Antibiotic Therapy of Pulmonary Infections in Cystic Fibrosis

Dosage Schedules and Duration of Treatment

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General principles of dosage and duration of treatment with antibiotics in patients with cystic fibrosis are discussed. The antibiotic treatment policy of the Stockholm Center for Cystic Fibrosis is presented. This treatment policy is mainly based on antibiotic treatment of very mild symptoms with high-dosage, short-term (less than 2 weeks) courses using combined therapy. So far no problems with multiply resistant strains have developed. During the last 2 years, treatment has mainly been given at home without any complications being reported.

It is widely agreed that antibiotic therapy is beneficial in the treatment of exacerbations of pulmonary infections in patients with cystic fibrosis (CF). Frequent antibiotic treatments have been shown to increase patient survival. Randomized, double-blind, crossover trials, which have shown the benefit of antibiotic therapy in acute exacerbations in patients with chronic obstructive pulmonary disease, have usually been considered unethical in CF. Difficulties in eradicating the colonizing microorganism from the lower respiratory tract have led to interest being focused on the dosages of antibiotics or special characteristics of the bacteria involved, but little attention has been devoted to the characteristics of the internal environment of the bronchi in the patients.

**General Views on Dosage**

Most studies on duration of therapy have recommended 2 weeks of treatment, and long-term prophylactic use of antibiotics is today seldom advocated. One reason to avoid long-term use of antibiotics in CF patients is the difficulty of obtaining adequate serum concentrations compared to those in healthy individuals or patients with other diseases. This problem, including enhanced clearance, has been shown to occur not only with antibiotics, but also with other drugs. The increased renal clearance in CF is attributed to an increased glomerular filtration rate and a disturbed tubular function. The cause of the increased nonrenal clearance is probably multifactorial. A changed distribution volume, related to a decreased lean body mass, and induction of microsomal enzymes in the liver, kidney, and lung—suggested to be the result of long-term pancreatic enzyme supplementation—have been proposed to account for the rapid clearance. The different explanations and conflicting results obtained in different studies might be related to the severity of the disease. Essential fatty acids are important constituents of membranes. Patients with CF develop an essential fatty acid deficiency, which might be related to the basic defect and not secondary to malabsorption. This deficiency may influence the clearance of drugs through several membranes in the body.

Antibiotics are given to treat infection in the lower respiratory tract. Difficulties in obtaining adequate concentrations in the bronchial secretion, concentrations exceeding the minimal inhibitory concentration (MIC) values of the bacteria, might be one of many possible explanations for failure to achieve more than temporary eradication of bacteria. The factors determining the penetration of antibiotics into the bronchial lumen are largely unknown. Sputum levels are usually low, the need to obtain sputum concentrations as high as possible means trying to achieve high antibiotic serum levels with minimal toxic side effects. When aminoglycosides are used, the postantibiotic effect and the area under the curve are probably more important than the peak value, while for β-lactams the time of exposure to concentrations above the MIC values is probably the most important factor for efficacy. By using a combination of a β-lactam and an aminoglycoside, a synergistic effect is obtained. Attacking the bacteria with 2 different kinds of antibiotics may further reduce the risk of development of resistance. The principle of antibiotic treatment should therefore be high-dosage/combined therapy for short periods during exacerbations, irrespective of whether these are primarily of viral or bacterial origin. If the time of treatment is limited, fewer pure cultures and resistant strains will develop and superinfection with fungi is reduced.

**Dosage Regimens**

Due to the high clearance rate in CF, the dosage of antibiotics is usually about twice that used in other diseases.

**Table 1—Recommended Dosage and Dose Interval of Antibiotics for Treatment of Pulmonary Symptoms in CF at the Stockholm CF Center**

<table>
<thead>
<tr>
<th>Organism/Antibiotic</th>
<th>Daily dose (mg/kg)</th>
<th>Dose Interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S. aureus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cloxacillin, IV</td>
<td>200</td>
<td>6</td>
</tr>
<tr>
<td>Dicloxacillin, PO, IV</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>Flucloxacillin, PO</td>
<td>100</td>
<td>6-8</td>
</tr>
<tr>
<td><strong>H. influenzae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pivampicillin, PO, IV</td>
<td>100-200</td>
<td>8</td>
</tr>
<tr>
<td>Cefuroxime, IV</td>
<td>100-200</td>
<td>8</td>
</tr>
<tr>
<td>Trimetroprim-sulfamethoxazole, PO, IV</td>
<td>8-12 + 40-60</td>
<td>12</td>
</tr>
<tr>
<td><strong>P. aeruginosa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azlocillin, IV</td>
<td>450-600</td>
<td>8</td>
</tr>
<tr>
<td>Piperacillin, IV</td>
<td>350-450</td>
<td>8</td>
</tr>
<tr>
<td>Carbencillin, IV</td>
<td>450-600</td>
<td>8</td>
</tr>
<tr>
<td>Cefazidime, IV</td>
<td>150-200</td>
<td>8</td>
</tr>
<tr>
<td>Cefslodin, IV</td>
<td>200</td>
<td>8</td>
</tr>
<tr>
<td>Imipenem</td>
<td>45-60</td>
<td>6-8</td>
</tr>
<tr>
<td>Aztreonam, IV</td>
<td>150-200</td>
<td>6-8</td>
</tr>
<tr>
<td>Gentamicin, IV</td>
<td>8-12</td>
<td>8-12</td>
</tr>
<tr>
<td>Tobramycin, IV</td>
<td>10-20</td>
<td>8-12</td>
</tr>
<tr>
<td>Netilmicin, IV</td>
<td>10-12</td>
<td>8-12</td>
</tr>
<tr>
<td>Amikacin, IV</td>
<td>15</td>
<td>8-12</td>
</tr>
<tr>
<td>Ciprofloxacin, PO, IV</td>
<td>15-30</td>
<td>8-12</td>
</tr>
</tbody>
</table>

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Figure 1. Granulocyte elastase-α1-antiproteinase complex (GEC) values before and after 45 intravenous courses of antibiotics. For further information see Ericsson-Hollsing et al.44

However, some patients with mild disease prove exceptions to this rule, and the serum concentrations must therefore always be monitored when potentially toxic drugs are used. The trough value and peak value usually provide sufficient information, and these should be checked within the first 2 days and at weekly intervals if the treatment continues for more than 10 days. This is especially important when aminoglycosides are used.36,37

The dosages of different commonly used β-lactams and aminoglycosides are given in Table 1. The recommended interval between doses is usually 6 to 8 hours for the β-lactams and 8 to 12 hours for the aminoglycosides. Although aminoglycosides have been given to CF patients at 24-hour intervals,38 this is not recommended, since P aeruginosa is less susceptible to such a regimen.39 The use of quinolones, especially ciprofloxacin, is an encouraging step in the development of oral antipseudomonal drugs. A 12-hour interval between doses (oral or intravenous) is commonly used,40,41 although some authors recommend more frequent administration.42 To avoid selection of strains, different β-lactams should be used for subsequent courses of treatment.

In order to improve serum concentrations without increasing the dosage of antibiotics, some inhibitors have been used. The most common of these is probenecid, which decreases tubular secretion of penicillins. The recommended dosage is usually 40 mg/kg/d in 4 doses.1 The Danish CF center often uses this drug,43 but a real benefit has not yet been demonstrated since the serum values reported by this group do not usually differ from those reported by other groups. Clavulanic acid, a β-lactamase inhibitor, has also been used in combination therapy but does not increase the serum concentration or modify the pharmacokinetics of concurrently administered penicillin.44 Mucus-dissolving agents have been found to modify antibiotic activity in vitro.45

Benefits of Treatment

For more than 10 years the policy of high-dosage combined antibiotic therapy for a limited time (usually 2 weeks) for mild symptoms of exacerbations, with antibiotics varied between courses, has been used in our CF center. For the

Figure 2. Vital capacity (●) and forced expiratory volume in one second (▲) in 4 representative patients chronically colonized with P aeruginosa (Ps) for 8 to 15 years.
past few years, this treatment has preferably been given at home (see pages 1625-665). Apart from the simple clinical symptom of failure to gain weight, the granulocyte elastase α-subunit proteinase complex (GEC) has been found to be the most sensitive marker of infection as an indication for antibiotic therapy (Fig. 1). Staphylococcal antibodies to teichoic acid and α-toxin have also been shown to be valuable markers of infection, especially in patients colonized with both Staphylococcus aureus and Pseudomonas aeruginosa. Serum antibodies to specific exoproteins of Pseudomonas aeruginosa were, however, poor indicators of low-grade infection.

So far we have had no problem with multiply-resistant strains of Pseudomonas despite an active antibiotic treatment policy. Our policy of varying the antibiotics used might be one of the reasons behind this. Patient survival has improved considerably, as reflected in a median age of 15.5 years (range, 6 months to 68 years) in patients under care at our CF center. Many adult patients are in excellent clinical condition with only minor changes on pulmonary radiographs and almost normal lung function. This is illustrated in Figure 2 for four patients who have been chronically colonized with Pseudomonas aeruginosa for 8 to 15 years. Sudden deterioration may occur in all types of patients. This is sometimes related to the occurrence of atypical mycobacteria in sputum, but other as yet unrecognized factors may also be important.

Future Prospects

The ideal dosage regimen is difficult to determine. Several studies have shown no benefit with very high dosages. A recent study found that resistance in Pseudomonas strains developed only in patients treated with the higher of 2 dose regimens of imipenem. Interactions between antibiotics should also be further evaluated. A better awareness of the postantibiotic effect, recently recognized in the aminoglycoside group, may lead to a better definition of dosage intervals in the future. The clinical status of the patient as well as disease-specific factors may further alter antibiotic metabolism. To establish the ideal dosage and dosage intervals, all these factors must be better defined and evaluated.

References

Discussion

Ronald Gold, M.D.*

Rational decisions concerning dosage schedules of antibiotics in the management of acute chest exacerbations in patients with CF can be made on the basis of a considerable body of detailed pharmacokinetic data. In contrast, decision-making about the duration of therapy is purely empirical, as no adequate clinical trials have been conducted comparing different durations of antibiotic therapy.

In any discussion of antibiotic therapy in CF, it is important to note that severity of illness at the time of hospitalization, i.e., at the start of antibiotic therapy, is a major determinant of outcome. Indeed, a recent randomized clinical trial demonstrated that patients with mild to moderately severe exacerbations, which were defined on the basis of ESR <50/ mm, WBC count <15,000, and fever <38.5°C, did equally well whether treated with ceftazidime or placebo. Most studies evaluating antibiotic therapy have failed to stratify by severity at the time of admission, making it difficult to interpret the results.

Almost all patients with mild to moderate infections defined on the basis of the above criteria show symptomatic improvement beginning within 3 days of hospitalization and reaching a peak within 7 to 10 days. Patients with more severe exacerbations almost always require more than 14 days of hospitalization.

Thus, as with most bacterial infections, the optimal duration of antibiotic treatment in CF patients with acute exacerbations is not known and must be based on the clinical response, especially changes in symptoms, weight, and pulmonary function.

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REFERENCES