Use of Aerosolized Antibiotics in Patients With Cystic Fibrosis

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Abbreviations: CF = cystic fibrosis; MIC = minimal inhibitory concentration; PFT = pulmonary function test

There has been a renewed interest in the use of aerosolized antibiotics in cystic fibrosis (CF) patients during the past decade. Potential benefits of delivering antibiotics by aerosol include the following: direct delivery of antibiotics to the endobronchial site of infection; decreased toxicity as systemic absorption is limited; reduced cost; and less disruption to patients’ lives, especially when compared with IV antibiotic administration. Several reviews have summarized the published literature on the subject.1–3

Purpose of Consensus Document

The authors of this document were convened to discuss the use of aerosolized antibiotics in CF patients. The document attempts to address four major questions: (1) What are the indications for the use of aerosolized antibiotics? (2) What is the appropriate dosage and delivery method for aerosolized agents? (3) How should patients receiving aerosolized antibiotics be monitored? (4) What are the microbiological implications of aerosolized antibiotics?

Each section of this document contains a review of the published literature. Whenever possible, evidence-based recommendations are made. The grading of evidence for our recommendations follows the US Preventive Services Task Force system.4 In addition, words defined in the glossary found in the appendix will be indicated by an asterisk (*) the first time they are used in the text.

Grading of Evidence

I Evidence obtained from at least one properly randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

What Are the Indications for the Use of Aerosolized Antibiotics?

Background Review of Efficacy

Investigators have primarily examined the efficacy of aerosolized antibiotics in reducing morbidity in patients in stable condition (suppression therapy), a few studies have examined the role of aerosol antibiotics as adjunctive therapy for acute exacerbations of pulmonary disease (treatment), and several have examined their role in delaying chronic Pseudomonas aeruginosa infection/colonization* (prevention). Aerosolized aminoglycosides, β-lactams, and polymyxins have been studied.

Studies Using Aminoglycosides

Aminoglycosides have been the most extensively studied class of aerosolized antibiotics. They are well-suited for inhalation because they remain bioactive when aerosolized and are poorly absorbed across epithelial surfaces. Thus, high concentrations in bronchial secretions can theoretically be achieved with minimal risk for systemic toxicity.

*Consensus Conference Committee members are listed at the end of the report.


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Suppression Therapy: In 1981, Hodson and colleagues carried out the first (to our knowledge) clinical trial of aerosolized gentamicin (Schering Corp; Kenilworth, NJ) and carbenicillin in 20 adult patients and found lung function to be modestly improved. Following this report, a number of studies with generally positive results were published in the 1980s. All but one of the studies that measured pulmonary function demonstrated significant improvement or a slower rate of decline during the study period. A trend toward decreased hospitalization rates was seen in four studies and improved nutritional status was seen in two studies. Interpretation of these earlier studies is hampered by small sample size, lack of appropriate controls, and failure to mask the taste of the antibiotic. Comparison between studies is difficult due to differences in dose of aminoglycoside, duration of therapy, type of nebulizers, patient ages and disease severity, and whether sputum colonization with P aeruginosa was required for study entry.

A multicenter trial of aerosolized tobramycin (Lederle Laboratories; Wayne, NJ) was designed to overcome some of the limitations of previous studies. Seventy-one CF patients with stable pulmonary status were enrolled in a multicenter, double-blind, placebo-controlled, taste-masked, crossover design study of tobramycin, 600 mg tid, delivered by ultrasonic nebulizer (Ultraneb 100/99; Sunrise Medical HHG; Somerset, PA). This dose effectively achieves sputum tobramycin concentrations >10 times the minimal inhibitory concentration (MIC*) of all tobramycin-susceptible P aeruginosa, a concentration shown necessary to overcome competitive binding of tobramycin by CF sputum. A 10% improvement in FEV1 during the first 28-day treatment period was noted during tobramycin administration compared with placebo; FEV1 increased by 3.72% predicted in the treatment group compared with a 5.97% decline in control subjects (p < 0.001). This effect continued during the three-period crossover analysis, although the difference between treatment and placebo was less, 4.32% predicted (p = 0.002). In addition, during the first 28 days of tobramycin therapy, a 100-fold mean reduction in the density of P aeruginosa in sputum was demonstrated.

Although the study demonstrated efficacy, the high dose and cumbersome ultrasonic nebulizer were not acceptable to patients and health-care providers. Subsequently, two identical phase III randomized, placebo-controlled parallel design studies were conducted to examine the safety and efficacy of preservative-free, nonpyrogenic, sterile 300-mg solution of tobramycin (TOBI; PathoGenesis; Seattle, WA) designed for administration by a specific nebulizer (Pari LC Plus Jet Nebulizer; Pari; Midlothian, VA) and compressor (Pulmo-Aide; Sunrise Medical HHG). Selection criteria for subjects included age ≥6 years, colonized with P aeruginosa, not colonized with Burkholderia cepacia, and FEV1 ≤75% and ≥25% predicted. The primary end points were assessment of FEV1, sputum bacterial density at 28 days, as well as at the end of three cycles (20 weeks). Secondary end points included FVC, rate of hospitalization, and IV antibiotic usage over the 6-month (20 weeks) study period. In total, 520 patients were enrolled at 69 centers and 464 patients completed the trial.

Tobramycin significantly improved pulmonary function, decreased sputum P aeruginosa bacterial density, reduced hospitalizations, and reduced the use of other antipseudomonal antibiotics. The tobramycin treatment effect on FEV1 percent predicted in both trials was approximately 12%.

In all subgroups analyzed, stratified by age, gender, disease severity, and concurrent use of rhDNase (Pulmozyme; Genentech; South San Francisco, CA), tobramycin-treated patients had greater improvements in pulmonary function test (PFT) results and greater reductions in P aeruginosa sputum bacterial density than patients receiving standard therapy without tobramycin.

Adjunctive Therapy for CF Pulmonary Exacerbations: Two studies have investigated the addition of aerosolized antibiotics to an antibiotic regimen in patients being treated for a pulmonary exacerbation. In both studies found similar improvement in pulmonary function and clinical measurements in the treatment groups whether or not patients received aerosolized aminoglycoside therapy. In one study, a temporary clearance of P aeruginosa from the sputum was seen in 70% of patients receiving inhaled antibiotic as compared to 41% of patients treated with IV antibiotics alone. The significance of this is unknown. To our knowledge, no study has assessed the efficacy of inhaled antibiotics in place of IV antibiotics for treatment of a pulmonary exacerbation.

Studies Using Polymyxins

Polypeptide antibiotics of the polymyxin class are poorly absorbed across mucosal surfaces, so that aerosol therapy offers the theoretical advantage of high respiratory tract levels with low systemic absorption, and a low risk of emergence of polymyxin-resistant P aeruginosa.

Suppression Therapy: The therapeutic efficacy of aerosol polymyxin (Parke-Davis; Morris Plains, NJ) as suppression therapy in CF patients has been
evaluated in two small clinical studies. Littlewood et al, in an open-label case series of young CF patients treated with 500,000 U of colistin bid, suggested that the frequency of isolation of *P. aeruginosa* decreased. Jensen et al randomized 40 patients to receive either colistin, 1 million units bid, or saline solution control for 90 days and found a slower rate of decline in FVC in treated patients. No adverse reactions to colistin were noted.

In a nonrandomized trial, 20 CF patients awaiting lung transplantation were begun on a regimen of aerosolized colistin 75 mg twice daily when a multiply antibiotic-resistant *P. aeruginosa* was cultured from their sputum. Ten other patients with multiply resistant *P. aeruginosa* were not offered colistin treatment. The mean FEV\(_1\) percent predicted was not significantly different between the treated and untreated patients, but treated patients were more likely to develop sensitive organisms (p < 0.05) more rapidly (p = 0.007) than untreated patients. Such a strategy merits a randomized, placebo-controlled trial.

**Therapy Designed To Delay Chronic Infection With *P. aeruginosa***: Three studies have evaluated the efficacy of oral ciprofloxacin (Miles Inc; West Haven, CT) used with aerosolized colistin alone or with aerosolized colistin and tobramycin together to delay chronic *P. aeruginosa* infection. Because historical controls were used and oral ciprofloxacin was administered concomitantly, the effect of aerosolized colistin is difficult to determine from these trials.

These preliminary studies suggest that aerosolized polymyxins may have a therapeutic role alone or in combination with other aerosolized or oral antibiotics. To our knowledge, however, no published studies have examined the biological activity or particle size distribution of polymyxins in aerosol form or measured sputum drug concentrations. Coly-Mycin, the most commonly prescribed polymyxin for aerosolization in CF, is a pro-drug that must be hydrolyzed to the bioactive form, colistin, and the rate of hydrolysis in airway secretions is unknown. Furthermore, studies of prophylactic polymyxin for the prevention of Gram-negative bacillary pneumonia in the ICU raised serious concerns about overgrowth by bacterial species inherently resistant to polymyxins such as *B. cepacia* and *Serratia marcescens*. To date, though, overgrowth of *B. cepacia* has not been a practical problem with long-term use of aerosolized polymyxins in England.

**Studies Using β-Lactam Antibiotics**

Studies examining aerosolized β-lactams are limited. Hodson et al carried out a crossover study of aerosolized carbenicillin and gentamicin administered for 6 months and found significant improvement in pulmonary function and a trend toward decreased hospitalizations. Of note, carbenicillin and gentamicin are incompatible in solution as inactivation of the gentamicin may occur. Nolan and colleagues examined the efficacy of aerosolized cephaloridine in patients with mild-to-moderate lung disease and found no beneficial effects.

**Conclusion**

Evidence-based recommendations for aerosolized antibiotic use in CF are possible only regarding their use as suppressive therapy. Although aminoglycosides, semisynthetic penicillins, and Coly-Mycin have demonstrated a variable clinical benefit, adequately powered trials have not been performed, with the exception of studies of preservative-free 300-mg per dose tobramycin. This preparation has undergone the most extensive clinical, safety, and pharmacokinetic testing.

**Recommendations for the Use of Aerosolized Antibiotics in CF**

1. The following patients may be considered as candidates for aerosolized preservative-free tobramycin: (1) ≥ 6 years of age; (2) FEV\(_1\) ≥ 25% and ≤ 75% predicted; (3) colonized with *P. aeruginosa*; and (4) able to comply with the prescribed medical regimen (consensus grade I).

**Comment**: The decision to initiate preservative-free 300-mg per dose tobramycin therapy should be based on the physician’s clinical judgment that the risk-benefit ratio is favorable for the patient. Potential clinical benefits include improved pulmonary function, decrease in hospitalization, and a decrease in antipseudomonal antibiotic use. This preparation was effective in patients receiving inhaled agents such as rhDNase, corticosteroids, and/or β-agonists. Potential risks include nephrotoxicity, ototoxicity, hoarseness, bronchospasm, acquisition of other intrinsically resistant organisms, and development of antibiotic resistance. Several relative contraindications to the use of aerosolized tobramycin exist. To our knowledge, there are no data regarding the use of inhaled tobramycin in pregnant women. In addition, tobramycin should be used with caution in patients with renal insufficiency or ototoxicity.

2. Physicians prescribing unapproved formulations of aerosolized antibiotics should do the following: (1) inform patients that the safety profile by the aerosolized route is unknown; (2) review known toxic reactions of the drug by
other routes (ie, IV) with the patient; (3) establish an individualized monitoring program based on the known systemic toxic reactions; and (4) describe known complications of aerosolization (consensus grade III).

3. Aerosolized preservative-free tobramycin might be considered for bacterial suppression in other patients. For example, a logical extrapolation of these data suggests that this therapy may also be efficacious in patients < 6 years of age, patients with FEV₁ < 25% or > 75% predicted, and patients colonized with other pathogens susceptible to tobramycin. However, to our knowledge, there are no data to support these extrapolations (consensus grade III).

4. Currently, we know of no studies supporting the routine use of aerosolized antibiotics as a replacement for, or as adjunct to, parenteral antibiotics for the treatment of a CF pulmonary exacerbation. The efficacy of aerosolized preservative-free tobramycin for the treatment of CF exacerbations has not been examined. Based on the clinical experience of CF physicians at the Consensus Conference, there may be individual situations when an aerosolized antibiotic may be used by itself or together with parenteral antibiotics and/or an oral fluoroquinolone for the treatment of a pulmonary exacerbation (consensus grade III).

Comment: Potential examples of such practices include, but are not limited to the following: (1) aerosolized antibiotics alone for a mild CF pulmonary exacerbation; (2) aerosolized antibiotics added to parenteral antibiotics for CF pulmonary exacerbations complicated by a resistant organism; and (3) aerosolized antibiotics added to oral fluoroquinolones for an uncomplicated CF pulmonary exacerbation.

5. Currently there have been no studies (to our knowledge) conducted to assess the ability of aerosolized antibiotics to prevent acquisition of *P. aeruginosa* (consensus grade III).

### What Is the Appropriate Dosage and Method of Delivery for Aerosolized Antibiotics?

**Introduction**

Since the 1960s, it has been known that the sputum of CF patients can antagonize the bioactivity of antibiotics such as neomycin and polymyxin.^{15,29} Aerosol antibiotic administration has been part of therapeutic regimens for patients with CF since 1964.^{30} However, only recently have the following factors been considered: the amount of drug needed in the lower respiratory tract to overcome sputum antagonism; the efficiency of aerosol delivery; and the particle size of nebulizer output necessary to deposit drug in the lower respiratory tract.

### Rationale for Aerosolized Antibiotic Dosage

Various factors, including sputum penetration, sputum components such as glycoproteins that antagonize antibiotic bioactivity, and the patient-to-patient differences in glycoprotein concentration, impact on the activity of antibiotics within the lung. These factors make estimating dosages difficult and are summarized below.

#### Sputum Penetration of IV Administered Antibiotics Is Poor

Studies with β-lactam agents have indicated that at most, 10 to 20% of the maximum serum concentration can be quantitated in the sputum. Virtually all these studies have used bioassays that may not detect antagonism of β-lactam action by sputum components.^{31}

Aminoglycosides have variable penetration into CF sputum.^{15} Data suggest that the maximal sputum concentration following IV administration is often below and rarely exceeds the MIC* for *P. aeruginosa* when studied in vitro.^{15}

#### Sputum Components Antagonize the Bioactivity of Aminoglycosides

The sputum from CF patients is known to antagonize antibiotic activity. There appears to be two classes of antagonistic components in sputum: small molecules adversely affect the penetration of the antibiotic into the bacterium and large molecules sequester the aminoglycoside through binding.^{14} This binding is almost exclusively due to sputum mucins (95%), since removing DNA in sputum by DNase does not affect activity.^{32} Soluble components in sputum, such as monovalent and divalent cations, which can also antagonize the bioactivity of aminoglycosides, vary little from patient to patient.

#### Glycoprotein Concentration Varies Among CF Patients

Due to variability in the degree of purulence, there is a wide range in the concentration of sputum glycoproteins (ie, mucins and DNA) among CF patients. The average sputum glycoprotein content is 60 mg/g but can be as high as 155 mg/g. Thus, the amount of tobramycin that needs to be deposited in the lower respiratory tract to achieve a bactericidal concentration can vary substantially from patient to patient.

#### Extrapolating the Ideal Dosage of Aerosolized Tobramycin

To determine the ideal dosage of aero-
sulfated antibiotics requires extrapolation from the following: (1) *in vitro* measurements of sputum-tobramycin interaction; (2) assumptions made about the physical characteristics of the nebulizer and the amount of antibiotics reaching the site of infection; and (3) the concentration of antimicrobial agent needed to inhibit most strains of *P. aeruginosa*. The 600-mg dose studied sought to achieve a minimum peak sputum tobramycin concentration of 400 μg/g of sputum in every patient. This calculation was based on the “worst case” sputum and an MIC for tobramycin of 4 μg/mL for susceptible *P. aeruginosa*. The median peak sputum concentration achieved with the 600-mg dose was 4,000 μg/g of sputum, indicating that many patients actually received more antibiotic than needed to kill *P. aeruginosa*. These observations led to the 300-mg twice-daily dose of preservative-free tobramycin used in the phase III trials.

### Pharmacokinetics

**Absorption of Bioavailability of Inhaled Tobramycin:** Absorption of tobramycin from the respiratory tract, following administration by inhalation, is a complex phenomenon. For most nebulizer systems, it is estimated that approximately 10% of the mass of drug initially nebulized is deposited in the lungs and the remaining 90% either remains in the nebulizer, is impacted on the oropharynx and swallowed, or is exhaled into the atmosphere. Thus, describing the relationship between administered doses and serum tobramycin concentrations is complicated by the inability to measure the actual dose of drug delivered to the site of absorption in different animal test systems or in humans. In a pharmacokinetic evaluation of aerosolized tobramycin (400- or 600-mg dosages) delivered by ultrasonic nebulizer, of 10 patients studied had peak serum tobramycin concentrations < 1 μg/mL. However, the peak concentration for one patient was > 20 μg/mL. The authors of this study suggest obtaining a blood sample 1 to 2 h following administration of nebulized tobramycin to monitor for tobramycin systemic absorption. However, other studies of aerosolized tobramycin have not noted similar elevations in peak serum concentrations. Absolute bioavailability was not directly measured in the preservative-free tobramycin 300-mg bid phase III trials but was estimated to be 11.7%. Peak serum concentrations from the 300-mg preservative-free tobramycin trials are comparable to those reported in the literature and are significantly lower than reported systemic concentrations following parenteral administration of therapeutic doses of tobramycin (Table 1).

These data demonstrate that even with the more efficient nebulizer (Pari LC Plus), mean serum concentrations of tobramycin following a twice-daily 300-mg aerosol dose still averaged 1 μg/mL. Even though serum concentrations obtained by inhalation were approximately one tenth those observed following parenteral administration, the mean peak concentrations of tobramycin in the sputum were at least 15-fold greater following aerosol administration than those achieved after parenteral administration. Although sputum concentrations are not homogenous and their measurement does not represent the true deposited dose, the ability to achieve high local concentrations in the sputum, while keeping low serum levels, suggests a potential clinical advantage of aerosol administration of tobramycin over parenteral administration. However, there remains concern about the distribution of aerosolized antibiotics due to extensive airway obstruction from sputum.

**Overview of Nebulizer Options**

**Basics of Aerosol Delivery: Ideal Particle Size and Particle Clearance** Aerosols are droplets suspended in air. For most aerosols, deposition in the lower airway and alveolar space in humans occurs with particles between 1 and 5 μm, the larger of which tend to be deposited more proximally. Particles < 1 μm have insufficient mass for effective drug delivery and many submicronic particles are exhaled. Particles > 5 μm are usually deposited in the oropharynx and are subsequently cleared by swallowing.

Following inhalation and lung deposition of an

### Table 1—Tobramycin Serum and Sputum Concentrations Following Aerosol and Parenteral Administration

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Nebulizer</th>
<th>Dosage, mg/Route</th>
<th>Mean Peak Serum Concentration, μg/mL</th>
<th>Mean Peak Sputum Concentration, μg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eisenberg et al</td>
<td>60</td>
<td>Pari LC</td>
<td>300 mg bid/aerosol</td>
<td>0.57 ± 0.38</td>
<td>687 ± 663</td>
</tr>
<tr>
<td>Ramsey et al</td>
<td>247</td>
<td>Pari LC Plus</td>
<td>300 mg bid/aerosol</td>
<td>1.01 ± 0.57</td>
<td>1799.2</td>
</tr>
<tr>
<td>Mendelman et al</td>
<td>10</td>
<td>NA1</td>
<td>6.0-10.8 mg/kg/IV</td>
<td>7.5</td>
<td>82</td>
</tr>
</tbody>
</table>

*Medic-Aid, Sussex, UK.

1NA = not applicable.
aerosol, clearance results from three mechanisms: absorption, mucociliary clearance, or expectoration of sputum. The latter two mechanisms usually only occur with drug deposited in the airways.36

Classes of Inhalation Devices: There are five current classes of inhalation devices that can deliver drug to the respiratory tract: dry powder inhalers, metered-dose inhalers, micronebulizers, ultrasonic nebulizers, and jet nebulizers.37,38 In their current form, dry powder inhalers and metered-dose inhalers are impractical to deliver the mass of aminoglycoside antibiotics required for efficacy. Micronebulizers are devices that produce aerosols by forcing a solution through a sieve at high pressure and have not been clinically tested for antibiotic delivery.

Ultrasonic Nebulizers: Ultrasonic nebulizers work by shearing forces created by a piezoelectric crystal and particle size is a function of driving frequency and nebulizer baffles. Advantages of ultrasonic nebulizers include a gas or air pressure source is not required and aerosol output is relatively high. Disadvantages include the following: the aerosol solution becomes heated unless a water bath device is used; the output is decreased as the solution’s osmolality increases; and the cycle life is relatively short. The average cycle life of an ultrasonic nebulizer is 600 to 1,000 uses, which is easily reached within one year by a CF patient receiving multiple medications.37

Jet Nebulizers: Jet nebulizers work by shearing the liquid solution by gas pressure. Larger particles are baffled out and recycled into the nebulizer solution. There are two major classes of jet nebulizers in clinical use at this time: standard and breath-enhanced.37

The advantages of the standard jet nebulizer are low cost as the disposable plastic device has a unit cost of $<1 and relative efficiency as standard jet nebulizers deliver approximately 5 to 10% of drug to the lung, but the balance is left in the device or exhaled.37 Disadvantages include quality control problems as particle size and output vary, and that although disposable, jet nebulizers have been used repeatedly by patients without proper cleaning techniques. Bacteria have been cultured from used jet nebulizers, but the actual risk to patients is unknown.

The advantages of breath-enhanced jet nebulizer are improved antibiotic delivery as 10 to 20% of the patient’s inspiration must go through the nebulization chamber where the aerosol cloud is generated and compared with the standard jet nebulizer, the breath-enhanced system generally has fewer quality control problems.39 The disadvantages are the relatively high unit cost of approximately $20 and the required cleaning between uses. However, the unit device can last for months. The nebulizer (PARI LC PLUS) used in the 300-mg preservative-free tobramycin studies was a breath-enhanced jet nebulizer.

Patient Factors Affecting Nebulizer Efficiency: Patient factors also increase the variability of aerosol delivery.40,41 These factors include minute ventilation, breathing pattern, presence of airway obstruction, cooperation, and position of the patient. The variability between patients may be as high as 10-fold; therefore, a wide safety margin for an aerosol drug is desirable.

Comparability of Nebulizers and Compressors: Due to the technical differences between devices and the physical and chemical differences between drugs, it cannot be assumed that equivalent efficacy will result from interchanging nebulizers and compressors or using alternative antibiotics.38

The Complexity of Sputum-Antibiotic Interaction in CF Patients: To date, studies with tobramycin represent the most complete understanding of sputum-antibiotic interactions in CF patients. Similar studies need to be performed with other antibiotics such as colistin, β-lactam agents, and newer compounds. Therefore, recommendations are limited to preservative-free tobramycin.

Recommendations for the Delivery and Dosing of Preservative-Free 300-mg Dose of Tobramycin

1. Preservative-free 300-mg dose of tobramycin should be delivered using a PARI LC PLUS nebulizer plus a De Vilbiss PulmoAide compressor (consensus grade I).

Comment: At present the largest study of efficacy has been done with the PARI LC PLUS nebulizer and a De Vilbiss PulmoAide compressor. Changing nebulizer cup or compressor type may affect lung deposition, clinical efficacy, and toxicity. Other breath-enhanced systems may have better in vitro delivery characteristics, but they have not been tested clinically (to our knowledge). Increasing lung deposition may also increase systemic absorption, potentially increasing toxic effects.

2. Based on similar sputum concentrations and proven clinical efficacy, a preservative-free 300-mg dose of tobramycin can be given to all patients ≥ 6 years (consensus grade I).
Comment: Lower doses of tobramycin in previous studies resulted in an inconsistent clinical response. To our knowledge, there are no data available in children <6 years of age. Infants and younger children may nose breathe, cry, or scream which can interfere with airway deposition. Younger children have low tidal volumes and may hold the aerosol mask away from their faces. Further studies are necessary to evaluate efficacy, safety, and delivery device requirements for children <6 years old.

3. Studies support the use of preservative-free 300-mg dose of tobramycin aerosolized twice a day for cycles of 1 month receiving drug, followed by 1 month not receiving drug (consensus grade I).

Comment: To our knowledge, there are no data supporting longer off periods, shorter cycles, or continuous aerosol treatment.

4. Admixing other medications with a preservative-free 300-mg dose of tobramycin cannot be recommended at this time (consensus grade III).

5. Based on the order of aerosolized medications used in the phase III clinical trial, the recommended order of aerosolized medications is (when prescribed) inhaled bronchodilators, DNase, and chest physiotherapy followed by aerosolized preservative-free 300-mg dose of tobramycin. When prescribed, inhaled corticosteroids or cromolyn/nedocromil sodium should follow inhaled tobramycin (consensus grade III).

**How Should Patients Receiving Aerosolized Antibiotics Be Monitored?**

**Background: Toxicology of Aerosolized Antibiotics**

Although numerous antibiotics have been studied as inhaled antibiotics, with few exceptions, the safety profiles of these drugs as delivered by aerosol are largely unknown. The potential for systemic exposure is great because the surface area of the lung far exceeds the surface area of the skin or GI tract. Long-term consequences of administering high doses of drug may be related to drug-specific toxicities, nonspecific irritation to the airways, and preservatives in the dosing formulations.

**Inhalation Toxicology for Tobramycin in Rats and Guinea Pigs:** Three inhalation toxicology studies of preservative-free aerosolized tobramycin were conducted in rats and guinea pigs at 3 to 109 times the estimated clinical dose in humans, for as long as 2 years, to evaluate the local effects on the respiratory tract. This was assessed mainly by histopathology and monitoring systemic exposure. These studies demonstrated that preservative-free tobramycin has a high safety margin with no irreversible toxicity observed at 12 times the intended human dose.

The predominant exposure-related change in the respiratory tract was the appearance of minimal to moderate microscopic lesions in the larynx and lungs of animals treated with multiples ≥12 times the human clinical dose. These changes are typical of aerosols and are considered adaptive responses to nonspecific irritation from treatments with high concentration aerosols.42 Many of the lesions resolved during the 4-week recovery period, which supports the 28-day on/off dosing regimen proposed for preservative-free tobramycin.

**Background: Safety Evaluation of Aerosolized Antibiotics**

Determining the safety of an aerosolized antibiotic requires assessment of patients for both expected and unexpected effects. Expected effects, which are derived from the known toxicities of an agent previously characterized in animals or humans, are generally derived from toxicities associated with the parenteral form of an antibiotic. Thus, the known ototoxicity and nephrotoxicity of tobramycin should be evaluated as well as local effects on airway reactivity. To capture unexpected effects, many diverse end points must be examined and analyzed in a descriptive fashion.

**Nephrotoxicity:** Nephrotoxicity has been documented with IV use of tobramycin. Nephrotoxicity has been evaluated in several studies of aerosolized tobramycin using several parameters to assess renal function (Table 2); to our knowledge, no studies have documented nephrotoxicity.

**Ototoxicity:** Ototoxicity has been documented with IV use of tobramycin. The study by Ramsey et al,12 using 600 mg of aerosolized tobramycin three times a day, assessed vestibular function and hearing. The dynamic E test did not document vestibular toxicity and audiograms performed between 500 and 8,000 Hz did not document hearing loss as defined by a >20-dB increase in threshold after enrollment. Likewise, Smith et al13 did not detect a change in auditory threshold up to 20,000 Hz or in performance of the dynamic E test.

**Bronchospasm:** Bronchospasm occurs in some asthmatic patients with inhalation of sulfites. Pretreatment with β-agonists decreases this side effect. Antioxidants such as sodium bisulfite and preserva-
tives such as phenol are contained in commercial preparations of tobramycin for parenteral use. Thus, a preservative-free preparation has been developed for aerosol use in CF patients.

Safety of Aerosolized Preservative-Free 300-mg Dose of Tobramycin

The phase III preservative-free tobramycin trials are the most comprehensive examination of the safety of aerosolized tobramycin. The nonmicrobiological risks of aerosolized tobramycin include those related to systemic exposure and local airway effects.

Tinnitus was experienced by 8 of 258 (3%) tobramycin-treated patients and in none of the patients who received placebo. All of the episodes were transient and characterized as mild or moderate in severity. In these patients, results of audiology testing were normal, although not always performed during tinnitus, and none of the patients discontinued tobramycin treatments. None of the remaining patients had evidence of ototoxicity. Nephrotoxicity as determined by BUN and creatinine values was not seen in treated patients.

The only adverse event related to aerosol delivery was voice alteration that occurred in 30 of 258 (12%) of patients receiving aerosolized 300 mg of preservative-free tobramycin. Most episodes were characterized as mild in severity. Spirometry obtained immediately before and 30 min after the nebulized dose detected that 62 of 258 (24%) patients in the treatment group experienced a ≥ 10% decrease in FEV1 30 min after study drug administration. All but four of these patients had been prescribed bronchodilators prior to baseline, suggesting a history of bronchospasm.

Safety of Colistin

Both nephrotoxicity and neurotoxicity have been documented with IV use of colistin. Signs and symptoms of neurotoxicity include dizziness, numbness and paresthesias (perioral), nausea, vomiting, muscle weakness, and peripheral neuropathy that can progress to confusion and seizures.43 Such symptoms have not been described with aerosolized colistin, but relatively small numbers of patients have been studied. However, chest tightness has been documented with use of aerosolized colistin in adult CF patients.44

Safety of β-Lactam Agents

To our knowledge, there are no published data on the safety profile of inhaled β-lactam agents. However, there is cause for concern due to the high incidence of allergy to these drugs in the general population. Thus, the risk of environmental exposure and allergic reactions, including anaphylaxis, during aerosolization exists for patients, families, and health-care workers. Until further information regarding safety is available, inhaled β-lactam antibiotics should be used with caution.

Recommendations for Monitoring CF Patients Receiving Aerosolized Antibiotics

1. Physicians prescribing unapproved formulations of aerosolized antibiotics should do the following: (1) inform patients that the safety profile by the aerosolized route is unknown; (2) review known toxicities of the drug by other routes (ie, IV) with the patient; and (3) establish an individualized monitoring program based on the known systemic toxicities (consensus grade III).

2. Serum levels following aerosol administration of preservative-free 300 mg of tobramycin rarely achieve levels above 2 μg/mL (trough level for IV administration), and there is no evidence of accumulation. Thus, routine monitoring of serum levels is not necessary; however, serum levels should be obtained during IV administration, as recommended in the CF Foundation Clinical Practice Guidelines45 or

### Table 2—Evaluation of the Effect of Aerosolized Tobramycin on Renal Function

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Duration (Dosage)</th>
<th>Parameter of Renal Function Assessed</th>
<th>Findings*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al13</td>
<td>22</td>
<td>12 wk (666 mg tid)</td>
<td>BUN, Cr,† urinary microglobulin urine analysis, Cr clearance, plasma/renal iothalamate CI</td>
<td>No changes</td>
</tr>
<tr>
<td>Ramsey et al12</td>
<td>71</td>
<td>4 wk (600 mg tid)</td>
<td>BUN, Cr</td>
<td>No difference</td>
</tr>
<tr>
<td>MacLusky et al11</td>
<td>27</td>
<td>32 mo (mean 50 mg tid)</td>
<td>BUN, Cr</td>
<td>No changes</td>
</tr>
<tr>
<td>Steinkamp et al16</td>
<td>14</td>
<td>20 mo (mean 50 mg tid)</td>
<td>Cr, N-acetyl-β-D-glucosaminase</td>
<td>No changes</td>
</tr>
<tr>
<td>Ramsey et al16</td>
<td>249</td>
<td>6 mo (300 mg bid)</td>
<td>Cr</td>
<td>No difference</td>
</tr>
</tbody>
</table>

*No changes refers to individual patients’ parameters when no control group was used. No difference refers to parameters of treatment group compared with control group when relevant.

†Cr = creatinine.
when indicated by the clinical status of the patient (eg, renal insufficiency) (consensus grade II).

3. Monitoring for renal tubular toxicity and reduced renal clearance should include the following: (1) urinalysis, BUN, and creatinine results obtained after each course of IV therapy or after 180 accumulative days of aerosolized aminoglycoside therapy; and (2) creatinine clearance if a 100% increase in creatinine is documented on two occasions at least a week apart (consensus grade III).

4. Monitoring for eighth nerve toxicity should include an audiogram (500 to 8,000 Hz range) after two to four courses of IV therapy or 180 accumulated days of aerosol therapy (consensus grade III).

5. The initial dose of a newly prescribed aerosolized antibiotic should be given in the presence of an appropriately trained health-care provider to monitor for wheezing, respiratory distress, and to instruct in proper technique. Patients should be trained to monitor themselves for potential bronchospasm and to immediately stop taking the medication and administer a bronchodilator if indicated (consensus grade III).

6. If a patient experiences an adverse reaction (bronchospasm, chest tightness, anaphylaxis, urticaria, perioral or periorbital edema) during an inhalation treatment, the patient should stop taking the drug and consult his/her physician. If indicated, subsequent drug administration should occur in the presence of a health-care provider (consensus grade III).

7. Hemoptysis is a common complication in CF patients with moderate to severe pulmonary disease. Although there is no evidence that aerosolized antibiotics increase the incidence of hemoptysis, they should be used with caution during clinically significant hemoptysis (consensus grade III).

8. PFTs are the best measure of short-term efficacy as PFT results have been shown to improve as early as 2 weeks after the initiation of therapy. Follow-up PFTs 2 to 4 weeks after starting therapy are recommended to assess efficacy (consensus grade I).

Comment: Lack of improvement 2 to 4 weeks after starting therapy does not rule out improvement later. Thirty percent of early nonresponders in phase III trials with preservative-free 300 mg of tobramycin demonstrated improvement in PFTs results by 3 months.

9. Evaluation of measures of long-term efficacy, such as a reduction in the frequency of hospitalization and IV antibiotic usage, is recommended 6 to 12 months after beginning therapy (consensus grade I).

Comment: Measuring the effect of aerosolized antibiotic use on frequency of hospitalization and IV antibiotic usage requires a longer duration of aerosolized therapy. In phase III trials with preservative-free 300 mg of tobramycin, an impact on these two measures did not occur until approximately 4 to 6 months. Some individuals who did not have significant short-term or initial improvement acutely in PFT results did demonstrate a reduction in hospitalization and/or IV usage.

10. Other long-term outcome measures that could be followed include the patient’s sense of well-being, work or school performance and absenteeism, and cough frequency (consensus grade III).

Comment: As pulmonary exacerbations will occur while patients are receiving aerosolized antibiotics, long-term efficacy should not be assessed during an acute period of increased symptoms. However, if a patient has had a consistent decline in PFT results from baseline or increased IV antibiotic usage while receiving aerosolized antibiotics, it may be necessary to re-assess the patient’s microbiology status and to look for other etiologies of declining health status.

WHAT ARE THE MICROBIOLOGICAL IMPLICATIONS OF AEROSOLIZED ANTIBIOTICS?

There is understandable concern that prolonged use of aerosolized antibiotics could lead to the development of significant antibiotic resistance in P. aeruginosa and that intrinsically resistant bacterial and fungal pathogens could emerge during therapy.

Development of Resistance in P. aeruginosa While Receiving Aerosolized Antibiotics

Several studies of antibiotic resistance following aerosolized antibiotics in CF patients have been published. In some, the use of aerosolized antibiotics has not been associated with the emergence of resistance and in others, aerosolized antibiotics were associated with the emergence of resistance that appeared to be transient as organisms became susceptible after antibiotic treatment was discontinued. In these latter studies, the emergence of resistance did not appear to have clinical consequences.

Treatment with preservative-free tobramycin, 300
mg bid, was associated with increased tobramycin MICs at the end of the study in 15% of treated patients as compared with 3% of placebo-treated patients. The clinical significance of increasing tobramycin MICs in patients treated with tobramycin has not been determined. *P aeruginosa* respiratory tract isolates from patients in this study were categorized in three ways: all isolates; highest-density isolates; and highest MIC isolates. MIC$_{50}$* and MIC$_{90}$* of treatment and placebo groups are presented in Table 3. In general, the highest-density isolates were not the isolates with the highest MIC. This implies that treatment with aerosolized tobramycin did not select for a large population of resistant isolates during the 6-month study.

**Methodologic Issues for Determining Resistance to Aerosolized Antibiotics**

Studies of the development of resistance in *P aeruginosa* require a standardized, validated method for susceptibility* testing.* The susceptibility breakpoints used currently in clinical microbiology laboratories most likely do not apply to aerosolized antibiotics, as significantly higher concentrations of drug can be delivered directly to the CF lung. Thus, a method that determines a wide range of MICs rather than categorization of strains as susceptible or resistant is needed to monitor resistance to aerosolized antibiotics. For example, during the preservative-free aerosolized tobramycin study, a semiautomated broth microdilution technique was utilized that was able to measure MICs as high as 1,024 μg/mL (Sensititre; Accumed; West Lake, OH).

To define a breakpoint for resistance to aerosolized tobramycin, efforts to correlate the MIC of *P aeruginosa* isolates and clinical efficacy were made in the preservative-free tobramycin study. There was no significant difference in clinical response among patients with isolates with MICs $\leq 8$ vs $> 64$ μg/mL. Unfortunately, too few patients had high-level resistance (defined as MIC $\geq 128$ μg/mL) to correlate a breakpoint with clinical efficacy. Ongoing studies of this group of patients may enable definition of a new breakpoint for resistance when using aerosolized tobramycin.

**Emergence of Intrinsically Resistant Pathogens**

Organisms such as *B cepacia*, *Stenotrophomonas maltophilia*, and *Alcaligenes xylosoxidans* are virtually always resistant to aminoglycosides and many are resistant to colistin as well. *B cepacia* is recognized as an important pathogen in patients with CF, but the role of *S maltophilia* and *A xylosoxidans* in CF lung disease is less clear. To date, only a limited number of studies have examined the emergence of these organisms during treatment with aerosolized antibiotics. During continuous administration of aerosolized colistin for 3 months, no resistant pathogens or fungal colonization occurred.* MacLusky et al* identified five patients harboring *B cepacia* prior to treatment in both the control and treatment groups and subsequently identified four additional patients with this pathogen during treatment (three control patients and one patient in the treatment group). Ramsey et al* found two patients at entry and three patients who acquired *B cepacia* and 10 who acquired *S maltophilia* while enrolled in the aerosolized tobramycin, 600 mg tid, treatment trial.

In the preservative-free 300-mg tobramycin study, colonization with *B cepacia* was an exclusion criterion at entry. Only one patient in the placebo group acquired *B cepacia*. Six patients in the treatment group and 10 patients in the placebo group acquired *S maltophilia* and *A xylosoxidans* was acquired by

**Table 3—Summary of the *P aeruginosa* Tobramycin MIC (μg/mL) as Determined in the Phase III Aerosolized Tobramycin Trial of 300 mg bid**

<table>
<thead>
<tr>
<th>Isolates</th>
<th>Aerosolized Tobramycin Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wk 0</td>
<td>Wk 20</td>
</tr>
<tr>
<td>All isolates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIC$_{50}$</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>MIC$_{90}$†</td>
<td>8.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Highest-density isolates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIC$_{50}$</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>MIC$_{90}$</td>
<td>4.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Highest MIC isolates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIC$_{50}$</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>MIC$_{90}$</td>
<td>16.0</td>
<td>64.0</td>
</tr>
</tbody>
</table>

*The tobramycin susceptibility of the *P aeruginosa* isolates in this study was analyzed in three ways: all isolates together, the MIC of the organism present in the highest concentration, and the organism with the highest MIC.

†There was a trend toward higher MIC$_{50}$ in the treatment group across all three categories of isolates (all, highest density, highest MIC) that was not statistically significant.
one patient in the treatment group and three patients in the placebo group. In this same study, 24 patients in the treatment group and only one patient in the placebo group became colonized with Candida albicans. The number of patients with Aspergillus species detected in sputum increased from 52 to 70 in the treatment group but decreased from 62 to 47 in the placebo group. The clinical significance of this colonization is unclear, but it bears further observation. Thus, it did not appear that patients receiving aerosolized tobramycin were at higher risk of acquiring intrinsically resistant bacterial pathogens than patients receiving placebo during the 6 months of the trial.

**Recommendations for Addressing Microbiological Implications of Aerosolized Antibiotics**

1. It is strongly recommended that all efforts be made to define a breakpoint to correlate in vitro susceptibility with in vivo efficacy for antibiotics delivered by the aerosol route, because at present, there are inadequate data to establish this breakpoint (consensus grade I to III).

Comment: The National Committee for Clinical Laboratory Standards defines MIC breakpoints for parenteral tobramycin as follows: $\geq 4 \mu g/mL$, susceptible; $8 \mu g/mL$, intermediate; and $\geq 16 \mu g/mL$, resistant. These levels are derived from an assessment of clinically achievable antibiotic concentration in serum, the relatively narrow therapeutic index needed to avoid nephrotoxicity and otoxicity, and studies of clinical efficacy. It is well recognized that much higher drug concentrations can be achieved by the aerosol route. This is in part necessary to overcome the inhibitory effects of sputum on drug bioactivity. It also has the potential benefits of overwhelming certain mechanisms of resistance and of possibly allowing penetration of antibiotics into biofilms.

2. Standardized method for determination of high-level resistance needs to be established for CF isolates of P aeruginosa (consensus grade III).

Comment: Currently, most commercially available susceptibility testing cannot detect high-range MICs ($> 8 \mu g/mL$). However, conventional antibiotic susceptibility testing is still necessary for parenteral agents, and clinical microbiology laboratories should continue to employ National Committee for Clinical Laboratory Standards standards for antibiotic susceptibility testing. At present, the best method for determining antibiotic susceptibility for strains with MICs beyond conventional levels of resistance is uncertain. Thus, it is critical to establish a standardized method for in vitro testing of high-level antibiotic resistance that can be used in all settings. Clinical measures should be used to assess aerosolized antimicrobial efficacy rather than in vitro antibiotic susceptibility.

3. The presence of P aeruginosa is a microbiological indication for the use of aerosolized antibiotics. There are no absolute microbiological contraindications to the use of aerosolized antibiotics. Patients who have either high-level or multiply resistant P aeruginosa or other intrinsically resistant organisms such as B cepacia should not be excluded from receiving aerosolized antibiotics (consensus grade III).

4. At present, there are no microbiological indications to discontinue treatment with aerosolized antibiotics. The emergence of resistant P aeruginosa or acquisition of intrinsically antibiotic-resistant organisms such as B cepacia and S maltophilia does not preclude the continued use of nebulized agents intermittently (consensus grade II-2).

Comment: Several previously published studies have shown transient emergence of resistant P aeruginosa during therapy with aerosolized antibiotics that reverted to a susceptible phenotype with discontinuation of treatment with the nebulized agent. This supports the practice of alternate on and off months of therapy and may suggest that more prolonged suspension of aerosol treatment could be useful.

5. Processing of CF respiratory tract specimens should be performed according to the recommendations of the previously published CF consensus document, Microbiology and Infectious Disease in CF (CF Foundation Clinical Practice Guidelines, Appendix VIII) and CF Center Directors should meet with their laboratory directors to discuss their concerns (consensus grade III).

Comment: Baseline susceptibility testing should be considered prior to initiation of treatment with aerosolized antibiotics. When clinically indicated, determining the susceptibility of strains at the end of the “off cycle” might aid in the detection of reemergence of susceptible strains. It is strongly recommended that susceptibility testing be performed if there is a significant deterioration in pulmonary function or clinical status.
6. Many institutions have software systems in place to detect trends in antibiotic resistance patterns for specific pathogens and specific patient populations. Consideration to perform such monitoring for CF patients and for P aeruginosa should be given at individual centers (consensus grade III).

7. Reference laboratories are currently available to identify putative B cepacia strains, to assess patient-to-patient spread, to perform synergy studies, and to examine strains with high level MICs. Clinicians are encouraged to use these resources. Quantitative assessment of sputum flora is routinely available only in research settings (consensus grade III).

8. Each center should develop a formal policy for aerosolized antibiotic use in the home, clinic, and inpatient facility. Such a policy should address barrier techniques, filters, exhaust, environmental contamination, disposal of unused product, and cleaning of nebulizers (consensus grade III).

**Future Studies**

It is recommended that future studies of aerosolized antibiotics address the following topics: (1) pharmacologic and safety testing of other antipseudomonal antibiotics alone or in combination; (2) efficacy trials to determine the effect of aerosolized antibiotics when used to treat pulmonary exacerbations; (3) long-term suppression trials to determine if bacteriologic and clinical effect are maintained; (4) prospective controlled trials to determine the efficacy of aerosolized antimicrobial therapy to prevent or delay chronic P aeruginosa infection; (5) development of improved methods of measuring active drug in the sputum; (6) development of new aerosolized antimicrobial therapies must include extensive clinical safety and pharmacokinetics testing; (7) a phase IV study of patients receiving longer treatment with preservative-free tobramycin, 300 mg bid, is needed to address the following: (a) emergence of resistance among P aeruginosa strains; (b) molecular epidemiology of P aeruginosa isolates with MICs to tobramycin > or = 16 mg/mL; (c) emergence of other intrinsically resistant pathogens such as B cepacia; (d) cross-resistance to other aminoglycosides; (e) mechanisms of aminoglycoside resistance; and (f) ongoing clinical efficacy as determined by pulmonary function; (8) studies to track the general usage of aerosolized agents are needed; (9) studies to track overall tobramycin resistance in P aeruginosa are needed that will require participation of a reference laboratory to detect high-level resistance; (10) studies to track the incidence of intrinsically resistant pathogens are needed; (11) studies of adjuvant medications such as surfactant to improve aerosolized delivery of antibiotics should be performed more extensively; and (12) studies of more rapid delivery methods such as the dry powder inhaler being developed are important as well.

**References**

21 Baudhoff GS, Nunley DR, Manzetti JD, et al. Use of aerosolized colistin sodium in cystic fibrosis patients awaiting lung transplantation. Transplantation 1997; 64:748–752
27 Trissel LA. Handbook on injectable drugs. 4th ed. 1996
36 Brain JD, Valberg PA. Deposition of aerosol in the respiratory tract. Am Rev Respir Dis 1979; 120:1325–1373
40 Smaldone GC. Deposition of nebulized drugs: is the pattern important? J Aerosol Med 1994; 7:525–533
45 Cystic Fibrosis Foundation. Clinical practice guidelines 1997; 2:30
46 Cystic Fibrosis Foundation. Clinical practice guidelines 1997; 2:12
47 Microbiology and Infectious Disease in Cystic Fibrosis, Consensus Conference. Concepts in care. CF Foundation (vol V, section 1); 1994

**Glossary**

These are the consensus definitions that are indicated by an asterisk (*) the first time they are used in the document.

**Chronic colonization**—persistent presence of pathogens despite antibiotic therapy

**Chronic suppression**—therapeutic strategy to decrease microorganism burden and/or inflammatory process

**Colonization**—presence of microorganisms without biochemical or clinical evidence of inflammation

**Continuous**—persistent presence of bacteria over 6 months or longer

**First acquisition**—initial recovery of pathogen from a respiratory tract specimen

**Infection**—presence of microorganisms with clinical or biochemical signs of accompanying inflammation

**Intermittent**—inconsistent recovery of a pathogen from the respiratory tract

**MIC**—minimal inhibitory concentration is the lowest concentration of an antimicrobial agent that will inhibit the growth of a microorganism in *vivo*

**MIC**—the MIC that inhibits 50% of the organisms under study

**MIC**—the MIC that inhibits 90% of the organisms under study

**NOAE**—no observed adverse effect level is a dosage of an agent (in excess of the projected human dosage) used in animal toxicology studies to study potential toxicities

**Prophylaxis**—therapeutic strategy used to prevent acquisition of a pathogen

**Resistance**—antimicrobial is not active in *vivo* against a microorganism at the predicted concentration of an antimicrobial achievable at a specific body site; in standardized susceptibility testing, the body site under consideration is the serum

**Susceptibility**—antimicrobial is active in *vivo* against a microorganism at the predicted concentration of antimicrobial achievable at a specific body site, generally the blood

**Therapeutic index**—ratio of the toxic dose in animals to the therapeutic dose in humans used to assess relative risk to humans

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