The prognosis for patients with cystic fibrosis (CF) has improved dramatically over the past 20 years with the median survival in Canada increasing from 22 to 40 years. This enhanced life expectancy is probably due to a complex range of factors, but improved therapy of bacterial lung infections has undoubtedly played a major role. Respiratory tract infections continue to be the leading cause of death among patients with CF, and Pseudomonas aeruginosa is the predominant respiratory tract pathogen. The chronicity of P. aeruginosa infections in CF, its high level intrinsic antimicrobial resistance and its propensity to develop resistance during prolonged antimicrobial therapy have all presented major therapeutic challenges to CF caregivers. To counter these challenges, new antibiotics have been introduced and novel approaches have been employed, including inhalational therapy and home administration of intravenous antimicrobial therapy.

The concept that anti-Pseudomonas therapy is of little or no benefit in the management of acute pulmonary exacerbations in CF was introduced by Beaudry and colleagues in 1980. They compared an anti-Pseudomonas regimen consisting of carbenicillin and gentamicin to cefoxitin and demonstrated no difference in outcome. The study involved a small number of patients and the dose of...
gentamicin (5 mg/kg/day) may have been too low to result in therapeutic sputum concentrations. A similar study was performed by Hyatt et al.3 and reached a different conclusion. They compared oxacillin plus sisomicin and carbenicillin to oxacillin alone in the management of acute pulmonary exacerbations, and the patients who received the anti-*Pseudomonas* therapy responded better than the placebo group in terms of both clinical and bacteriological outcome criteria. In another study, tobramycin monotherapy appeared marginally superior to placebo4. Recently Gold and colleagues have rekindled the controversy by suggesting that antibiotics are not required in the management of CF patients with mild to moderately severe pulmonary exacerbations5. Each of these studies employed a somewhat different design, perhaps explaining the conflicting conclusions. Nonetheless, most clinicians caring for patients with CF believe that antimicrobial therapy is useful in the management of lung infections and administer specific anti-*Pseudomonas* antimicrobial therapy to CF patients colonized with *P. aeruginosa* who experience moderate to severe pulmonary exacerbations6.

Although there is considerable evidence that properly administered antimicrobial therapy decreases the density of *P. aeruginosa* in the sputum of patients with CF and improves pulmonary function of patients who are experiencing a pulmonary exacerbation7, 8, the optimal means of therapy has not been clearly established. A wide range of approaches have been advocated, including (i) admission to the hospital at regular intervals for parenteral therapy irrespective of clinical status9, (ii) admission to the hospital for intravenous therapy only when dictated by pulmonary exacerbation10, (iii) inhalational antimicrobial therapy11–20, (iv) parenteral therapy at home21–27, and (v) continuous oral therapy28. Whereas each of these approaches has inherent advantages, they have not all been compared in a careful prospective randomized fashion. It is therefore impossible to determine the optimal antimicrobial approach, and therapeutic decisions are often made empirically. This chapter does not provide simple answers to the complex questions about antimicrobial therapy in CF, but rather an overview of anti-pseudomonal therapy in CF, including: a description of agents currently available, special considerations for therapy of patients with CF, a description of various routes of antibiotic administration, and future prospects.

ANTIBIOTICS WITH ACTIVITY AGAINST *PSEUDOMONAS AERUGINOSA*

**β-LACTAMS**

*In vitro activity*

*P. aeruginosa* has been a major target for pharmaceutical companies developing new β-lactams. Semi synthesis programs aimed at improving anti-pseudomonal activity have been applied to several core structures. Early β-lactams had no activity, but the development of the α-carboxypenicillins, carbenicillin and then ticarcillin represented a major breakthrough (Table 1). However, the moderate activities and high susceptibility of these compounds to β-lactamases severely limited their use29. Newer penems, the acylureido penicillins mezlocillin, piperacillin and azlocillin, had improved activity but were still susceptible to β-lactamase hydrolysis. However these β-lactams have found some usage in combination with aminoglycosides and will probably be administered in the future together with β-lactamase inhibitors.

The carbapenems, e.g. imipenem, have excellent activity against *P. aeruginosa* but have substantial problems with rapid development of resistance30. Similarly cephalosporins (cephems) have been developed that have excellent anti-pseudomonal activity, starting with the third generation cephalosporins cefoperazone, and especially ceftazidime31. More recently, the fourth generation cephalosporins, cefpirome, cefepime and ceftazidime, with positively charged quaternary ammonium functions in the 3 position have been developed since they are better taken up across the outer membrane and are more effective against mutants with derepressed β-lactamase32. Another class of β-lactams, the monobactams, has aztreonam as its sole representative. Although containing an aminothiazole oxime side chain like the above cephalosporins, it has somewhat inferior activity.

**Mechanism of action**

β-lactams act by inhibiting enzymes (penicillin binding proteins—PBPs) involved in peptidoglycan (cell wall) biosynthesis and/or triggering enzymes called autolysins33. All β-lactams are capable of binding to multiple PBPs, but generally speaking bind preferentially34 to one of the seven well-characterized PBPs, either PBP1a (ampicillin, carbenicillin), PBP2 (imipenem) or PBP3 (cefotaxime, ceftazidime, cefpirome, piperacillin and aztreonam). Recent experiments have indicated that a single PBP is usually the killing target since, for example, overexpression of PBP3 from its cloned gene increases resistance only to PBP3-targeted β-lactams35.

In Gram negative bacteria, PBPs are sequestered behind a barrier, the outer membrane, and thus accessibility to these target proteins is limited, especially in *P. aeruginosa* which has an outer membrane with 12–100 fold lower permeability to β-lactams than e.g. *E. coli*36. The reason for its lower permeability is deficiencies in the porin pathway whereby the majority of its outer membrane porins contain channels that are too small to permit rapid diffusion of β-lactams36–39 whereas those porins that are large enough (e.g. OprF) demonstrate poor activity, with only a small number of functional channels per cell36. Despite this permeability defect, β-lactams can equilibrate across the outer membrane in as little as 2 to 20 seconds. Thus reduced outer
membrane permeability works only by slowing down the entry of β-lactam molecules into the periplasm (the location of the cell wall and the catalytic sites of the target PBPs), permitting a secondary defence mechanism to function. Two such secondary defence mechanisms have been suggested, β-lactamases and active efflux. The latter topic is discussed in more detail below; however, it has not yet been convincingly demonstrated that active efflux is involved in shuttling β-lactams from the periplasm across the outer membrane into the external medium, and the influence of efflux mutants on β-lactamase inducibility, PBP interaction and outer membrane permeability has not yet been studied. Therefore, we will only discuss β-lactamases here.

The interplay of outer membrane permeability, β-lactamase activity and target PBP interactions is given by a rearrangement of the Zimmermann and Rosselet equation

\[
\text{MIC} = \text{Sp}(1 + \frac{\text{Vmax}}{\text{PA}(\text{Sp} + \text{Km})})
\]

where: Sp = the concentration of β-lactam in the periplasm to which the PBPs are exposed, when the external concentration = MIC; Vmax and Km are the kinetic constants of β-lactamase; PA = the outer membrane permeability coefficient; and A = the area of the outer membrane.

Thus according to equation 1, increasing maximal hydrolytic activity (Vmax) or increasing the binding affinity of β-lactam to β-lactamase (i.e. decreasing Km), will increase the MIC. Two types of enzymes are influential. One type comprises plasmid-borne class A penicillinas. At least 15 of these have been identified, but generally speaking they are not of major importance for clinical resistance. The second type comprises a single chromosomally-encoded cephalosporinase, the class C enzyme found in all Pseudomonas strains. This enzyme is inducible by β-lactams themselves and although found at a basal level in cells not exposed to β-lactams, it may be induced during antibiotic treatment. This induction can substantively increase MICs, as revealed by comparison of normally-inducible strains and their non-inducible mutants.

Mechanisms of resistance

The most significant and widespread mechanism of resistance studied to date is due to mutations leading to derepressed production of the chromosomal β-lactamase. Such mutations make P. aeruginosa clinically resistant to all β-lactams with the exception of the carbapenems and fourth generation cephalosporins. They are commonly observed after long-term therapy of P. aeruginosa with β-lactams, e.g. in CF patients who have long-term, chronic infections.

Imipenem is a potent inducer of chromosomal β-lactamase and results in β-lactamase levels equivalent to those observed in the above derepressed mutants. Thus it cannot be used in conjunction with other β-lactams. On the other hand, it is potentially effective against derepressed mutants since β-lactamases, being fully expressed, cannot further influence activity. One of the major reasons why imipenem retains substantive activity against such derepressed mutants is a combination of its resistance to the hydrolytic activity of β-lactamases combined with its ability to access a special pathway of uptake involving the porin OprD. OprD falls into the class of specific porins and has, as its natural substrate, basic amino acids and small peptides containing such amino acids. Imipenem is taken up through the OprD channel because it mimics a basic amino acid containing dipeptide, but the OprD channel is essentially impermeable to other antibiotics. Unfortunately resistance to imipenem occurs very commonly in patients with CF complicated by P. aeruginosa infections, due to mutational loss of OprD.

Mutations resulting in altered PBPs such that these proteins can still fulfil their enzymatic functions, but do not bind specific β-lactams, have been observed but are not common. Similarly, OprF-deficient porin mutants have been observed after quinolone therapy and result in moderate β-lactam resistance, but these are also uncommon. A third class of clinical mutants involves those with so-called high intrinsic resistance to β-lactams and other antibiotics. It has been proposed that these are mutants with enhanced antibiotic efflux.

Future prospects

Three classes of β-lactams show some promise for the future. Fourth generation cephalosporins which are, at the time of writing, just being introduced into the marketplace, are relatively less affected by derepression of chromosomal β-lactamase. Novel carbapenems with two basic groups appear unaffected by OprD mutations, although they can result in resistant mutants by other mechanisms. Catechol β-lactams overcome the outer membrane permeability barrier by binding Fe and achieving passage through iron scavenger uptake pathways. However, such β-lactams have been reported in the literature for years, but have not as yet progressed far through clinical trials.

An even more exciting prospect is provided by compounds designed to be utilized in combination with β-lactams to overcome potential or actual resistance mechanisms. These include β-lactamase inhibitors, aimed at chromosomal β-lactamase, and polycationic peptides known as permeabilizers, which overcome the outer membrane permeability barrier.

AMINOGLYCOSIDES

In vitro activity

Aminoglycosides remain one of the most valuable tools, used by physicians in combination with a β-lactam, to overcome serious Gram negative infections,
especially P. aeruginosa. Although limited or unpredictable penetration can be a problem, they can be formulated to permit inhalation therapy in CF patients. They have the potential problem of irreversible ototoxicity and reversible nephrotoxicity, a concern that relates to dosage and is more often observed in elderly and debilitated patients.

Of the many known aminoglycosides, only gentamicin, amikacin and tobramycin are commonly used against P. aeruginosa. However, their peak serum levels (approximately 6 μg/ml) at the usual dose (5 mg/kg/day) are similar to their MICs (Table 1), and animal studies clearly indicate a disparity between in vivo and in vitro activities. Therefore aminoglycosides are usually used in combination with β-lactams.

Mechanism of action
Aminoglycosides interact directly with the outer membranes of Gram negative bacteria to permeabilize them to other molecules of aminoglycoside in a process termed self-promoted uptake. At the same time they enhance uptake of other molecules, explaining in part their synergy with β-lactams. The observation that they utilize this non-porin mediated pathway of uptake in P. aeruginosa and E. coli, explains why they have similar efficacies against these two species (cf. other antibiotics; Table 1).

Table 1 Comparison of P. aeruginosa and E. coli susceptibilities to antibiotics

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Representative antibiotics</th>
<th>E. coli</th>
<th>P. aeruginosa</th>
<th>S. maltophilia</th>
<th>B. cepacia</th>
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</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>Ampicillin</td>
<td>4</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td></td>
<td>Carbenicillin/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ticarcillin</td>
<td>4</td>
<td>32–64</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td></td>
<td>Piperacillin</td>
<td>2</td>
<td>2</td>
<td>&gt;128</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Azlocillin</td>
<td>16</td>
<td>4</td>
<td>&gt;128</td>
<td>16</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Imipenem</td>
<td>0.25</td>
<td>2</td>
<td>16</td>
<td>32</td>
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<tr>
<td>Cephalosporins</td>
<td>Cefoperazone</td>
<td>0.12</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefotaxime</td>
<td>0.12</td>
<td>32</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefazidim</td>
<td>0.12</td>
<td>2</td>
<td>&gt;128</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
<td>0.04</td>
<td>2.5</td>
<td>64</td>
<td>8</td>
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<tr>
<td>Monobactams</td>
<td>Aztreonam</td>
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<td>2</td>
<td></td>
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</tr>
<tr>
<td>β-lactams</td>
<td>Gentamicin</td>
<td>0.5</td>
<td>2</td>
<td>64</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Tobramycin</td>
<td>0.5</td>
<td>0.5</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>2</td>
<td>4</td>
<td>&gt;64</td>
<td>&gt;64</td>
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<tr>
<td>Polymyxins</td>
<td>Colistin</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>&gt;64</td>
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<tr>
<td>Quinolones</td>
<td>Ciprofloxacin</td>
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<td>0.1</td>
<td>1</td>
<td></td>
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<tr>
<td>Others</td>
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<td>32</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
<td>4</td>
<td>64</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>64</td>
<td>200</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
</tbody>
</table>

*Normal MIC of strains lacking resistance transfer plasmids, derepressed chromosomal β-lactamase or increased intrinsic resistance due to porin alterations.

Antibiotics for Pseudomonas

After entering the periplasm, aminoglycosides pass across the cytoplasmic membrane by a process that is energized by the protonmotive force (electric potential component) and requires an electron transport chain component proposed to be respiratory quinones. Energized uptake occurs in two phases, EDP (energy dependent phase I), a slow but accelerating phase, and EDP II, a rapid uptake phase. The transition from EDP I to EDP II appears to occur at the same time as the lethal bactericidal event triggered by aminoglycosides. This lethal event is still controversial, despite decades of research. The usual suggested mechanism, protein synthesis inhibition or misreading during translation appears to be at most a codeterminant, and a favour inhibition of DNA synthesis initiation as the primary lethal target.

Mechanism of resistance
Most large studies of the clinical outcome of aminoglycosides have demonstrated frequencies of gentamicin resistance of between 5 and 12%. There are two major causes of resistance. Acquisition of certain plasmids can lead to the production of enzymes which modify the aminoglycoside by various acetylating, adenylating or phosphorylating the antibiotic molecule. This results in reduced uptake and/or reduced efficacy of the modified aminoglycoside. Such enzymatic resistance tends to be high level resistance but is relatively specific. Alternatively, strains can acquire lower level resistance to all aminoglycosides. Such resistance is usually due to decreased uptake resulting from either reduced outer membrane or inner membrane passage.

Another type of resistance, demonstrated mostly in animal models, is adaptive resistance (also called persistence by Bryan). Such resistance is favoured by high numbers of cells in late stages of logarithmic growth, and is favoured by delayed administration of aminoglycosides. Adaptive resistance is phenotypic rather than mutational, and easily reversed upon in vitro subculturing.

Future prospects
Virtually no developmental work is being pursued with this class of antibiotics and it is one of the least studied antibiotics in the research laboratory. All anti-pseudomonal aminoglycosides are now off patent. Thus we must nurture those compounds that are available, by using them cautiously to maintain the current rather predictable levels of susceptibility and clinical outcome.

QUINOLONES

In vitro activity
The introduction of the fluoroquinolones in recent years has provided a major hope for anti-pseudomonal therapy. The most effective and clinically mos
utilized agent has been ciprofloxacin with an MIC\(_{90}\) of around 0.25 to 1 µg/ml. However, even with this compound, therapeutic results have been quite disappointing, in part because of resistance development\(^{75,76}\). Nevertheless, although in CF patients bacteriological cures are rare and resistance development common, there is often an improvement in lung function\(^{75,76}\) that has been ascribed to down-regulation of virulence factors. Combinations of quinolones with other agents tend to be additive rather than synergistic\(^{77}\), and unfortunately can still lead to resistance development.

**Mechanism of action**

Quinolones act upon the enzyme DNA gyrase\(^{78}\). However, whether they bind directly to DNA gyrase or to the tertiary complex of DNA with DNA gyrase has not yet been definitively established. Quinolones are bactericidal antibiotics, and the induction of the SOS mechanism of DNA repair during quinolone action rather suggests that irreversible damage to DNA represents the major basis for this bactericidal action.

The mechanism of quinolone uptake is quite controversial and has been discussed in detail elsewhere\(^{79}\). It has been suggested that quinolones utilize either porin or non-porin uptake pathways across the outer membrane, although we feel that there is more evidence for the latter. Similarly Nikaido\(^{80}\) has argued convincingly that quinolones can spontaneously convert with low efficiency to an uncharged form that can passively diffuse across the cytoplasmic membrane. Most of the controversy in the literature probably arises from the difficulties in measuring productive quinolone uptake due to non-specific binding and the existence of a saturable efflux system (which of course impacts variably on net uptake depending on the concentration of antibiotic used for measurements).

There are thought to be at least three efflux systems in *P. aeruginosa* based on resistant mutant studies in which these systems have been derepressed\(^{81}\). The most important in wild-type cells, and the best studied, is that based on the *mexA*, *mexB*, oprM (formerly called oprK) operon\(^{82}\). Interposons in the inner membrane component MexA or the outer membrane component OprM are supersusceptible to ciprofloxacin due to decreased efflux\(^{82}\).

**Mechanism of resistance**

The mechanism of quinolone resistance in the clinic has been investigated in one larger study with 13 mutants, looking for the ability of the cloned *E. coli* gyrA gene (for DNA gyrase subunit A) to complement the mutant to greater quinolone susceptibility\(^{83}\). Twelve of the 13 mutants could be at least partly complemented suggesting that they contained gyrA mutations (one other mutant could be complemented with the cloned gyrB gene for DNA gyrase subunit B). In addition the evidence suggested that at least seven mutants had other mutations.

Other mutants have been identified with complex phenotypes including cell envelope changes (e.g. OprF loss, overexpression of a 50 kDa protein and/or lipopolysaccharide (LPS) changes\(^{79,81}\)), often accompanied by transport deficiencies. Some of these mutations are probably efflux mutants which have been better described in the laboratory as resulting from derepression of OprM, OprN or OprJ (in conjunction with derepression of inner membrane components of an efflux system\(^{82}\)). One item of major concern is the tendency of quinolones to select mutants that are resistant to more than one class of antibiotics due to either the broad specificity of efflux systems\(^{79}\), or regulatory mutants affecting more than one resistance mechanism simultaneously\(^{84}\), or the possibility that quinolones, being DNA-damaging agents, may be mutagenic.

Resistance development has been modelled in the laboratory by successive selection of increasingly resistant strains on two-fold the MIC of ciprofloxacin. Increasing MICs up to eight-fold the MIC of the parental strain were due to changes in DNA gyrase. Further increases in MIC were mirrored by changes in the cell membrane (including OprF deficiency) and corresponding alterations in susceptibility to other antibiotic classes\(^{84}\). Increased resistance to other drug classes but not quinolones could be partly complemented by the cloned OprF gene. Other laboratory mutiresistant mutants involving derepression of efflux systems have been isolated as single-step mutants. Typically these mutants can be recognized by acquisition of a 48–50 kDa outer membrane protein (oprM, N or J) which is part of the efflux machinery\(^{81}\).

**Future prospects**

Many fluoroquinolones have been isolated, but to date none has exceeded the activity of ciprofloxacin against *P. aeruginosa*. Furthermore, all known resistance mechanisms result in simultaneous cross-resistance to all known quinolones. Thus it is safe to say that it seems unlikely that this class of antibiotics will see many improved compounds in the future. One class of compounds that would be of interest would be one that inhibits efflux pumps for use in combination with quinolones, thus overcoming an important resistance mechanism.

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**SPECIAL CONSIDERATIONS FOR ANTIBIOTIC THERAPY IN CYSTIC FIBROSIS**

**PHARMACOKINETICS**

Patients with CF dispose of many drugs more rapidly than do other individuals and require extraordinarily high doses of most antimicrobial agents to achieve
therapeutic concentrations in serum or sputum. Antimicrobial agents of various classes, including aminoglycosides, penicillins and trimethoprim-sulphamethoxazole, are cleared at enhanced rates and require appropriate dosing adjustments. Conversely, ciprofloxacin pharmacokinetics appear to be normal in patients with CF and dosing adjustments are not necessary. Whereas the peculiar pharmacokinetics of antimicrobial agents in CF has not been fully explained, there appears to be an expanded venous plasma volume and enhanced renal elimination of \( \beta \)-lactams but not aminoglycosides. As a result of the enhanced drug disposition, CF patients can tolerate very large doses of aminoglycosides, e.g. 150–200\% standard dosage, without evidence of nephro- or otoxicity. Serum peak and trough aminoglycoside levels should be measured after the fourth dose and dosage should be adjusted accordingly.

Dissociation of P. aeruginosa

During the course of chronic respiratory tract infection in CF, strains of P. aeruginosa may undergo a range of phenotypic changes; they often become mucoid, nonmotile and susceptible to the bactericidal effects of normal human serum. Multiple different phenotypic variants of P. aeruginosa are often recovered from a single sputum culture (mucoid, nonmucoid, dwarf, pigmented, etc.); these variants may be genetically indistinguishable (Mahenthiralingam and Speert, unpublished) but very different in their susceptibility to antimicrobial agents. It is impossible to determine the relative importance or prevalence of each bacterial phenotype in the lower respiratory tract, and therapy should be determined after considering the susceptibility pattern of each variant. Colonial appearance and antimicrobial susceptibility appear to vary independently of one another, although the mucoid exopolysaccharide of mucoid strains may interfere with the penetration of certain antibiotics to their site of action.

Development of Resistance During Therapy

Patients with CF are chronically colonized with P. aeruginosa and most appear to persistently harbour the same genetic type (Mahenthiralingam and Speert, unpublished). Since patients are typically infected with high bacterial densities and are exposed frequently to antibiotics, one would predict that resistance would develop during therapy—such is the case. Although resistance may develop during the course of therapy, reversion to susceptibility often occurs after the antimicrobial agent has been withdrawn. Since antimicrobial resistance fluctuates unpredictably among bacterial isolates from each patient, therapy must be guided by the susceptibility pattern of the bacterial isolate obtained immediately prior to initiation of therapy. Furthermore, cultures should be obtained at regular intervals during the course of therapy and adjustments made accordingly.

Antibiotics for Pseudomonas

Failure to Achieve Therapeutic Antimicrobial Activity in Sputum

Infections in patients with CF occur predominantly in the endobronchial space and only invade the parenchyma of the lung late in the course of disease. Antimicrobial agents must therefore penetrate to endobronchial secretions (including sputum) in order to achieve an effect. Whereas aminoglycosides penetrate to and accumulate in, CF sputum, their bioactivity is low. In one study, eradication of P. aeruginosa from CF sputum was only achieved when sputum aminoglycoside concentrations exceeded the MIC of the infecting bacteria by 20-fold. Furthermore, the mucoid exopolysaccharide secreted by mucoid strains may impede the penetration of certain antimicrobials to their site of action. These factors may conspire to create an environment where suboptimal antimicrobial activity is achieved at the site of infection. Failure to attain a therapeutic success may therefore be a result of local effects in the lung of CF patients rather than antimicrobial resistance of the infecting bacteria.

Adverse Effects from Antimicrobial Therapy

Patients with CF are treated with high doses of various antimicrobial agents, often for prolonged periods. Furthermore, atopy is relatively common in this group. Allergy to \( \beta \)-lactam antibiotics occurs frequently in CF patients and dictates alteration in therapy. Various approaches that have been employed include discontinuation of the drug, modification of the dose and desensitization. Since semi-synthetic penicillins are such valuable agents for therapy of P. aeruginosa infections in CF, efforts should be made to preserve their use. In the event of apparent allergy, consultation with an allergist should be obtained. Usually, modification in dosage or intravenous desensitization will allow the use of the drug to be continued. Other adverse effects to \( \beta \)-lactam agents, including haemorrhagic cystitis, have been described in patients with CF and are reversible.

Oral Antimicrobial Therapy

Agents with Activity Against P. aeruginosa

Most antimicrobial agents with activity against P. aeruginosa, with the exception of fluoroquinolones, must be given parenterally. The quinolones provide a novel mechanism of antibacterial activity as well as the potential for treating infections with P. aeruginosa, Burkholderia cepacia and Stenotrophomonas maltophilia outside the hospital.
PRACTICAL CONSIDERATIONS

Whereas quinolones can be used to treat Pseudomonas infections orally, concerns have been raised about both (i) their propensity for enhancing development of antimicrobial resistance and (ii) their safety in children. In adults with CF, oral ciprofloxacin appears to be equivalent to intravenous tobramycin plus azlocillin for therapy of acute pulmonary exacerbations. Resistance to fluoroquinolones may appear during therapy, and short, intermittent courses are therefore recommended as opposed to chronic therapy. Concerns have been raised about the potential for cartilage toxicity when fluoroquinolones are administered to children under 18 years of age. Nonetheless, these drugs appear to be perfectly safe in children, and they may be used if alternatives do not exist and if toxicity is monitored carefully.

PARENTERAL THERAPY

INDICATIONS

Parenteral therapy remains the optimal means of treating P. aeruginosa respiratory tract infections in patients with CF. Although the indications for parenteral therapy vary widely from centre to centre, it is usually initiated when there is clinical evidence of a pulmonary exacerbation—increased respiratory rate, increasing cough with production of purulent sputum, loss of weight, decreased exercise tolerance, fatigue, decreased appetite, and (sometimes) fever. Laboratory evidence includes hypoxaemia, new infiltrates on chest X-ray and deterioration in pulmonary function testing.

PREFERRED ANTIMICROBIAL AGENTS AND COMBINATIONS

Therapy of pulmonary exacerbations, due to P. aeruginosa, usually consists of a combination of a semisynthetic penicillin, such as ticarcillin or piperacillin and an aminoglycoside, such as tobramycin. These drugs have been shown to be synergistic in vitro against P. aeruginosa (see above). Other agents that have proven to be effective in treating pulmonary exacerbations in CF include quinolones and newer β-lactams such as cefoperazone, ceftriaxone, aztreonam and imipenem. These agents may be given singly or in combination with an aminoglycoside, but they should be chosen in the light of results from in vitro antimicrobial susceptibility testing. Some of the newer β-lactams, such as imipenem, induce β-lactamase activity and should not be given in combination with other β-lactams. Often, a clinical improvement may be seen even when antimicrobial agents are administered to which the infecting strain of P. aeruginosa is resistant in vitro.

Antibiotics for Pseudomonas

FREQUENCY AND DURATION OF THERAPY

Strategies for administering parenteral antimicrobial therapy for pulmonary exacerbations in patients with CF differ markedly. For instance, in Denmark intravenous antibiotics are given at regular intervals three or four times per year irrespective of the patient's clinical status. This regimen was introduced by Høiby and colleagues in 1976, and since that time, survival rates have improved substantially; unfortunately, their observations are uncontrolled and the improved survival could be due to improvements in the general care of patients with CF, as has been seen generally in CF centres throughout North America. In most North American CF centres, parenteral antimicrobial therapy is reserved for patients experiencing a pulmonary exacerbation as defined above. Parenteral antibiotics are usually administered for approximately 14 days, but the duration may be modified depending upon clinical response.

HOME INTRAVENOUS THERAPY

With increasing costs of hospitalization and the concern about acquisition of nosocomial pathogens, caregivers have been prompted to adopt alternative strategies for administering parenteral antimicrobial therapy. Home intravenous therapy of patients with CF has been widely embraced in a number of CF centres and has been shown to be equivalent in efficacy to intravenous therapy delivered in the hospital. Home intravenous therapy is substantially less expensive than hospital-based therapy and is better accepted by patients. Nonetheless, such therapy is not appropriate for all patients; a number of critical criteria must be assessed to assure that the medication can and will be administered properly.

INHALATIONAL THERAPY

As described above, local factors in the endobronchial space interfere with the antibacterial activities of intravenously administered antibiotics. Concentrations of antibiotics many times above the MIC for P. aeruginosa may be necessary to achieve antimicrobial activity. One strategy for circumventing this problem has been to deliver the antibiotics directly to the site of infection by the aerosol route. Although this approach appears to be attractive theoretically, a number of practical implications must be considered. To deliver the drug to the site of infection in the lower respiratory tract, the aerosol must be between 1 and 5 μm in diameter; certain aerosol generators appear better suited than others to deliver appropriate aerosols. Large doses of drugs are required, but the cost may be offset by the decreased need for
hospital admission for parenteral therapy. Inhaled antimicrobial agents used in patients with CF have included carbenicillin, gentamicin, cephaloridine, tobramycin, colistin, polymyxin B and amikacin alone or in combination with parenteral antibiotics. Results from clinical trials have been mixed as has been the quality of the study design. A recently reported placebo-controlled crossover study evaluated the efficacy of inhaled tobramycin, patients received either 600 mg tobramycin or saline daily for each of three 28-day periods. Those who received the drug had a significant improvement in pulmonary function and a decrease in sputum density of P. aeruginosa without an acceleration in rate of acquisition of antibiotic-resistant isolates or evidence of oto- or nephrotoxicity.

THERAPY OF 'HONORARY PSEUDOMONADS': B. CEPACIA AND S. MALTOPHILIA

WHY THESE BACTERIA ARE DIFFERENT FROM P. AERUGINOSA

For years B. cepacia and S. maltophilia bore the family name Pseudomonas. However, it was recognized, based on taxonomic studies including rRNA:DNA hybridization, that they were taxonomically distinct from the fluorescent (group 1) Pseudomonas species, into which group P. aeruginosa falls. Thus the genus name Pseudomonas has been preserved for the group 1 cluster, whereas Pseudomonas cepacia was renamed Burkholderia cepacia and Pseudomonas maltophilia as Xanthomonas maltophilia and subsequently Stenotrophomonas maltophilia (when it was realized it also differed from most Xanthomonas spp.).

Both species are resistant to multiple antibiotics and are capable of infecting the lungs of patients with CF. Both are also reasonably nutritionally versatile and can be difficult to identify in the clinical laboratory. S. maltophilia is a natural methionine auxotroph.

SUSCEPTIBILITY AND RESISTANCE TO ANTIMICROBIALS

Both B. cepacia and S. maltophilia are notoriously resistant to antibiotics (Table 1). The mechanisms of B. cepacia resistance have been studied in detail and include a deficient hydrophilic uptake pathway due to the narrow channels of B. cepacia porins, and an inducible type C cephalosporinase which limits β-lactam activity. In addition, the outer membrane apparently lacks a self-promoted uptake pathway rendering this organism aminoglycoside resistant. Furthermore at least one efflux pathway, homologous to the mexA, mexB, oprM pathway, exists (J. L. Burns, personal communication).

Antibiotics for Pseudomonas

S. maltophilia has also been proposed to have low outer membrane permeability. In addition it expresses two inducible β-lactamasases, a type C cephalosporinase (named L2) and an inducible type D metallo-β-lactamase (a so-called imipenemase named L1). However, relatively little research on resistance mechanisms has been done on this organism.

THERAPY

Therapy of infections with these 'honorary' Pseudomonas species in patients with CF should be guided by the same principle as therapy for P. aeruginosa. Antimicrobial therapy is based upon in vitro susceptibility, and the duration is routinely for two to three weeks. Since both B. cepacia and S. maltophilia are highly resistant to many antibiotics, the regimen of ticarcillin and tobramycin (which is often effective for P. aeruginosa) is usually not appropriate. Antimicrobial agents with in vitro activity against either or both of these two species include ceftazidime, ticarcillin-clavulanate, trimethoprim/sulfamethoxazole and ciprofloxacin.

OTHER THERAPIES

No other antibiotic classes have seen substantive use against P. aeruginosa. Colistin (polymyxin E), which like aminoglycosides is a polycation (but a cyclic lipopeptide rather than a trisaccharide), has been used in the past against P. aeruginosa in combination with other antibiotics. Novel glucosylcholine dicationic compounds, distantly related to vancomycin, have minimal anti-pseudomonal activity. Small cationic peptides with MICs in the 2–4 µg/ml range are also being developed as anti-Pseudomonas antibiotics. Each of these classes is taken up by the self-promoted uptake pathway across the outer membrane, indicating a possible design feature for future drug classes against this organism.

Another therapeutic approach under active consideration involves compounds that are non-antibiotic but block adherence, and consequently tissue localization, in the lung. In this regard, dextrins are able to block adherence of P. aeruginosa to epithelial cells and are currently being considered for clinical trials, whereas peptides analogous to the epithelial cell binding ligand of pili are also under active consideration.

The successful application of quinolones in improving lung function in CF patients colonized by quinolone-resistant mutants suggests a further approach, that of utilizing antibiotics to suppress the production of virulence factors. In this regard other classes of antibiotics may have similar properties in vivo.
CONCLUSIONS

The antimicrobial therapy of respiratory tract infections in patients with CF presents a number of major challenges. Conventional approaches to the therapy of acute or chronic infections are not appropriate as the features of bacterial lung infection in CF are unique. Since the respiratory tract infections cannot usually be eradicated, the criteria for therapeutic success are largely clinical in nature—symptomatic improvement without bacteriological 'cure'. Whereas the antimicrobial susceptibility of the infecting bacterial isolate is useful in guiding the choice of therapeutic regimen, clinical improvement is often seen even when drugs are used to which the bacteria are resistant in vitro.

Since it is virtually impossible to eradicate *Pseudomonas* from the respiratory tract of patients with CF, new approaches to prevention of infection are needed. Various novel strategies are currently under investigation, but none has yet entered clinical evaluation. At present, the accepted approach to therapy of *Pseudomonas* infection in North American patients with CF is reactive rather than proactive—administration of aggressive anti-pseudomonal therapy when patients experience signs and symptoms of pulmonary exacerbation. Although this approach cannot prevent the inevitable fatal respiratory compromise typical of CF, it has likely been responsible for the dramatic improvement in life expectancy witnessed over the past several decades.

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**Chapter Thirteen**

**Aspergillus Lung Disease in Cystic Fibrosis**

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The term Aspergillus, which encompasses about 150 species, was coined by Micheli, a botanist and priest, in 1729. The name itself is derived from the Latin *asperge* meaning to scatter.

Aspergillus species are ubiquitous and thrive over a wide temperature range, from 12°C to 53°C. Thus they are abundant in damp, decaying vegetation heated by bacterial fermentation, but they are also present in the air, in newly cut grass and in a variety of moist situations. In houses they are found especially in basements, bedding and house dust. Some Aspergillus species also grow as a commensal in the human respiratory tract, with the potential to spread to other organs and body cavities.

**HUMAN ASPERGILLOSIS**

This was first described in 1847 by Sloyter. Despite the high number of Aspergillus species, only a few affect humans, with Aspergillus fumigatus (AF) accounting for more than 90% of infections or allergic responses. Other species implicated are *A. niger*, *A. flavus*, *A. terreus*, *A. clavatus*, *A. glaucus*, *A. nidulans*, *A. oryzae* and *A. nivens*.

*A. fumigatus* is the most widely distributed of all microorganisms and a troublesome contaminant in microbiology laboratories. It liberates its spores...