Ventilator-associated pneumonia (VAP) is an important cause of morbidity and mortality in intensive care unit (ICU) patients and the most frequent nosocomial infection in this patient population. The reported incidence of VAP varies widely from 10 to 85%, although the true incidence has been difficult to determine because the criteria that are normally used to diagnose pneumonia in non-mechanically ventilated patients (fever, leucocytosis, purulent secretions and new or progressive infiltrates on a chest X-ray) are not specific to infection in mechanically ventilated patients and may be associated with several non-infectious processes that mimic infection, including the adult respiratory distress syndrome, haemorrhage, pulmonary embolism, lung contusion, atelectasis, fat embolism, pulmonary oedema and aspiration pneumonitis. The use of clinical criteria alone, therefore, has led to high rates (30–60%) of misdiagnosis. In addition, the isolation of potentially pathogenic bacteria from endotracheal secretions does not necessarily reflect the flora of the lower respiratory tract, owing to contamination by bacteria colonizing the upper tract. These difficulties have confounded efforts to confirm the diagnosis of VAP, to define the relationship between VAP and mortality and to draw meaningful conclusions from clinical trials designed to determine the optimal therapeutic regimen for patients who develop this complication.

A number of other diagnostic techniques, both bronchoscopic and non-bronchoscopic, have been introduced and many of these have improved the accuracy of diagnosing VAP, particularly if carried out before antibiotic therapy has been initiated or modified, and have reduced the number of patients who have been treated unnecessarily. However, there has been no agreement on the optimal technique and many of the investigations are expensive, time-consuming and associated with unacceptably high false-negative rates, the implication being that patients who genuinely have pneumonia will not receive treatment. For the time being, it is likely that most ICUs in the UK will continue to rely on standard clinical, radiological and microbiological criteria, reserving invasive procedures for those patients who have failed to respond to empirical therapy.

The administration of appropriate antibiotic therapy to patients with VAP is clearly important, there being a statistically significant association between the use of inappropriate treatment and death in such patients. However, a recent survey of 305 ICUs in the UK and Ireland confirmed that there is no consensus regarding the optimal empirical therapeutic regimen (author’s unpublished data). Of 133 evaluable responses, 25 different antibiotic regimens were recommended as first-line therapy of patients with VAP. Second- or third-generation cephalosporins (with or without an aminoglycoside and/or metronidazole) accounted for 90 of the 133 (68%) regimens. Other less commonly administered agents included piperacillin/tazobactam (6%), a quinolone (6%), imipenem (5%) and co-amoxiclav (4.5%); aminoglycosides formed part of 8% of the regimens.

A number of criteria can be used to facilitate the choice of empirical therapy. Foremost amongst these is the recognition of the probable pathogen(s), early onset infections (i.e. those presenting within 4 days following admission to hospital) being caused primarily by Streptococcus pneumoniae, H. influenzae and, in patients who have undergone neurosurgery or who have sustained head injuries, Staphylococcus aureus. Late onset pneumonias (those presenting >5 days after admission), on the other hand, are caused principally by aerobic Gram-negative bacilli (AGNB), including Pseudomonas aeruginosa, various Enterobacteriaceae and, increasingly, Acinetobacter spp.; the importance of anaerobes in the aetiology of VAP is controversial. The susceptibilities of the likely pathogens, which are in turn influenced by local experience, the duration of hospitalization and the previous years, have been documented by a number of authors and have been used to guide the choice of empirical therapy.

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administration of antibiotics, must also be considered; in one study, the incidence of pneumonia caused by P. aeruginosa or A. cinetobacter spp. was 65% in patients who had received antibiotics for any reason within ten days of the onset of pneumonia, compared with 19% in those who had not received antibiotics (P < 0.01). The severity and rate of progression of the pneumonia will have an influence on the choice of therapeutic regimen, there being little margin for error in severely ill patients. A count must also be taken of pharmacokinetic and pharmacological properties of the antibiotics and patient factors, such as renal and hepatic functions, that will affect these. Other considerations include the potential impact of the choice of therapy on the ecology of the ICU, excessive use of third-generation cephalosporins and glycopeptides being associated with the emergence of extended spectrum β-lactamase-producing strains of A GNB and vancomycin-resistant enterococci, respectively, and cost. On the basis of these principles and the results of the previously mentioned questionnaire, the recommendations that appear in Table I are suggested for use in most ICUs.

But what about patients with severe pneumonia, especially those who are also septicaemic, shocked and/or who have multiple organ failure? In the past, a combination of a β-lactam and an aminoglycoside was the most widely used regimen. However, the introduction of antibiotics with very broad spectra of activity (third-generation cephalosporins, carbapenems and quinolones) has made monotherapy an acceptable alternative. What then are the therapeutic options?

The aminoglycosides have several attractive features, including activity against a wide range of A GNB, potent bactericidal activity (which is greater than that of β-lactam antibiotics against certain A GNB), the potential for synergic activity (with β-lactams) against A GNB and a lack of inoculum dependence. They are also less likely to promote the development of resistance during courses of therapy and may even provide some protection for the partner β-lactam. On the other hand, they have narrow therapeutic ratios, penetrate poorly into the tissues of the respiratory tract, have poor activities under conditions of low pH and/or redox potential and have been associated with inferior clinical response rates when used alone. The efficacy of once-daily aminoglycoside dosing in patients with V A P caused by A GNB has not been assessed.

Several β-lactams have sufficiently broad spectra of activity against A GNB (including P. aeruginosa and other multi-resistant strains) to enable them to be used as empirical therapy in this clinical setting. They also have moderate-to-good penetration into the respiratory tract and good safety profiles and have produced clinical and bacteriological response rates of between 60% and 90%. However, some of these agents have reduced activities against Gram-positive cocci, including pneumococci and S. aureus, and they have been associated with the emergence of resistant strains during courses of therapy. Cefazidime is particularly active against P. aeruginosa and has been the most widely evaluated of these agents. In several clinical trials, its efficacy has been shown to be comparable to that of various β-lactam/aminoglycoside combinations. Other β-lactams and quinolones. Other β-lactams that have been assessed, albeit less extensively, as therapy of patients with severe lower respiratory tract infections and shown to be effective include cefoperazone, aztreonam and piperacillin/tazobactam.

The carbapenems (imipenem and meropenem) are extremely broad-spectrum antibiotics, but the incidence of resistance to them, especially amongst P. aeruginosa isolates, is increasing. There have also been reports of resistant strains emerging during courses of therapy and these were associated with treatment failures. Following a trial in which imipenem was compared with pefloxacine, Giamarelou et al. reported that 16 of 31 (52%) imipenem treatment failures were caused by P. aeruginosa strains and that of 18 pathogens that had not been eradicated from patients in the imipenem group, 12 became resistant to this.
agent; ten of these 12 were *P. aeruginosa* isolates. Similar observations have been reported for imipenem and, more recently, for meropenem.

The quinolones exhibit activity against most *A G N B* and are concentrated in the tissues of the respiratory tract, but they have only modest activities against streptococci and *S. aureus* and the incidence of resistance amongst *P. aeruginosa* isolates has been increasing. Open or comparative trials have shown that at least three of these agents (ciprofloxacin, ofloxacin and pefloxacin) are effective therapy of patients with nosocomial pneumonias.

In a large multicentre study comparing ciprofloxacin with imipenem in hospitalized patients (79% of whom were mechanically ventilated) with severe pneumonias (78% of which were nosocomial), the clinical response rate was significantly higher in patients who had received ciprofloxacin than in those who had been given imipenem (P < 0.05). However, there was no significant difference between the groups in terms of the bacteriological response rate. Moreover, both agents failed to eradicate the majority of *P. aeruginosa* strains, of which 33% and 53% in the ciprofloxacin and imipenem groups, respectively, became resistant during or following completion of therapy. The investigators concluded that infection with *P. aeruginosa* is a risk factor for failure of treatment with either agent and that neither should be used alone to treat patients with V A P caused by this pathogen.

When it comes to a choice between monotherapy and combination therapy there are arguments both for and against each strategy. In favour of combination therapy are the enhanced spectrum of activity and the reduced likelihood of resistant strains emerging during courses of therapy. There may also be greater potency as the result of the potential for synergy, support for this contention having been provided by Hilf et al. who demonstrated a statistically significant reduction in the mortality rate (35%) in patients with *P. aeruginosa* bacteraemic pneumonia receiving combination therapy, compared with that (88%) in patients receiving monotherapy. On the other hand, there is a greater risk of toxicity, especially with regimens which include an aminoglycoside, the costs are higher and there is, to date, no convincing evidence, based on prospective, randomized clinical trials, that combination therapy is superior to monotherapy in patients with severe V A P. Indeed, there have been numerous trials that have demonstrated that the latter compares favourably with the former. However, a critical review of these studies reveals that, without exception, they are characterized by one or, more commonly, several flaws in their design and/or execution. Many of them involved small numbers of patients, were non-comparative and/or enrolled heterogeneous populations of patients, i.e. not only those with nosocomial pneumonia, but also those with community-acquired pneumonia, septicaemia, peritonitis or pyelonephritis. In most studies, the majority of patients were not mechanically ventilated and extrapolation of results of antibiotic trials on non-mechanically ventilated patients to those who are mechanically ventilated may be unreliable. Frequently, investigators excluded patients with diseases associated with high mortality, such as those with severe pneumonia, those who required mechanical ventilation and those who were shocked or had significant renal or hepatic impairment—precisely those patients in whom the efficacy of monotherapy has not yet been demonstrated. Because the clinical diagnosis was infrequently confirmed by an invasive procedure, it is likely that significant percentages of patients who did not have pneumonia were included in the analyses. Similarly, as the putative pathogens were usually identified by culture of tracheal aspirates, there is a high probability that the data relating to the aetiological agents of V A P are inaccurate. In a number of studies, aminoglycosides were combined with agents, such as clindamycin, which have no activities against *A G N B* in general or with those, such as ampicillin, cefazolin, cefuroxime or ceftriaxone, which are not active against *P. aeruginosa* specifically; thus many patients effectively received monotherapy with an aminoglycoside. Finally, it has been shown that in patients with pneumonia caused by *A G N B*, a favourable outcome correlated with peak serum gentamicin or tobramycin concentrations of > 7 mg/L. A s Table II shows, many patients enrolled in published clinical trials received aminoglycosides in dosages that would have produced serum concentrations lower than that. It is tempting to speculate that the response rates in patients receiving combination therapy might have been higher than those reported had they been given single daily dosages of 5–6 mg/kg, a strategy that has not yet been evaluated in this clinical setting. For all of these reasons, the results of virtually every clinical trial that has compared monotherapy with combination therapy are unreliable and to conclude that the former is equivalent to the latter is, therefore, not based on sound scientific evidence.

What can be deduced from the published studies and a critical analysis of them? Firstly, while many investigators have claimed that combination therapy is comparable to monotherapy, they have none the less recommended the

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former regimen if infection caused by P. aeruginosa cannot be excluded; in practice, however, it is often difficult, if not impossible, to rule out this pathogen before the results of culture are available. Secondly, it is apparent that there has not been a well-designed and well-executed clinical trial, in which subjects in the combination group received aminoglycoside dosages that consistently produced therapeutic concentrations, that has demonstrated convincingly that monotherapy is at least as effective as combination therapy. Unless, and until, such a trial confirms this to be the case, the ‘gold standard’ of empirical antimicrobial therapy for mechanically ventilated patients with severe nosocomial pneumonias, especially those with multiple organ failure/sepsis syndrome, should be an aminoglycoside, at optimal dosage, combined with a β-lactam, i.e. a third-generation cephalosporin with activity against P. aeruginosa, piperacillin, piperacillin/tazobactam, aztreonam or a carbapenem. (A β-lactam agent with reliable activity against anaerobic bacteria should be included when aspiration pneumonia has been diagnosed.) Such a regimen benefits from the potency of the aminoglycosides and the potential for synergy, both of which contribute to more rapid bacterial clearance and, consequently, less pulmonary tissue damage. It might also prevent the development of resistance to the β-lactam and increases the likelihood that the in-vitro activity of at least one component of the regimen (the aminoglycoside) will be maintained throughout the treatment course. (This recommendation is consistent with guidelines issued recently by the American Thoracic Society, although the Society proposed that a fluoroquinolone might be used as an alternative to an aminoglycoside as part of a combination regimen with a β-lactam.45) If, after 3–4 days of combination therapy, a patient has exhibited a good clinical response, it seems reasonable to convert to monotherapy with an appropriate β-lactam or quinolone. Most investigators have treated patients with V A P for 7–10 days, although the optimal duration of therapy has not been determined and shorter courses may be equally effective. Finally, until monotherapy has been confirmed as being comparable to combination therapy, there should be a moratorium on clinical trials comparing one single-agent regimen with another in this clinical setting.

As well as the conventional treatment modalities, there are several additional therapeutic adjuncts, two of which are worthy of mention here.

Some bacterial species, including P. aeruginosa and S. aureus, elaborate exopolysaccharide biofilms or ‘slimes’ which surround these organisms when they are attached to endotracheal tubes and which make them relatively resistant to the actions of both antibiotics and host defences.44 Shedding of bacteria from the biofilm into the airways may contribute to the development of V A P or to relapses in patients who have already been treated for this complication. It would be sensible therefore to change the endotracheal tubes of patients with V A P, especially those with infections caused by P. aeruginosa or S. aureus, before or soon after antibiotic therapy is completed.

A nother therapeutic strategy that has been evaluated almost exclusively in patients with cystic fibrosis, but that might also have a role in the management of patients with V A P, is the use of aerosolized antibiotics. A aerosolized aminoglycosides, in particular, produce high concentrations in the bronchial lumen, low systemic absorption45,47 and an absence of toxicity.48–51 A number of studies have described improved pulmonary function in patients with cystic fibrosis following the administration of aminoglycosides by aerosol in dosages of 40–80 mg42–54 and, more recently, investigators have similarly demonstrated low systemic concentrations and an absence of toxicity even when much higher dosages (400–600 mg once to three times daily) were used.50,51 In addition, Ramsey et al.50 reported improved pulmonary function, a 100-fold reduction in the number of P. aeruginosa in sputum and no emergence of resistant strains. This strategy for delivering high antibiotic concentrations directly to the site of infection warrants further assessment in patients with V A P.

References


of ceftazidime and imipenem/cilastatin in patients with severe


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**Antimicrobial treatment of pulmonary colonization and infection by *Pseudomonas aeruginosa* in cystic fibrosis patients**

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Cystic fibrosis (CF) is the most common, serious, genetically inherited disease, affecting between 1 in 2000 and 1 in 4500 children of Caucasian origin.¹ It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, the most common of which occurs at position 508 (∆F 508) and accounts for 70% of all CF mutations.² These mutations increase the cellular absorption of sodium ions and block the secretion of chloride ions. The resultant dehydration of secretions and hindrance of mucociliary clearance mechanisms give rise to the charac-

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teristic features of the disease: pancreatic insufficiency, recurrent bacterial infection of the lower respiratory tract and, in the male, obstruction or absence of the vas deferens.

Lung infection with Pseudomonas aeruginosa is associated with the greatest morbidity and mortality in CF. Over 90% of patients will suffer from chronic endobronchial infection with this bacterium at some time and, once established, it is seldom eradicated. Following its acquisition, the sputum of most patients will contain P. aeruginosa on an intermittent basis for up to 2 years, but they will suffer few, if any, symptoms. However, about 20% of patients will progress from initial colonization to chronic infection almost immediately. This progression is often associated with the development of the mucoid P. aeruginosa phenotype. Production of alginate and extracellular enzymes such as elastase is thought to interfere with the eradication of the bacterium by host defences. The resultant microenvironment is also inhibitory to the efficient functioning of antibiotics. Bacterial biofilms and alginate, the slow growth phase of P. aeruginosa, macromolecular binding and the ionic milieu of sputum all contribute to reducing antibacterial activity.

There is no consensus between clinicians caring for patients with CF regarding the most appropriate management of chronic P. aeruginosa infection. A survey of the antimicrobial prescribing practices of 26 clinicians from centres in the U K and E ire revealed a wide variation in the agents used and the strategies used to deliver them. This is not surprising given the lack of conclusive scientific evidence for best practice from clinical trials. We shall discuss the most contentious issues of anti-pseudomonal antibiotic treatment, namely combination therapy versus monotherapy, appropriate routes of administration and the periodicity of treatment. The negative effects of prolonged and repeated antibiotic exposure and new developments will also be discussed. The role of adjunctive therapies, such as immunoglobulins and vaccination, are beyond the scope of this article and are discussed elsewhere.

Reviews of trials of iv therapy published in the 1980s highlighted many problems. The trials suffered from variable definitions of an infective exacerbation, a reliance on subjective rather than objective outcome measurements and a lack of well selected control groups, and many had too few patients to generate meaningful results. Some trials even cast doubt on the effectiveness of antibiotics in the treatment of acute exacerbations, claiming patients derived more benefit from oxygen, bronchodilators, musculotics and physiotherapy. However, recent studies have shown a significant correlation between the onset of acute exacerbations and increased tumour necrosis factor-α and C-reactive protein concentrations in host plasma and production of P. aeruginosa exoenzymes elastase, exotoxin-A and alkaline protease. Treatment of exacerbations with antibiotics reduces the levels of all of these markers to pre-exacerbation levels and brings about significant improvements in respiratory function. Sputum counts of P. aeruginosa are also significantly decreased by antibiotic therapy (although these usually remain >10⁶ cfu/g). Resting energy expenditure is also significantly reduced by antibiotic therapy, reflecting a dampening effect on host immune response.

Trials have failed to demonstrate any significant differences between regimens used to treat acute exacerbations. No particular iv regimen has proved significantly more effective nor has oral therapy (with ciprofloxacin) been shown to alter outcome significantly relative to standard iv treatment. Most clinicians chose an aminoglycoside (usually tobramycin) in combination with a β-lactam (usually an anti-pseudomonal penicillin) as first-line treatment. The choice of tobramycin is based on superior in-vitro activity against P. aeruginosa rather than any demonstrable benefit of tobramycin over other aminoglycosides in improving the patient’s condition, pulmonary function or sputum bacterial load in clinical trials. The decision to use it in combination with a β-lactam is based on the assumption that synergy will occur. A study of 122 strains of P. aeruginosa isolates from CF patients showed in-vitro synergy with tobramycin plus ticarcillin, tobramycin plus piperacillin, tobramycin plus ceftazidime, and tobramycin plus imipenem for 32%, 31%, 39% and 19% of strains, respectively. No combination exhibited antagonism for any of the strains examined. Earlier studies demonstrated synergy with aminoglycoside/β-lactam combinations for even greater numbers of strains. Synergy is not limited to aminoglycoside/β-lactam combinations. Synergy between ciprofloxacin plus aztreonam (4–30% of strains tested), ceftazidime plus aztreonam (29%) and ciprofloxacin plus ceftazidime (12–34%) has also been reported with P. aeruginosa strains from CF patients.

Most clinicians base their choice of antibiotic therapy on the most recently available susceptibility data. However, the unpredictable occurrence of synergy, even when strains are resistant to one or both agents of a given antibiotic combination, means that traditional methods of reporting strains as ‘susceptible’ or ‘resistant’ may be too crude for predicting clinical outcome. Consequently, synergy testing of various combinations against all isolates, where facilities exist, has been advocated. Outcome of therapy may also be better predicted by the use of serum bactericidal titres, or by determination of the relationship between peak serum concentrations and the MIC of antibiotics selected for treatment of P. aeruginosa. Unfortunately these techniques are time-consuming, fraught with technical difficulties and too costly to be offered routinely by the majority of laboratories.

Monotherapy is used as first-line treatment by a minority of clinicians but most clinicians use it occasionally. Ceftazidime is the most commonly employed agent. It has obvious advantages in terms of ease of administration, no requirement to measure serum concentrations, and low toxicity. It also makes home iv therapy more convenient. In two trials where ceftazidime was compared with combina-
tion treatment consisting of an aminoglycoside and an antipseudomonal penicillin no advantage for the latter therapy could be demonstrated. \(^{13}\) One study of ceftazidime with or without sisomicin showed no difference in outcome between the two groups. \(^{25}\) Carbapenems have also been used as monotherapy. A study comparing meropenem with ceftazidime monotherapy showed that the two regimens were equally successful in treating acute exacerbations of lung disease in CF, in terms of clinical response, improvements in respiratory function, and reduction of bacterial load. \(^{26}\) Trials of monotherapy with other agents, particularly anti-pseudomonal penicillins, have yielded less impressive results. \(^{13}\)

There is no direct evidence of resistance emerging during ceftazidime monotherapy. \(^{25,27}\) However, the use of ceftazidime monotherapy has been associated with two large outbreaks of multiple \(\beta\)-lactam-resistant \(P.\) aeruginosa in CF units. The first, in Denmark in the early 1980s, resulted in 69 of 119 patients chronically infected with \(P.\) aeruginosa acquiring a multi-resistant strain. \(^{28}\) Most were of the same serotype and phage type. Restrictive use of antibiotics was not sufficient in eradicating resistant strains, which persisted in 42% of patients, and patient isolation was required to curtail spread of the organism. The authors believed that extensive use of monotherapy with third-generation cephalosporins, particularly ceftazidime, was an important factor in promoting the outbreak. A more recent outbreak was documented in the UK. \(^{29}\) Sixty-five of 92 patients chronically colonized with \(P.\) aeruginosa harbouring ceftazidime-resistant strains. Fifty-five of these (85%) were shown by DNA macrorestriction to be the same epidemic strain. The authors in this report also believed that ceftazidime monotherapy was a contributory factor to the outbreak.

A much smaller unit reported a low incidence of resistance problems related to ceftazidime monotherapy. \(^{30}\) Over a 5 year period consideration had to be given to prescribing alternative agents in only about 10% of patients each month. Because most patients received their antibiotic treatment at home the authors speculated that this may have limited any spread of resistance.

Imipenem resistance was noted to increase between 1988 and 1992 during use at one Spanish clinic. \(^{31}\) Twelve (28.5%) of 42 patients carried imipenem-resistant strains of \(P.\) aeruginosa at some time and this resistance was associated with the loss of oprD. Sixty-four percent of imipenem-resistant strains were also meropenem-resistant. There was little increase in the resistance of \(P.\) aeruginosa to meropenem during the trial reported by Byrne et al. \(^{32}\) However, the longer term impact of meropenem use on resistance rates remains to be seen.

There is much debate regarding the most appropriate strategies for use of iv anti-pseudomonal antibiotics in chronic \(P.\) aeruginosa infection. Most clinicians in a UK/Eire survey used iv antibiotics for acute exacerbations only. \(^{9}\) Some reserved regular elective iv therapy for those patients with severely compromised lung function or who were rapidly deteriorating. A small minority (five of 26) used regular iv antibiotics at 3-4 month intervals (whether or not there was any evidence of acute exacerbation) for all patients chronically infected with \(P.\) aeruginosa. The philosophy behind this strategy, pioneered in the Danish CF Center, is that the host’s immune response to chronic \(P.\) aeruginosa infection may be in part responsible for progressive lung damage. By administering frequent courses of ‘maintenance’ chemotherapy the antigenic load in the lungs may be reduced, slowing the rate of progressive lung damage and minimizing further loss of pulmonary function.

Jensen et al. \(^{32}\) compared the outcomes of 51 patients receiving treatment for acute infective exacerbations during 1971–1975 (group A) with those of 99 patients receiving regular iv maintenance therapy at 3–4 month intervals during 1976–1985 (group B). Five year survival in group A was 51% and ten year survival in group B was 90%. Pulmonary function was stabilized and the rate of increase of precipitating antibodies to \(P.\) aeruginosa in serum was diminished. Whilst the results of this study are impressive it used historical controls and there will inevitably have been some increase in life expectancy due to other management developments in the 15 year study period. There are also concerns regarding the disruptive effect and cross-infection risks of frequent hospitalization, promotion of resistance and patient drug sensitization, and the additional costs that this approach entails. Supporters of this strategy point out the improvements in lung function, patient longevity and overall quality of life that it brings. This debate will only be resolved by direct comparison of the two treatment approaches using well controlled clinical trials. One year-long study using regular oral ciprofloxacin for 10 days every 3 months in comparison with placebo showed significant improvements in peak expiratory flow rate (PEFR) during therapy but not in other lung function tests. \(^{33}\) Oral therapy did not reduce hospital admissions or the need for iv antibiotics. The median MIC of ciprofloxacin increased from 0.5 mg/L to 0.75 mg/L during therapy, but this was not statistically significant. A longer study is required to assess if this approach is justified.

Another approach for maintenance therapy between exacerbations is the use of long-term nebulized antibiotics. They were used on an ad hoc basis before the first controlled trials were carried out in the early 1980s. Many of these trials suffer from the same problems as trials of iv therapy, i.e. small numbers of patients, lack of placebo controls, and conflicting results. \(^{34–37}\) There are also unique problems such as the wide variation in nebulizer design giving rise to variation in the size of aerosol particles. Various agents, either singly or in combination, have been assessed, including gentamicin with \(^{38}\) or without \(^{39}\) carbencillin, tobramycin alone \(^{40}\) or with ticarcillin, amikacin, \(^{41}\) colistin \(^{42}\) and ceftazidime. \(^{43}\) All have had a significant impact on respiratory function, either by generating short-term improvements or by slowing decline in comparison
with placebo-treated patients. Tobramycin plus ticarcillin was shown to reduce significantly hospital admissions for acute infective exacerbations in a small group of 11 patients (31 admissions pre-therapy compared with five after therapy; \( P = 0.005 \).40 Consumption of additional oral or parenteral antibiotics was significantly reduced during a placebo-controlled study of tobramycin aerosols.36 Forty-nine percent of patients required additional antibiotics whilst on placebo compared with 15% on therapy (\( P = 0.006 \)). Nebulized tobramycin has also been shown to reduce significantly sputum counts of \( P. \) aeruginosa (by a factor of 100) and total peripheral white cell counts.36 No study has shown any significant emergence of antibiotic resistance in \( P. \) aeruginosa or drug-related toxicity during nebulized therapy. There is little information regarding the effectiveness of nebulized antibiotics in treating acute infective exacerbations. One small study comparing iv tobramycin and ticarcillin with nebulized tobramycin and carbenicillin showed no differences in outcome between the two approaches.44 The addition of nebulized amikacin to iv amikacin plus ceftazidime yielded no clinical benefit compared with the use of iv antibiotics alone.41

A chronic \( P. \) aeruginosa infection is seldom eradicated, attempts have been made to arrest the progression from initial colonization to infection by early treatment. The use of nebulized colistin after initial isolation of \( P. \) aeruginosa was shown to reduce significantly the number of subsequent positive sputum cultures for \( P. \) aeruginosa.45 A later trial, using oral ciprofloxacin in conjunction with nebulized colistin for 3 weeks versus no treatment on each occasion that \( P. \) aeruginosa was isolated from sputum, showed a reduction in the number of patients progressing from colonization to chronic infection in the treated group (58% versus 14%, \( P < 0.05 \)).46 A follow-up study of this approach showed that the median age for onset of chronic \( P. \) aeruginosa infection increased from 6 years to 15 years, with corresponding improvements in lung function.47 The administration of oral ciprofloxacin for 2 weeks in conjunction with long-term nebulized tobramycin plus colistin has been shown to reduce serum precipitins to \( P. \) aeruginosa significantly in cases compared with controls.48

The recurrent exposure of chronically infected patients to broad-spectrum antibiotics is not without its problems, and these are often cited as reasons against elective antimicrobial therapy. Persistence of \( P. \) aeruginosa in CF patients may be related in part to its ability to develop resistance in response to repeated antibiotic exposure. Increases in resistance to all agents correlates with long-term administration of anti-pseudomonal antibiotics,49 although it does not directly correlate with the number of courses received.50 A number of different mechanisms are involved. Increased activity of class I \( \beta \)-lactamases in the sputum has been shown during therapy with piperacillin, ceftazidime, cefsulodin and imipenem but not during aztreonam therapy, perhaps as a result of \( \beta \)-lactamase inhibition by this agent.51 Resistance to ciprofloxacin emerges during therapy due to alterations to DNA gyrase and outer membrane proteins.52 A daptose resistance to aminoglycosides has been observed in vivo following administration of aerosolized tobramycin.53

Superinfection may also occur. Colonization with Burkholderia cepacia is associated with acute deterioration, pneumonitis, septicaemia and death in about 20% of those affected.53 Several outbreaks have been described in CF clinics worldwide and the main mode of transmission in these cases appears to have been patient-to-patient transfer of highly transmissible strains.54 Although inherently resistant to colistin, there is no association between colistin use and the emergence of \( B. \) cepacia.55 However, Stenotrophomonas maltophilia colonization of CF patients is significantly associated with previous use of anti-pseudomonal antibiotics.56 The use of permanent iv access devices is increasingly popular in CF units and, given the frequent administration of broad-spectrum antibiotics, it is not surprising that, if access devices become infected, yeasts are often responsible.57,58 Line removal is mandatory to effect a cure in such cases.

The pharmacokinetics of aminoglycosides and \( \beta \)-lactams are altered in CF patients.59,60 Increased clearance and/or larger volume of distribution coupled with the reduced susceptibility of the infecting organism means that larger doses of antibiotics must be given to derive therapeutic benefit.61 Fortunately aminoglycoside-associated ototoxicity and nephrotoxicity in CF appears to be uncommon.62 \( \beta \)-Lactam allergy is, however, common, occurring in as many as 62% of patients in one study.63 The overall frequency of reactions (based on the number of courses) was 4.5%. The highest rate of reactions involved piperacillin (51% of patients) and the lowest involved imipenem (4%) and aztreonam (7%). Most patients with severe hypersensitivity reactions to other \( \beta \)-lactam antibiotics appear to tolerate aztreonam therapy.64

Aminoglycoside therapy for CF patients is expensive. Estimates suggest that long-term nebulized antibiotics cost approximately £2600–6000/patient/year, depending on the agent used,38,41 and that admission to hospital for a 2 week course of iv antibiotics every 3 months cost approximately £11,000/year.65 If these are given at home, the costs of iv therapy can be reduced to approximately £6000/year.65 The development of home iv therapy has also had the benefit of reducing disruption to work, schooling and family life, and minimizing the risks of cross-infection.66,67 The future adoption of once-daily aminoglycoside therapy may further improve the convenience of home iv therapy. Once-daily aminoglycoside therapy was studied in CF patients as long ago as 1983 and was shown to be as effective as continuous infusion.68 More recent trials on small numbers of patients have shown no significant differences between once-daily and three times daily therapy in terms of pharmacokinetics, toxicity or clinical response.69,70

Despite the paucity of evidence defining ‘best practice’ most authorities believe that anti-pseudomonal antibiotics
have been vital in delivering improvements in longevity and lung function of CF patients. The life expectancy of a child born with CF is today over 40 years in many centres. Despite the exciting developments in CF management, particularly gene therapy, antipseudomonal antibiotic therapy will remain a major component of patient care for the foreseeable future. Many issues, particularly those relating to the risk–benefit of early treatment and elective iv therapy, need to be addressed by clinicians caring for CF patients so that improvements in survival and quality of life can continue to be delivered.

References

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