Update on the treatment of *Pseudomonas aeruginosa* pneumonia

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*Pseudomonas aeruginosa* is an important cause of nosocomial pneumonia associated with a high morbidity and mortality rate. This bacterium expresses a variety of factors that confer resistance to a broad array of antimicrobial agents. Empirical antibiotic therapy is often inadequate because cultures from initial specimens grow strains that are resistant to initial antibiotics. Surveillance data, hospital antibiogram and individualization of regimens based on prior antibiotic use may reduce the risk of inadequate therapy. The use of combination therapies for *P. aeruginosa* pneumonia has been a long-advocated practice, but the potential increased value of combination therapy over monotherapy remains controversial. Doripenem and biapenem are new carbapenems that have excellent activity against *P. aeruginosa*; however, they lack activity against strains that express resistance to the currently available carbapenems. The polymyxins remain the most consistently effective agents against multidrug-resistant *P. aeruginosa*. Strains that are panantibiotic-resistant are rare, but their incidence is increasing. Antibiotic combinations that yield some degree of susceptibility *in vitro* are the recourse, although the efficacy of these regimens has yet to be established in clinical studies. Experimental polypeptides may provide a new therapeutic approach. Among these, the anti-PcrV immunoglobulin G antibody that blocks the type III secretion system-mediated virulence of *P. aeruginosa* has recently entered Phase I/II clinical trials.

Keywords: combination therapy, multidrug resistance, antimicrobials

**Introduction**

*Pseudomonas aeruginosa* is a Gram-negative non-fermenting bacillus that belongs to the family Pseudomonadaceae. It was first isolated from green pus in 1882. More than half of all clinical isolates produce the blue-green pigment pyocyanin. It has minimal nutrition requirements, which contribute to its broad ecological adaptability and distribution. The large genome of *P. aeruginosa* provides a tremendous amount of flexibility and the metabolic capability to thrive in environments that are inhospitable to most other organisms.¹ The complete sequencing of wild-type *P. aeruginosa* (PA01) at the turn of the century has provided a great deal of useful information, concerning not only its pathogenicity but also its potential for resistance.¹ In addition to mediator activation via release of endotoxin, *P. aeruginosa* possesses a repertoire of exotoxins and enzymatic products designed to evade host defences.² It has also an array of chromosomal and plasmid-mediated antibiotic resistance factors, making antibiotic treatment difficult and potentially unsuccessful.

According to data from the US Centers for Disease Control and Prevention and the National Nosocomial Infection Surveillance System, *P. aeruginosa* is the second most common cause of nosocomial pneumonia (17%), the third most common cause of urinary tract infection (7%), the fourth most common cause of surgical site infection (8%), the seventh most frequently isolated pathogen from the bloodstream (2%) and the fifth most common isolate (9%) overall from all sites.³ More importantly, it is the most common multidrug-resistant (MDR) Gram-negative pathogen causing pneumonia² in hospitalized patients.

Over the last decade, substantial attention has been given to the development of agents to combat Gram-positive cocci while the pursuit of antimicrobials for use in infections caused by Gram-negative bacilli has lagged behind. With the pipeline of new antimicrobial agents running dry, treatment of *P. aeruginosa* continues to rely on the theoretical advantages of combination therapy and the revival of old drugs previously abandoned because of serious toxicity.³
The purpose of this review is to discuss the current approach to antimicrobial therapy for *P. aeruginosa* pneumonia and to present the novel therapeutic modalities under development.

**Approach to treatment of *P. aeruginosa* pneumonia**

**Selection of antibiotics**

The array of traditional antibiotics with antipseudomonal activity includes the aminoglycosides, ticarcillin, ureidopenicillins, ceftazidime, cefepime, aztreonam, the carbapenems (except for ertapenem), ciprofloxacin and levofloxacin. The question of which of these agents is the preferred antimicrobial in the treatment of *P. aeruginosa* pneumonia is difficult to answer because of a lack of comparative randomized double-blinded studies showing significant differences in efficacy. The current guidelines from the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) on the management of community and hospital-acquired pneumonia advocate a therapeutic selection based on the severity of the infection, awareness of underlying risk factors and co-morbid diseases, recognition of the epidemiology and resistance phenotypes in individual settings, and knowledge of pharmacokinetic–pharmacodynamic parameters. However, certain antibiotics are more prone to resistance developing during therapy, leading potentially to treatment failures. In three controlled studies comparing imipenem with ceftazidime, ciprofloxacin or piperacillin/tazobactam, emergence of resistance to imipenem was reported more frequently. The adjusted hazard ratio for developing imipenem resistance in *P. aeruginosa* strains was 2.8 compared with 0.7 for ceftazidime, 0.8 for ciprofloxacin and 1.7 for piperacillin.

Faced with these uncertainties, general principles have been adopted over the last few years based mostly on expert opinion. Upon suspicion of *P. aeruginosa* pneumonia, an aggressive approach for pathogen retrieval should be initiated, preferably prior to initiation of the first dose of antimicrobial therapy. Reliance on prescribing the same antibiotic regimens for all patients suspected with similar infection is no longer considered a logical approach. Increased rates of resistance leading to inadequate empirical therapy may well result in adverse patient outcomes. However, initiation of antibiotics may not necessarily await sampling of the respiratory tract. Delay in treatment has been linked to increased mortality even when a patient is considered clinically stable. Four methods have been suggested to improve the adequacy of antimicrobial coverage against *P. aeruginosa*. First, examination of national surveillance data provides an important gauge of the extent of resistance against antipseudomonal agents. While the reliability of these reports may be questionable because of interlaboratory variations, the overall trend in pathogen susceptibility may suggest a geographical cluster of resistant strains to a particular class of antibiotics. This could prove helpful to clinicians when prescribing empirical coverage for presumed *P. aeruginosa* pneumonia in patients transferred from other facilities. Second, knowledge of the susceptibility profile of recently isolated pathogens may predict not only the causative organisms but also the resistance pattern of *P. aeruginosa* if it was determined to be the culprit pathogen. For example, in patients who are ventilated, colonization with antibiotic-resistant *P. aeruginosa* predisposes the patient to subsequent infection with these same highly virulent microorganisms. Two recent studies have shown that routine quantitative cultures of endotracheal aspirates conducted once or twice weekly in all mechanically ventilated patients may help to improve the adequacy of empirical antibiotic therapy for ventilator-associated pneumonia (VAP). Third, presence of risk factors for MDR *P. aeruginosa* and prior exposure to antibiotics may determine the extent of broad-spectrum coverage. In a secondary analysis of a large multicentre study with suspected VAP, independent risk factors for isolation of MDR *P. aeruginosa* included the number of days (≥48 h) in hospital prior to intensive care unit (ICU) admission and prolonged duration of ICU stay. These results were in keeping with earlier work by Trouillet et al., who found that prior duration of mechanical ventilation is associated with increased rates of infection with MDR *P. aeruginosa*. Comparable studies identified exposure to previous antimicrobial therapy as a significant factor for drug-resistant *P. aeruginosa*. Contrary to previous reports that have typically found only one or two antibiotic classes to be predictive of MDR *P. aeruginosa* all antipseudomonal agents can be linked to MDR *P. aeruginosa*. However, the duration of prior antibiotic exposure associated with MDR *P. aeruginosa* may vary among the antipseudomonal classes. The shortest duration of prior antibiotic exposure associated with MDR *P. aeruginosa* was observed for the carbapenems and fluoroquinolones; the longest duration was noted for cefepime and piperacillin/tazobactam. Fourth, access to local antibiograms can be useful in assessing local susceptibility rates in *P. aeruginosa* and in monitoring resistance trends over time. Based on the ATS/IDSA recommendations of using combination therapy in cases of nosocomial pneumonia, one centre devised a local ‘combination’ antibiogram to achieve optimal coverage for *P. aeruginosa*. Although this new combination antibiogram modality allowed modest fine-tuning of empirical antimicrobial regimens, the antimicrobial choices did not differ substantively from those based on a standard antibiogram. It should be pointed out that while antibiograms provide susceptibility data and aid in monitoring resistance trends over time, they do not reveal additional information concerning the timing of the isolate in relation to the patient’s hospital admission.

**Monotherapy versus combination coverage**

The potential clinical significance of combination therapy over monotherapy for *P. aeruginosa* pneumonia has been a controversial subject for many years. The use of combination therapy is thought to minimize the emergence of resistance and to increase the likelihood of therapeutic success through antimicrobial synergy. A contemporary *in vitro* study suggested that levofloxacin and imipenem might be an effective combination for preventing the emergence of resistance during treatment of *P. aeruginosa* infections. The theory behind the use of this combination is that the molecular mechanisms responsible for *P. aeruginosa* developing resistance to fluoroquinolones and imipenem during therapy do not overlap. Mutational decreases in the expression of OprD in the outer membrane of *P. aeruginosa* can lead to the development of resistance to imipenem during the course of therapy, but this mechanism does not affect susceptibility to fluoroquinolones. Likewise, mutational changes in fluoroquinolone targets or mutations leading to increased expression of multidrug efflux pumps can result in the emergence of resistance to fluoroquinolones during therapy but do

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not directly affect susceptibility to imipenem. The one potential exception associated with the levofloxacin/imipenem combination is the dual resistance to fluoroquinolones and imipenem that develops when mutants overexpress the mexEF–oprN efflux pump.\(^29\) Although this efflux pump does not directly affect imipenem activity, mutational increases in the expression of this pump are associated with a concurrent decrease in the transcriptional and translational expression of oprD, leading to dual resistance to both drugs. While this is plausible in theory, prevention of this type of antibiotic resistance by combination therapy has yet to be validated in clinical trials.

The clinical utility for combination therapy in *P. aeruginosa* pneumonia ultimately rests on reducing the likelihood of inappropriate treatment. In a retrospective, multicentre, observational study of Spanish hospitals that included 183 episodes of monomicrobial *P. aeruginosa* VAP, the use of two empirical antipseudomonal antibiotics resulted in less microbiological failure and improved survival.\(^30\) However, the use of monotherapy in the definitive regimen did not influence mortality, length of stay, development of resistance or appearance of recurrences. In contrast, a recent meta-analysis of 11 trials, of which 13.8% were infected with *Pseudomonas* species, compared monotherapy with combination therapy in clinically suspected VAP.\(^31\) No mortality differences were observed between any of the regimens compared. Rates of mortality and treatment failure for monotherapy compared with combination therapy were also similar. The study was limited by the low percentage of episodes of VAP caused by MDR or difficult-to-treat organisms in the trials. Because these patients would be expected to benefit the most from empirical combination therapy, it was not surprising that there was no benefit of empirical combination therapy over monotherapy. Heyland and co-workers\(^32\) subsequently conducted a multicentre, randomized trial to compare the effect of combination therapy with the effect of monotherapy with broad-spectrum antibiotics on 28 day mortality in the initial treatment of critically ill patients who had suspected late-onset VAP. Overall, monotherapy was associated with similar outcomes compared with combination therapy, but in a subgroup of patients who had infection due to *Pseudomonas* species, *Acinetobacter* species and MDR Gram-negative bacilli at enrolment, the adequacy of initial antibiotics (84.2% versus 18.8%, \(P<0.001\)) and microbiological eradication of infecting organisms (64.1% versus 29.4%, \(P=0.05\)) was higher in the combination group than in the monotherapy group. A shorter duration of ventilation and ICU stay, and lower ICU and hospital mortality were also reported. Albeit there were no differences in clinical outcomes, this subgroup analysis was underpowered to demonstrate statistical significance. In the absence of strong evidence to the contrary, a combination strategy of two active anti-pseudomonal agents should be initiated when the local resistance patterns and individual patient risk factors suggest the possibility of *P. aeruginosa* pneumonia.

**Duration of treatment**

The optimal duration of antimicrobial therapy for *P. aeruginosa* pneumonia remains uncertain. For uncomplicated, bronchoscopically diagnosed VAP, a short course of therapy (8 versus 15 days) was as effective as a traditional long-course therapy.\(^33\) In the 8 day group, the number of antibiotic-free days by day 28 increased and the isolation of resistant pathogens when recurrence was diagnosed decreased. Mortality rate in the 8 day group was 18.8% compared with 17.2% in the 15 day group, an absolute difference of 1.6% (90% confidence interval \(-3.7\%\) to \(-6.9\%)\). Theoretically, this approach reduces ecological pressure and diminishes side effects without compromising outcome. However, a subgroup of patients with non-fermenting Gram-negative bacteria (including *P. aeruginosa*) had a higher recurrence of pulmonary infection with the 8 day treatment regimen. One of the potential causes of delayed eradication of *P. aeruginosa* bacteria from the alveolar space may be attributed to the presence of the type III secretion system that interferes with neutrophil functions.\(^34\) Longer therapy for VAP caused by non-fermenting Gram-negative bacilli may be considered,\(^35\) but whether prolonged antibiotic therapy will contribute to improved outcomes or decreased relapses remains unknown. An alternative approach would be to implement a surveillance strategy coupled with early bronchoscopic intervention following discontinuation of a short course of antibiotic therapy.\(^33\) Further studies are needed to confirm the safety and efficacy of these approaches.

**Antipseudomonal therapy**

**Polymyxins**

The absence of new classes of antibiotics in development for MDR Gram-negative bacteria has led to the resurgence of old antibiotics as a last resort in the treatment of MDR *P. aeruginosa* pneumonia.\(^36\) Polymyxins are cyclic, positively charged peptide antibiotics derived from various species of *Paenibacillus (Bacillus) polymyxa*. Of the five polymyxins (polymyxins A–E) originally described, two [polymyxin B and polymyxin E (colistin)] have been used in the clinical setting. The mechanism of action of these compounds involves a detergent-like effect that disrupts membrane integrity and results in leakage of intracellular components.\(^37\) Because of this distinctive property they are sheltered from cross-resistance with other antipseudomonal agents and are protected from the rapid selection of resistance.\(^38\)

Most of the reintroduction of polymyxins during the last decade has focused on colistin. Colistin has increasingly been used as salvage therapy\(^39\) alone or in combination with one or more antibacterials for the treatment of pneumonia with MDR strains.\(^40–46\)

In the absence of therapeutic alternatives, the efficacy of intravenous colistin for treating serious infections caused by MDR *P. aeruginosa* has outweighed its risk of nephrotoxicity and neurotoxicity. Recent studies using intravenous colistin have reported nephrotoxicity rates ranging from 8% to 36%.\(^39\) The risk of nephrotoxicity appears related to baseline renal function and prolonged courses (>4 weeks) of colistin. In comparison, 7%–29% of colistin recipients develop neurotoxicity in the form of oral and perioral paraesthesias, visual disturbances and polyneuropathy, with rare cases of respiratory failure or respiratory apnoea.\(^31,50\)

The *in vitro* synergy between colistin and rifampicin has resulted in the use of combination therapy in a few patients with pneumonia due to MDR *P. aeruginosa* infection.\(^47,51\) However, the evidence from the limited clinical studies suggests that this combination therapy was not superior to colistin monotherapy.\(^46,52,53\) Other antimicrobial agents have also been used in combination with colistin, including imipenem, meropenem, aztreonam, piperacillin, ceftazidime and ciprofloxacin, but none of these regimens showed improved outcome in clinical studies.\(^53\)
Sporadic cases of infections by colistin-resistant 
P. aeruginosa have been reported. Colistin resistance has been also confirmed in metallo-β-lactamase-producing 
P. aeruginosa. In one report, clinical cure of these infections was observed in two out of three suspected pneumonia patients with combination of colistin and β-lactam antibiotics. Prolonged colistin exposure (>2 weeks) was a prerequisite for resistance development in these particular strains. The mechanism involves an altered PmrAB activated by a sensor phosphokinase, with concomitant selective suppression of the corresponding deactivator PmrB phosphatase. This results in constitutive activation of the PmrA regulon, which stimulates aminooarabinose synthesis. Other proposed mechanisms include overexpression of OprH caused by mutation or as a result of adaptation to an Mg\(^{2+}\)-deficient medium.

Compared with colistin, there is very limited clinical experience with polymyxin B in the treatment of 
P. aeruginosa pneumonia. To our knowledge, four studies have examined the use of intravenous polymyxin B for treatment of lower respiratory tract infections caused by MDR 
P. aeruginosa. Furtado and co-workers analysed retrospectively 74 patients with MDR 
P. aeruginosa pneumonia who were treated with polymyxin B by continuous infusion over 24 h. Concomitant antibiotic therapy was prescribed for 28 patients (37.8%). Imipenem was the most common agent administered in combination. The duration of polymyxin B therapy ranged from 5 to 38 days. Although 35 patients (47.3%) had complete or partial resolution of symptoms and signs by the end of treatment, in-hospital mortality was elevated at 74.3%. Two other studies, investigated intravenous use of polymyxin B in a subgroup from a cohort of patients with infections caused by metallo-β-lactamase-producing 
P. aeruginosa. Twenty-two patients had nosocomial pneumonia, including 10 patients with VAP. Despite receiving adequate therapy, 30 day mortality exceeded 50%. Previously, Sobieszczuk and colleagues conducted a retrospective analysis of 25 critically ill patients with pneumonia who received 29 courses of polymyxin B administered in combination with another antimicrobial agent. Six of those courses were given in aerosolized form. 
P. aeruginosa was isolated from 41% of the cases. The mean duration of polymyxin B therapy was 19 days (range 2–57 days). Forty-one per cent achieved microbiological clearance. Mortality at the end of treatment was 21% and overall mortality at discharge was 48%. Nephrotoxicity was observed in three patients (10%) and did not result in discontinuation of therapy.

Considering the preliminary data from observational studies that support the non-inferiority outcome of intravenous polymyxins, therapy should be restricted to MDR strains for ≤2 weeks while optimizing pharmacokinetics and pharmacodynamics. De-escalation should be strongly pursued whenever culture results permit replacement with another antibiotic. Meanwhile, future randomized controlled trials are needed to evaluate the efficacy of colistin monotherapy or combination therapy in the management of MDR 
P. aeruginosa pneumonia.

New antipseudomonal antibiotics

Doripenem

Doripenem is a new carbapenem with potent in vitro activity against various aerobic and anaerobic Gram-positive and Gram-negative bacteria. It is stable against many β-lactamases, except for the class B metallo-β-lactamases, and, like meropenem, has some stability against human renal dehydropeptidase I. It binds to penicillin-binding proteins, causing cell wall damage and bacterial death. Renal dose adjustment is required since the drug is cleared by the kidney. In vitro antibacterial activity against wild-type 
P. aeruginosa is 2–4-fold more potent than meropenem and imipenem. In a study comparing the in vitro activity of doripenem with other antipseudomonal antibiotics (imipenem, levofloxacin, piperacillin, ceftazidime, aztreonam, tobramycin and cefepime), the MIC of doripenem was lower than those of all comparative agents against 
P. aeruginosa isolates. Based on MIC\(_{50}\) and MIC\(_{90}\) data, doripenem was the most potent carbapenem tested. Doripenem had MIC\(_{50}\)s of 2 and 16 mg/L for ceftazidime-susceptible and -resistant isolates, respectively, compared with meropenem (8 and 32 mg/L, respectively) and imipenem (16 and 32 mg/L, respectively). In addition, the propensity to select for resistant 
P. aeruginosa mutants in vitro was lower for doripenem than for the other carbapenems.

Two clinical studies evaluating the efficacy of doripenem in nosocomial pneumonia have been published recently. The first randomized, open-label, Phase III study of 531 patients compared doripenem with imipenem. Patients were randomized to receive one of three treatment regimens: 500 mg doripenem every 8 h via 4 h intravenous infusion, 500 mg imipenem every 6 h via 30 min infusion or 1000 mg imipenem every 8 h via 60 min intravenous infusion for 7–14 days. Patients assigned to imipenem received either 500 mg every 6 h or 1000 mg every 8 h depending on the practice of the institution. These two imipenem regimens were considered pharmacodynamically equivalent. There was no statistically significant difference in clinical cure between the two groups (68.3% for doripenem and 64.8% for imipenem). In a subgroup analysis, 
P. aeruginosa was isolated from 28 patients in the doripenem group and 25 in the imipenem group. The MIC was <8 mg/L for all isolates at baseline and 18% in total (baseline and follow-up cultures) in the doripenem group compared with 13.2% at baseline and 64% in total (baseline and follow-up cultures) in the imipenem group (P < 0.01). There was also a statistically non-significant trend towards higher clinical cure rates with doripenem [16/20 (80%)] versus imipenem [6/14 (42.9%)]. A second randomized, Phase III, prospective, open-label study of 448 patients with nosocomial pneumonia or early onset VAP (<5 days) compared doripenem with piperacillin/tazobactam. Patients were randomized to receive either 500 mg doripenem intravenously every 8 h as a 1 h infusion or 4.5 g piperacillin/tazobactam intravenously every 6 h as a 30 min infusion. Step-down therapy to oral levofloxacin was allowed after ≥72 h. Overall, the microbiological and the clinical cure rates in the clinically evaluable population were 84.5% and 81.3% for doripenem and 80.7% and 79.8% for piperacillin/tazobactam (P = NS), respectively. Favourable microbiological outcome rates against 
P. aeruginosa were higher in the doripenem arm than in the piperacillin/tazobactam arm, but the difference was not statistically significant. As a result, a higher dose of doripenem (1 g infused over a 4 h period every 8 h) is being compared with imipenem/cilastatin (1 g intravenously every 8 h) in a randomized, double-blind, multicentre study in subjects with VAP, under the assumption that this dose would provide a more sustained duration of free drug level above the MIC than the previously used 500 mg dose for most organisms that cause VAP, including the more resistant 
P. aeruginosa and Acinetobacter species.
Biapenem

Biapenem is a parenteral carbapenem antibacterial agent that was launched in Japan in 2002 and is currently in Phase II trials in the USA. It has a broad spectrum of in vitro antibacterial activity against Gram-negative (including β-lactamase-producing strains and P. aeruginosa), Gram-positive and anaerobic bacteria. Biapenem shows a good post-antibiotic effect, similar to imipenem, and has a high bactericidal activity against Pseudomonas biofilm-forming strains and several efflux system mutants. The mean plasma half-life is ~1 h and the recommended dosage is 300 mg administered as an intravenous infusion twice daily. The dosage must be adjusted in the presence of renal impairment.

Although the in vitro activity of biapenem against P. aeruginosa tends to be similar to that of imipenem in most investigations, two studies have suggested that biapenem was more active than imipenem. For example, of 67 clinical isolates of P. aeruginosa, 98% were susceptible to biapenem at concentrations of ≤8 mg/L, compared with 84% susceptible to imipenem (at concentrations of ≤8 mg/L). In clinical trials, 300 mg biapenem twice daily showed clinical and bacteriologic efficacy similar to that of 500 mg imipenem/cilastatin twice daily (each given for up to 14 days) in adult patients with various types of bacteriologically documented lower respiratory tract infections, including those with P. aeruginosa. Clinical efficacy rates in the biapenem and imipenem/cilastatin groups were 94.8% (73/77 patients) and 92.8% (64/69), respectively. Bacterial eradication was achieved in 90.9% (20/22) of biapenem and 93.1% (27/29) of imipenem/cilastatin recipients.

Tomopenem

Tomopenem (CS-023) is a novel 1-β-methylcarbapenem that has a very broad-spectrum activity against Gram-positive and Gram-negative bacteria, including P. aeruginosa, methicillin-resistant Staphylococcus aureus and penicillin-resistant Streptococcus pneumoniae. In vitro and in vivo murine studies showed that tomopenem exhibited improved activity against P. aeruginosa. Its potent, broad-spectrum activity is thought to be related to its strong affinity for penicillin-binding proteins 2 and 3. Similar to other new carbapenems, tomopenem demonstrates a very low tendency for the spontaneous emergence of resistance.

In a murine model of chronic airway infection by P. aeruginosa, tomopenem significantly reduced the number of viable bacteria compared with controls. What is more promising is that tomopenem remained active against laboratory mutants of P. aeruginosa characterized by overproduction of chromosomally encoded AmpC β-lactamase, deficiency in OprD and overproduction of the multidrug efflux pumps MexAB–OprM and MexCD–OprJ. Hitherto, all data are derived from in vitro studies and no clinical trials have been initiated so far.

Ceftobiprole

Ceftobiprole is a fifth-generation cephalosporin with properties similar to those of tomopenem in its strong affinity for penicillin-binding proteins. Ceftobiprole medocaril is a water-soluble prodrug that is rapidly converted (in seconds) to the active drug, diacetyl and carbon dioxide by plasma esterases. An insignificant amount of ceftobiprole is converted to an open-ring metabolite via hydrolysis. The antipseudomonal activity of ceftobiprole is similar to that of cefepime, displaying identical MIC50 and MIC90 in vitro studies. In a study assessing 741 isolates of P. aeruginosa, 72% of isolates were inhibited by ≤4 mg/L ceftobiprole, compared with 68% and 73% of isolates being inhibited by ≤4 mg/L cefepime and ceftazidime, respectively.

Ceftobiprole has completed one Phase III investigation for the treatment of hospital-acquired pneumonia (HAP) including a subgroup of patients with VAP. Participants were randomized to receive 500 mg ceftobiprole intravenously every 8 h as a 2 h infusion or ceftazidime plus linezolid for a total of 7–14 days. Seventy patients had P. aeruginosa pneumonia. Overall, 69% of the clinically evaluable (CE) patients were cured with ceftobiprole compared with 72% of patients treated with combination therapy. The study met non-inferiority criteria in both CE and intent-to-treat populations. In the CE patient population excluding VAP, clinical cure rates were 77% for ceftobiprole and 76% for combination therapy. However, the cure rates in the VAP patient subset were lower for ceftobiprole-treated patients and non-inferiority could not be established. Interestingly, the difference in microbiological eradication rates between treatment groups that favoured the ceftazidime/linezolid arm was not related to P. aeruginosa.

Sitafloxacin

Sitafloxacin has activity comparable to that of ciprofloxacin towards wild-type strains of P. aeruginosa, but shows lower MICs for gyrA or parC mutants, due to a better affinity for the mutated targets. Phototoxicity is a major drawback of all 8-chloro-derivatives of the fluoroquinolone class. A Phase II, randomized, open-label, multicentre study demonstrated that sitafloxacin (400 mg once daily) was as safe and as well tolerated as imipenem (500 mg three times a day) for the treatment of pneumonia, including two cases of P. aeruginosa pneumonia, one in each group.

Aerosolized antibiotics

Aerosolized antibiotics have been used for pneumonia treatment and prophylaxis, mainly in patients with underlying chronic pseudomonal infections as found in cystic fibrosis. However, there are not enough data to support using aerosolized antibiotics for HAP and VAP caused by P. aeruginosa in non-cystic fibrosis patients. The ATS/IDSA guidelines for the treatment of HAP and VAP recommend using aerosolized antibiotics only in selected patients who are not responding to systemic antibiotics. Recently, a Phase II study (AMIK-04-02) of aerosolized BAY 41-6551 delivered through the patented Pulmonary Drug Delivery System in intubated and mechanically ventilated patients with VAP or HAP was completed. Eligible patients were randomized in a 1:1 fashion to receive either aerosolized BAY 41-6551 (400 or 800 mg) or placebo every 12 h for a period of 7–14 days. Sixty-nine patients were enrolled in this multicentre, multinational study, with 67 patients receiving at least one dose of study medication. The delivery of aerosolized amikacin (Amikacin Inhale; Nektar, CA, USA) achieved high aminoglycoside amikacin concentrations in the fluid lining the airways.
epithelial surface of the lower respiratory tract, including in the pneumonia area of the lung, while maintaining safe serum concentrations. No serious events were reported. Building on the results of this trial, a dose of 400 mg every 12 h was chosen for the Phase III trial that is currently underway (conducted by Bayer Healthcare and Nektar Therapeutics).

In parallel, there is a paucity of data regarding the use of aerosolized colistin in patients without cystic fibrosis. Despite the lack of randomized controlled trials, the efficacy of inhaled colistin for MDR *P. aeruginosa* pneumonia has been suggested in recent studies. Pereira et al. described clinical features and outcomes of 19 patients treated with inhaled polymyxin B. Fourteen of them had nosocomial pneumonia (11 had VAP) and were concomitantly treated with intravenous polymyxin B. *P. aeruginosa* was the aetiological agent in 11 of these 14 patients. Nine (64%) of the 14 patients died during hospitalization, although 13 (93%) of them were described initially as having a favourable response. Interestingly, most of the patients selected for this study had previously failed intravenous polymyxin B therapy. A similar study of 60 critically ill patients infected with MDR Gram-negative bacteria received 2.2 ± 0.7 million IU aerosolized colistin for VAP. *P. aeruginosa* was reported in 12 patients. Bacteriological and clinical response was observed in 50/60 (83.3%) patients, with an overall mortality of 25%. No adverse effects related to inhaled colistin were recorded. Recently, Falagas et al. reviewed published data on monotherapy treatment with aerosolized antibiotics for pneumonia in 63 cases. *P. aeruginosa* isolates accounted for 16% of all pathogens. Colistin (49%), penicillin (37%) and aminoglycosides (17%) were the antimicrobials administered via the respiratory tract. Concurrent systemic antimicrobials were given to 33% (21/63) of patients. Clinical cure and bacteriological eradication from the aforementioned specimens were observed in 86% (54/63) and 85% (33/39) of patients, respectively. For the 31 patients for whom data were available, all-cause mortality and attributable mortality were 36% (11/31) and 10% (3/31), respectively. In another meta-analysis of five randomized controlled trials of 176 patients with nosocomial pneumonia (including *P. aeruginosa* pneumonia), Ioannidou and colleagues compared administration of antimicrobials via the respiratory tract (with or without concurrent usage of systemic antibiotics) with control treatment. Tobramycin was used in three studies, sisomycin in one and gentamicin in another. Concurrent systemic antibiotic was allowed to be used in four studies. Higher treatment success was observed in patients with nosocomial pneumonia who received treatment with antibiotics via the respiratory route (inhaled or endotrachially instilled). However, neither the mortality rate nor the incidence of resistance was statistically different.

New formulations for inhaled therapy are currently under investigation for ciprofloxacin and aztreonam. An inhaled liposomal formulation of ciprofloxacin was recently approved by the US FDA for the management of bronchiectasis. Designed to prolong the short-acting nature of ciprofloxacin and to localize its activity to the lungs, the aerosolized formulation is intended to allow sufficient pulmonary exposure to treat these infections. A Phase III trial is currently planned for assessing its efficacy in patients with VAP. Similarly, an inhalable formulation of aztreonam lysinate has been tested in Phase III clinical trials in patients with cystic fibrosis who are colonized with pulmonary *P. aeruginosa*. Preliminary data showed a significant reduction in *P. aeruginosa* colony-forming units compared with placebo. The drug is currently under review by the US FDA.

Although the available data seem to suggest that aerosolized antimicrobial therapy for *P. aeruginosa* pneumonia should not be excluded a priori, the lack of large randomized, controlled trials continues to raise concern about its efficacy and potential emergence of resistance.

**Novel antibacterial agents**

Increasing resistance to antibiotics and the emergence of MDR strains have led to the development of experimental new antibacterial agents beside antibiotics. While antibiotics target bacterial growth, an attempt to attenuate the bacteria by intervening in the release of virulence factors is a promising alternative to combat the growing incidence of MDR bacteria. Many of these agents are antibodies that bind to proteins or receptors located in the bacterial body and therefore inactivate one of the virulence systems responsible for its pathogenesis. While it is beyond the scope of this article to discuss all potential therapeutic targets, three monoclonal antibodies are undergoing clinical trials, with one of them being targeted for mechanically ventilated patients.

**Inhibition of type III secretion system**

Type III secretion system (TTSS) is one of the virulence mechanisms associated with severe disease and increased mortality in patients with VAP caused by *P. aeruginosa*. TTSS is a complex of bacterial structures that provide the Gram-negative bacteria with a potent virulence mechanism, enabling them to inject bacterial effecter proteins directly into the host cell cytoplasm, which allows the bacteria to cause changes in the cell immune system and epithelial cell injury. The system consists of three separate protein complexes: the secretion apparatus itself, the translocation or targeting apparatus (PcrV protein), and the secreted toxins (effecter proteins) and their cognate chaperones. The virulence of TTSS was observed not only in animal models but also in patients with *P. aeruginosa* VAP in whom the TTSS-positive phenotype was difficult to eradicate from the lung tissue even after appropriate antibiotic treatment.

In a mouse lung infection model, PcrV protein immunization provided protection against lethal lung infection, lung injury and cellular toxicity. Antibodies to PcrV also inhibited the translocation of type III toxins. Moreover, vaccination against PcrV increased the survival of challenged mice, and decreased lung inflammation and injury. These promising results paved the way for a Phase I/II human trial using monoclonal antibodies against PcrV. The antibody fragment, conjugated to polyethylene glycol (PEG), is currently in clinical development for the treatment of *P. aeruginosa* lung infections in cystic fibrosis and in mechanically ventilated patients. This drug candidate has novel properties that address potential problems with antibody-based antibacterial therapeutics. The activity of the Fab fragment is considered key in reducing sensitivity to *Pseudomonas* proteases that degrade IgG antibodies, while PEGylation extends in vivo half-life and further reduces susceptibility to proteolytic inactivation. The ability of the Fab fragment to inactivate the TTSS results in the prevention of toxin injection into cells and...
averts the direct killing of macrophages by the TTSS that occurs even in the absence of toxins.109

Conclusions

P. aeruginosa pneumonia is often a severe and life-threatening disease. Management of this infection represents a difficult therapeutic challenge for critical care physicians, as the increasing resistance level of these microorganisms to most classes of antimicrobial agents frequently leads to clinical failure. Choosing adequate antibiotics is crucial to increase survival rate. The new generation of antibiotics does not appear to offer significant advantages over the traditional arsenal of antimicrobial agents. For patients infected with MDR strains, very few clinical options exist. Colistin has emerged as a viable alternative for those infected with these strains. Whether combination therapy with colistin offers superior advantage over monotherapy requires future randomized trials. With a limited pipeline of new classes of antimicrobial agents, studying the bacterial genome has opened the possibility of identifying new targets; however, most of these agents are still under preliminary investigation and have just entered the clinical arena in Phase I/II trials.

Transparency declarations

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