Monte Carlo simulation results, it was predicted that 500 mg of doripenem administered over 1 hour every 8 hours would be effective against bacterial strains with MICs less than 2 μg/mL, whereas less susceptible strains would be treated with prolonged infusions [52].

Clinical trials

Doripenem is developed in an intravenous formulation as 250-mg vials and was launched in Japan, its first market, in 2005 [6]. An inhaled (nebulized) formulation is in phase I development in the United Kingdom for the treatment of CF-associated lung infections [53]. The drug is in phase III pivotal trials in North and South America and in Europe [6]. A total of six trials were conducted, including two each of complicated urinary tract infections and pyelonephritis, complicated intra-abdominal infections, and nosocomial pneumonia (including VAP) caused by various micro-organisms with successful therapeutic results. In October 2004, the US Food and Drug Administration granted fast-track status to doripenem for the treatment of nosocomial pneumonia, including VAP [6].

In phase II studies in 55 patients with chronic respiratory tract infections, doripenem in various doses resulted in promising clinical result in 95.2% of patients, with bacteriological eradication in 87.5% [54]. The propensity of *Pseudomonas* strains to develop resistance during therapy requires further study, however. Pooled results from two phase III randomized, double-blind, multicenter studies comparing 5–14 days of intravenous doripenem (500 mg every 8 hours) to intravenous meropenem (1 g every 8 hours) in adults who have complicated intra-abdominal infections recently became available as a meeting poster presentation [55]. A switch to oral amoxicillin/clavulanate after greater than or equal to nine doses of doripenem or meropenem was permitted. A total of 962 patients in both studies were randomized; 486 patients received doripenem and 476 patients received meropenem. The clinical cure rates in the microbiologically evaluable population were 84.6% for doripenem and 84.1% for meropenem (difference 0.5%; 95% CI, -5.5%–6.4%). The microbiologic cure rates were 84.3% for doripenem and 84.5% for meropenem. The microbiologic cure rate for infections caused by *P aeruginosa* was 85% for doripenem versus 75% for the comparator.

Toxicity and adverse reactions

In general, doripenem was well tolerated. The most common adverse event was headache, which was observed in 33% and 50% of patients who received 500 mg every 8 hours and 1000 mg every 8 hours, respectively, versus 13% in the placebo recipients [56]. Infection site erythema was frequently reported [50], whereas gastrointestinal disorders—expressed as nausea and diarrhea—were reported in 3.7% and 2.5% of patients, respectively [54]. Somnolence and postural dizziness were also described at similar frequencies [50]. There was no evidence of a dose response in any adverse event [50].

Conclusions

Based on in vitro activity and the clinical outcome, it seems that doripenem could play an important role in patients with serious nosocomial infections,

including ICU patients, particularly in hospital settings with high rates of MDR gram-negative bacteria, including *P aeruginosa*. The potential development of in vivo resistance of doripenem should be carefully studied, however.

Epilogue

There is no doubt that antipseudomonal antibiotic overuse and misuse are strongly connected with the emergence of MDR *P aeruginosa* [57]. In the effort to improve therapeutic results while preserving the power of antibiotics, several policies have been suggested and applied successfully (ie, restricting or banning certain classes of antibiotics, cycling antibiotics, performing surveillance cultures, determining risk factors that indicate the presence of MDR *P aeruginosa*, using appropriate dosing and mode of administration of antibiotics according to PK/PD indications, decreasing the duration of therapy, applying de-escalation of antibiotics given empirically, and obeying rules of hand hygiene) [1,14,58]. Approaching the officially predicted "End of Antibiotics" [57], it is certain that if physicians do not decrease the overuse and misuse of antibiotics, the emerging multidrug resistance problem of *P aeruginosa* will worsen while the era of "The End of Antipseudomonal Antibiotics" will become a nosocomial nightmare.

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