Inhaled Antimicrobial Therapy: From Cystic Fibrosis to the Flu

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Introduction

Dosing of Inhaled Antimicrobials
Antibacterials: Cystic Fibrosis
  Suppressive Therapy
  Acute Exacerbations
  Eradication/Prevention of Colonization
Antibacterials: Mechanical Ventilation
Pentamidine
Antifungal
Antiviral
Ribavirin
Zanamivir
Summary

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The successful development of aerosolized antimicrobial therapy depends on three major factors: the nature of the disease process, the delivery system, and the antimicrobial agent.6,7 Diseases that involve infection of the airway without a substantial systemic component (eg, cystic fibrosis, bronchiectasis) are much more suitable for aerosolized therapy than diseases of the parenchyma that are associated with substantial risk of systemic complications (eg, pneumococcal pneumonia). The sophistication of aerosol delivery systems has also greatly increased over the past decades. The crude atomizers that produced largely nonrespirable aerosols that were used in the early days of aerosolized antibiotic therapy have given way to modern jet and ultrasonic nebulizers and dry powder devices that produce particles that are much more likely to be respirable and can therefore be targeted to the lower airways.

The third factor is the nature of the antimicrobial agent. Until recently, inhaled antimicrobial therapy consisted of empirical trials of aerosolization of intravenous antibiotic formulations. However, the pharmaceutical industry has in recent years developed specialized formulations of existing agents that are designed for pulmonary delivery (eg, tobramycin5 and pentamidine8). In addition, advances in molecular pharmacology are likely to give rise to a wide variety of new chemical entities that may be suitable for aerosol delivery (eg, zanamivir, which is currently used to treat influenza9). With the continued development of new
aerosol delivery systems that can be used to target specific regions of the lung with greater degrees of accuracy, and with the development of new formulations or the discovery of new chemical entities, it is likely that the acceptance of aerosolized drug delivery will continue to grow in the near future.

Dosing of Inhaled Antimicrobials

In contrast to studies of inhaled bronchodilators or bronchoprovocative agents, in which administration of a single dose results in readily quantifiable changes in airway mechanics, detecting the response to inhaled antimicrobial agents often requires multiple doses and tends to be qualitative as well as quantitative. Furthermore, the relationship between nominal dose and bioavailability is much more difficult to characterize than is the case with oral antimicrobial therapy. To further complicate this issue, the regional distribution of the dose (eg, deposition in extrapulmonary regions vs central airways vs alveolar regions) may be as important as the dose depositing in the patient.

Before reviewing individual agents, let us briefly review some of the principles related to dosing of these agents. Figure 1 indicates some of the reasons why we cannot extrapolate the dose delivered to the lung from the nominal dose.7 The confounding factors can, however, be grouped in ways that may facilitate the development of logical strategies to optimize drug delivery. First, there are factors related to the delivery system, such as differences in output and particle size between different commercial delivery systems, the effects of tubing, holding chambers and other connections, and changes in drug formulation or dilution of solutions and suspensions for nebulization. All of these variables can be assessed in vitro prior to clinical studies. Furthermore, replication of inspiratory breathing patterns of the target population can be readily incorporated into bench models.10

However, there is a second group of factors that are much more difficult to replicate in vitro and that usually require clinical studies.11 These factors determine the fate of a particle after it is inhaled. Once an aerosolized drug particle of a given size has been inhaled at a given flow, the site of deposition is influenced by the anatomy of the upper and lower airways and by the patient’s breathing pattern, including breath-holding and the presence of expiratory flow limitation.6 Furthermore, the aerodynamic characteristics of an aqueous aerosol may be altered by the relative humidity of the airway.12

Measuring the dose delivered to the lung is the most difficult part of the dosimetry outlined in Figure 1, and has been reviewed elsewhere.6,7 Gamma scintigraphy is a technique by which the deposition of a radiotracer mixed with the drug being studied is measured using a gamma camera.6,13,14 It can be used to measure the total dose delivered to the lung, and to assess the regional distribution of deposited radioactivity (eg, extrapulmonary versus pulmonary, or central airways versus lung periphery).

To quantify the dose delivered to the patient without measuring the regional distribution, there are a number of alternatives to gamma scintigraphy. For example, filters or laser diffraction devices, placed near the patient’s mouth, can measure the drug delivered during inhalation and exhalation, and drug deposition is equal to the difference between the amounts inhaled and exhaled.14 If the aerosol does not contain a substantial fraction of particles 5 \( \mu \text{m} \) in diameter, such measurements are an accurate reflection of pulmonary drug deposition because relatively little drug will deposit in the pharynx during tidal breathing.

Pharmacokinetic assessments, sometimes combined with gamma techniques, are useful in characterizing the pulmonary deposition of inhaled antimicrobials.15–17 For example, Ilowite et al reported that sputum levels of gentamicin were two orders of magnitude greater than levels expected using the systemic route.15 However, sputum concentrations were more reflective of deposition in the central airways than of the total amount of drug deposited in the lung.

In addition to measuring drug levels in serum and respiratory secretions, urine collection for drug concentrations is a useful measure of the systemic bioavailability of inhaled aminoglycosides15 and pentamidine.16 Systemic bioavailability is useful as an indicator of the adequacy of
pulmonary drug delivery and as a safety index of the degree of exposure of other organ systems to the drug.

**Antibacterials: Cystic Fibrosis**

In a majority of patients with cystic fibrosis and bronchiectasis, the airways are usually colonized by Gram-negative organisms such as *Pseudomonas aeruginosa*. After persistent colonization, the *P. aeruginosa* is usually of mucoid phenotype associated with reduced penetration of antibiotics in airway secretions. Aminoglycosides, because of their poor penetration into sputum following intravenous administration, their potential for toxicity with high doses and prolonged concentration, and their activity against *P. aeruginosa* have been the most frequently prescribed inhaled antibiotics in cystic fibrosis. Tobramycin is the most frequently used aerosolized antibiotic because of higher rates of resistance with gentamicin and the higher cost of amikacin. Other antibiotics administered via inhalation include colistin and a few reports of cephalosporins. With the exception of the quinolones, these organisms are not usually sensitive to oral antibiotics and require intravenous antibiotic therapy. Unfortunately, after the colonization process has been established, intravenous antibiotic therapy is usually suppressive rather than eradicative.

Repeated courses of intravenous antibiotics lead to the development of drug resistance, as well to the complications associated with obtaining venous access for a long period of time. Though such suppressive therapy with aerosolized antibiotics has been undertaken for many years, large multicenter studies have only recently established that this treatment is in fact safe and effective. In a new formulation of tobramycin (TOBI, tobramycin solution for inhalation, PathoGenesis, Seattle), it has been found that administration of this agent twice a day for 28 days on alternate months is associated with improved pulmonary function and reduced rates of acute exacerbation. However, though suppressive therapy is the most common indication for prescribing aerosolized antibiotics in cystic fibrosis, there are two other areas of interest for the use of aerosolized antibiotics in cystic fibrosis. One is the use of aerosolized antibiotics to eradicate Gram-negative organisms in early disease and prevent colonization. The other is their potential as an adjunct to intravenous therapy in acute exacerbations.

Overall, the results of earlier inhaled antibiotic studies were somewhat difficult to interpret because of differences in study design. The doses of antibiotics have differed between studies and some may not have been adequately blinded because of the distinctive taste of some aerosolized agents. Likewise, the delivered dose has varied because of the use of different nebulizers and drug formulations.

**Suppressive Therapy**

Most of the clinical trials of inhaled antibiotics have concentrated on suppressive therapy in the period between acute exacerbations. The findings of these studies have been reviewed in greater detail elsewhere. Conclusions are difficult to draw from integration of these studies because of differences in study design, dosage, and delivery system. The majority of aminoglycoside studies used aerosolized tobramycin compounded from intravenous formulations. However, though earlier studies used lower doses and yielded various results, two recent large multicenter trials provided convincing evidence of the efficacy of aerosolized tobramycin therapy in cystic fibrosis. In the first of these studies, 71 patients were randomized to one of two groups. Group 1 received 600 mg of aerosolized tobramycin for 28 days, followed by placebo for two 28-day periods. Group 2 received placebo for 28 days, followed by tobramycin for two 28-day periods. Pulmonary function and the density of *P. aeruginosa* in sputum were assessed. Treatment with tobramycin in the first 28-day period was associated with a significant increase in forced expiratory volume in the first second (FEV₁) percent of predicted (p < 0.0001) and forced vital capacity, compared to placebo. A decrease in the density of *P. aeruginosa* in sputum, by a factor of 100, was found during all periods of tobramycin administration. Analysis of the three-period crossover demonstrated that tobramycin administration was associated with improvement in FEV₁ but that the magnitude of the treatment effect was approximately half the magnitude observed in the first period parallel analysis. No significant difference was found between tobramycin and placebo for forced vital capacity. No ototoxicity or nephrotoxicity occurred, and the emergence of tobramycin-resistant bacteria was similar between the treatment groups. Lastly, a treatment effect was maintained during a 28-day off-drug period after an initial 28-day on-drug period (600 mg tobramycin tid), suggesting that continuous therapy was not required to maintain improvements in pulmonary function.

Most recently, in a multicenter, controlled study, Ramsey et al. assessed TOBI, a formulation of tobramycin specifically designed for aerosolization. TOBI is a sterile, preservative-free solution containing 60 mg/mL of tobramycin. It is to be used in conjunction with the PARI-LC Plus jet nebulizer with a DeVilbiss Pulmo-Aide compressor. Two pivotal studies using TOBI at a dose of 300 mg bid demonstrated its safety and efficacy in cystic fibrosis patients. Because the aerosol was better characterized and the delivery system was probably more efficient, these utilized a lower dose and twice-daily administration, compared to the earlier 1993 study by Ramsey et al. A total of 520 patients were randomly assigned to receive either 300 mg of inhaled tobramycin or placebo twice daily for 4
weeks, followed by 4 weeks with no study drug. Treatment or placebo in 3 on-off cycles was administered for a total of 24 weeks. The end points included pulmonary function, the density of \( P. \) aeruginosa in sputum, and hospitalization. Patients treated with tobramycin had an average FEV\(_1\) increase of 10% at week 20, as compared with week 0, whereas the patients receiving placebo had a 2% FEV\(_1\) decrease (Fig. 2). During each period when the drug was not being administered, improvement in lung function was maintained while the density of \( P. \) aeruginosa sputum returned toward baseline values (Fig. 3). Treatment with tobramycin decreased the density of \( P. \) aeruginosa sputum and also decreased the risk of hospitalization. Subgroup analysis revealed that the most impressive response to TOBI was in teenagers, an important finding, because this group tends to have the most rapid rate of decline in lung function (Table 1). Tinnitus and alteration of the voice were the only adverse events reported in a significantly greater percentage of the tobramycin group than in the placebo group. The 8 cases of tinnitus reported in the tobramycin group were transient and mild or moderate in severity and did not lead to withdrawal from the study. Likewise, voice alteration was mild in most cases. No nephrotoxicity was detected. TOBI has superseded the "off label" use of parenteral Coly-Mycin for aerosol therapy is not supported by adequate and well controlled trials demonstrating its efficacy and safety, and it is associated (as are other polymyxins) with a substantial risk of severe bronchospasm, even after pretreatment with a \( \beta-2 \) adrenergic agonist.

**Acute Exacerbations**

In the treatment of acute respiratory exacerbations in cystic fibrosis patients, studies suggest that the addition of aerosolized antibiotics to intravenous antibiotic therapy offers little additional benefit.\(^{24,25}\) No significant improvement in symptoms, pulmonary function, or prevention of recolonization was noted when inhaled aminoglycosides were administered in conjunction with intravenous aminoglycosides and antipseudomonal \( \beta \)-lactams.\(^{24}\) Although this adjunctive inhaled aminoglycoside therapy led to increased rates of eradication of \( P. \) aeruginosa, compared to intravenous therapy alone, the eradication was transient and there was no correlation between bacteriologic response and clinical improvement.\(^{24}\) However, because these small studies may indicate a trend in favor of increased rates of
eradication with adjuvant therapy, it may be worth reevaluating this issue with emphasis on either enhanced pulmonary delivery of aerosolized antibiotics or, alternatively, by focusing on subgroups of patients (eg, those with early disease or those with more rapid declines in pulmonary function).

**Eradication/Prevention of Colonization**

Most studies of aerosolized antibiotics in cystic fibrosis have concentrated on treating or suppressing established infection/colonization, but Valerius et al. assessed whether chronic pulmonary colonization with *P. aeruginosa* in cystic fibrosis is preventable. Twenty-six patients who had never received anti-pseudomonal chemotherapy were randomized to receive either no antipseudomonal chemotherapy or oral ciprofloxacin and aerosol inhalations of colistin twice daily for 3 weeks, whenever *P. aeruginosa* was isolated from routine sputum cultures. During the 27 months of the trial, infection with *P. aeruginosa* became chronic in significantly fewer treated subjects than untreated subjects (2 [14%] vs 7 [58%], p < 0.05) and there were significantly fewer *P. aeruginosa* isolates in routine sputum cultures in the treated group (49/214 [23%] vs 64/158 [41%], p = 0.0006). The authors concluded that chronic colonization with *P. aeruginosa* can be prevented in cystic fibrosis by early institution of antipseudomonal chemotherapy. Though these preliminary data from Denmark are encouraging, this approach requires early detection of the disease, with close follow-up and intensive therapy for patients who are in many cases relatively asymptomatic. In addition, concerns about the emergence of drug resistance with early therapy need to be allayed. However, if these studies can be replicated on a wider scale, delaying the progression to severe disease may justify the expense of early intensive therapy.

**Antibacterials: Mechanical Ventilation**

Patients undergoing mechanical ventilation are predisposed to develop pneumonia. In addition, if mechanical ventilation is prolonged, a purulent bronchitis can develop that may interfere with attempts to wean the patient from the ventilator and necessitate a tracheostomy. Though the lower airway is sterile in normal subjects, patients undergoing mechanical ventilation quickly become colonized with Gram-negative organisms or *Staphylococcus aureus*. Antibiotic resistance is common. Though aerosolized antibiotics have been used for the prophylaxis of pneumonia and for the treatment of bronchitis, neither indication is adequately supported by well controlled trials. However, though the evidence suggests that routine prophylaxis of intubated patients with aerosolized antibiotics may not only be ineffective but could be counterproductive and dangerous, there is preliminary data that aerosolized antibiotics used selectively may have a role in the treatment of purulent tracheobronchitis and may be worthy of further study. In a small open-label feasibility study, administration of nebulized gentamicin to patients undergoing prolonged mechanical ventilation reduced the volume of purulent secre-

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FEV₁ = forced expiratory volume in the first second.

*The treatment effect was calculated as the difference between the mean changes in the tobramycin and placebo groups.
†For each subgroup, the first p value is for the overall comparison of the two treatment groups by analysis of variance; the other p values are for subgroup-treatment interactions.
(The largest response in FEV₁ was in teenage subjects, the smallest in adults.)

(Adapted from Reference 5, with permission.)
tions. However, simply reducing the volume of secretions may not necessarily be clinically important, and a number of key questions await further answers: Does the treatment of purulent tracheobronchitis affect, either beneficially or adversely, the incidence or the course of subsequent ventilator-associated pneumonia? Does such therapy facilitate weaning from mechanical ventilation or decannulation of tracheostomies? Does aerosolized antibiotic therapy promote drug resistance at rates greater than or less than systemic administration?

In order to address any of these issues in a clinically meaningful manner, it will be necessary to establish the dose of drug delivered to the lungs of intubated mechanically ventilated patients. Recent studies demonstrate that it is possible to achieve aminoglycoside levels in the secretions of such patients that are 10–50 times higher than serum concentrations achieved using the same nominal dose administered intravenously. However, in order to achieve such antibiotic concentrations, it is necessary to optimize a number of factors, including the ventilator settings, volume fill of the nebulizer, treatment time, interruption of humidification, and the type of nebulizer and ventilator.

Once it has been established that the drug has been delivered in adequate concentrations, the clinical issues listed in the preceding paragraph can then be explored. In the meantime we can only speculate. We believe that prophylactic or indiscriminate use of an antibiotic by any route, including inhalation, will inevitably lead to antibiotic resistance. However, studies in cystic fibrosis patients suggest that the risk of drug resistance is probably not greater through inhalation than through systemic administration. Furthermore, the high concentrations of drug in secretions achieved with optimized delivery should, theoretically, retard the development of resistance.

Reducing the volume of purulent secretions with antibiotic therapy could facilitate weaning or decannulation in some patients. However, depending on the chronicity of the hypersecretion, in many patients the reduction in volume is likely to be temporary. Though the indiscriminate prophylactic use of inhaled antibiotics is unlikely to be useful, it is not possible at this stage to predict whether intensive therapy of tracheobronchitis will prevent ventilator-associated pneumonia. Controlled clinical trials of aerosolized antibiotics in mechanical ventilation are needed before this mode of therapy can be recommended as effective or safe.

Pentamidine

Aerosolized pentamidine is used as prophylactic therapy against Pneumocystis carinii pneumonia (PCP) in patients with human immunodeficiency virus. Prior to its use as an inhaled formulation for PCP prophylaxis, pentamidine had been used for many years as a systemic therapy for tropical protozoal infections and for the treatment of rare cases of PCP in immunocompromised patients. With the advent of the acquired immunodeficiency syndrome/PCP pandemic in the 1980s, the use of intravenous pentamidine greatly increased. Because of the high incidence of PCP in patients with human immunodeficiency virus and the frequency of recurrence of the condition in patients with a prior episode, clinical trials of prophylaxis were undertaken with a formulation designed for inhalation. These studies found that aerosolized pentamidine was effective as secondary prophylaxis in patients with at least one prior episode of PCP and as primary prophylactic therapy in patients with CD4 counts of < 200/mm³. The widespread introduction of aerosolized pentamidine was associated with a significant reduction in the morbidity and mortality associated with PCP. Some reports also suggested that it could be used as therapy for a subset of patients with established PCP, but the inhaled drug is now rarely used for that indication. Even though it has been demonstrated that prophylaxis with trimethoprim-sulfamethoxazole was more effective and less expensive than aerosolized pentamidine, it continues to be used in a subset of patients who are allergic to or intolerant of sulfonamide-containing agents. The cumulative failure rate for aerosolized pentamidine prophylaxis in patients with CD4 counts of 100–200/mm³ was reported to be 21% over a 3-year period: a rate comparable to that of trimethoprim-sulfamethoxazole or dapsone. However, in patients with CD4 counts < 100/mm³, the failure rate with aerosolized pentamidine is 33%—significantly higher than with oral regimens. The oral regimens have the added advantages of providing protection against toxoplasmosis and of being less expensive. However, the patients who are more likely to require aerosolized pentamidine treatment because of intolerance to aerosolized pentamidine are also those with CD4 counts < 100 mm³, and, as a result, aerosolized pentamidine is more likely to be used in the group in whom it is less effective.

Radiologically, PCP usually presents as a diffuse multilobe pneumonia. However, it has been suggested that presentation with upper lobe disease may be more common in patients receiving aerosolized pentamidine. The possible interaction of regional distribution of inhaled pentamidine with the regional distribution of PCP has been discussed elsewhere.

Nebulizers for aerosolized pentamidine therapy have two requirements not routinely fulfilled by commercial jet nebulizers. First, they need to provide small particles (mass median aerodynamic diameter of approximately 1 μm) to optimize delivery to the lung periphery rather than to the central airways. Second, they must incorporate an exhalation filter to reduce environmental contamination. In the United States, the approved nebulizer for aerosolized pen-
tamidine therapy is the Respirgard II (Marquest Medical, Englewood, Colorado), although alternative devices have been used successfully in other countries. Its design incorporates an external baffle to remove large particles from the aerosol, and the treatment time is 40 minutes to nebulize 6 mL, with approximately 10% of the drug depositing in the lung.

Because alveolar clearance of relatively insoluble particles is slow compared to the clearance of particles depositing in ciliated airways (weeks instead of hours), the drug needs to be administered at only 2-week or 4-week intervals. Plasma levels are usually undetectable, but pentamidine is detectable in urine for weeks after administration of a single dose. Urine levels correlate with bronchoalveolar lavage fluid levels.16

Aerosolized pentamidine is a relatively safe and well tolerated medication for most patients. The most common adverse effects are cough and bronchospasm. However, pretreatment with a short-acting β-2 agonist can prevent or ameliorate these symptoms in most patients. There is some evidence that the incidence of pneumothorax may be higher in patients taking aerosolized pentamidine.31 Infection with Pneumocystis carinii can result in cystic changes in the lung, which can predispose to pneumothorax formation. Furthermore, if aerosolized pentamidine therapy induces frequent severe bouts of coughing, the risk of pneumothorax would theoretically increase. As a result, the drug should be prescribed with caution in patients considered to be at increased risk of this complication.

A further consideration with the use of aerosolized pentamidine concerns the exposure of health care workers to the drug.32 Indeed, some health care workers have had urinary levels that approached those of patients. Though most health care workers exposed to aerosolized pentamidine are asymptomatic, there are anecdotal reports of cough, aggravation of asthma, and at least one case of a worker developing a reduction in carbon monoxide diffusing capacity. The risk of exposure is increased by the fact that submicronic particles can stay suspended in room air for several hours and are thus respirable by bystanders. Loose-fitting face masks offer little protection because the inhaled airstream can bypass the mask. However, if patients are treated in well ventilated rooms with negative pressure and adequate air exchange (or, in some centers, specially designed booths), large numbers of patients can be treated without detectable systemic exposure of health care workers.33 Because the nebulizers that are used for aerosolized pentamidine include exhalation filters, the most important source of health care worker contamination may be inadequately supervised patients removing the device from their mouths either to cough or to converse without first switching off the compressed air supply.32 Ideally, patients should be observed through a window during treatment, in an adequately ventilated room or booth.

In conclusion, aerosolized pentamidine therapy continues to have a role for the prophylaxis of PCP in patients who are allergic to or otherwise intolerant of oral prophylaxis. The development of aerosolized pentamidine has yielded valuable insights into the evaluation of the dose response of inhaled drugs and increased our awareness of the need to protect health care workers from exposure to inhaled drugs.

Antifungal

Invasive pulmonary aspergillosis is one of the most devastating complications of bone marrow transplantation and aggressive anticancer chemotherapy regimens. Though intravenous amphotericin B is the most effective available treatment, this disease is frequently fulminant and fatal. In efforts to reduce the incidence of this condition, some investigators have prophylactically administered amphotericin B via inhalation. An aqueous formulation and a liposomal formulation have been tested.34,35 Both are well tolerated but it has not been determined whether one formulation is superior to the other. Theoretically, the liposomal formulation would have a longer residence time in the airway. Pilot studies suggest that inhaled amphotericin B is relatively well tolerated, though cough and wheeze is induced in some patients, especially those with a history of asthma or airway hyperreactivity. It appears that systemic exposure is low after administration via inhalation. Unfortunately, because of insufficient data, it is not possible to determine whether such treatment is effective. No large-scale studies have been published to date. Most studies have examined amphotericin B as prophylaxis for pulmonary aspergillosis in neutropenic patients following bone marrow transplantation, but the results were ambiguous because of inadequate study size or design.35–39 Because the incidence of this complication is relatively episodic, studies based on historical controls or on small sample sizes are likely to be inconclusive. One study examined the use of aerosolized amphotericin as prophylaxis against fungal infections following lung, heart-lung, and heart transplantation, and found a significant reduction in the incidence of fungal infections, compared to a case control group.38 At the present time, the role, if any, of inhaled antifungal therapy with amphotericin B remains undetermined. It is regrettable, given the seriousness of pulmonary aspergillosis in immunosuppressed patients, that inhaled amphotericin B, a potentially beneficial prophylactic therapy, has not yet been adequately evaluated.

Antiviral

Ribavirin

Ribavirin therapy for respiratory syncytial virus (RSV) infection was for many years the only accepted inhalation
therapy for viral illness.\(^{39,40}\) RSV infection is one of the main causes of acute bronchiolitis in children, most of whom are less than three years old.\(^{40}\) Inhaled drug delivery in very young patients poses technical challenges, and the drug is delivered via humidification tents or face masks. It has also been delivered to patients undergoing mechanical ventilation. However, in the latter setting considerable caution is required because the drug can precipitate in and obstruct ventilator tubing. The drug is delivered by way of a specialized small-particle aerosol generator supplied with the drug. This is the only device that should be used to deliver the drug, and ribavirin should not be mixed with other agents.\(^{39}\) Though the small-particle aerosol generator can be incorporated, with suitable precautions and adjustments, into mechanical ventilator circuits, it is recommended that such therapy be administered in centers with prior experience in this relatively complex protocol. Despite the extensive clinical experience with this drug, some controversy continues about its efficacy. It appears effective at reducing viral shedding from respiratory mucosa in patients with RSV, and most studies agree that if it is administered early in the course of illness, the duration and severity are shortened. In mechanical ventilation, controversy persists. One study that reported considerable benefit was subsequently criticized for having used water as a control.\(^{41}\) A later study, which used a saline control, reported a lack of efficacy, but was in turn criticized as underpowered.\(^{42}\) The current American Academy of Pediatrics recommendation is that this agent be considered in the setting of respiratory failure due to RSV and that requires mechanical ventilation. In addition to RSV, aerosolized ribavirin may have activity against influenza\(^{43}\) and adenovirus infections. When delivered parentally it has been reported as being useful in treating Hanta virus infection and Lassa fever.\(^{39}\)

Ribavirin is well tolerated but can precipitate cough and bronchospasm in occasional subjects. Though at least 20 deaths have been reported as possibly due to ribavirin administration, the severity of the patients’ conditions makes a causal relationship difficult to establish.\(^{39,40}\) Though human teratogenicity is unproven, there is persuasive evidence that ribavirin is teratogenic in most species studied. Thus, the drug should not be administered to women who may become pregnant or to lactating mothers. In addition, concern has been expressed about the potential dangers to health care workers exposed to ambient drug, and it is important that efforts be made to minimize exposure.\(^{38}\)

**Zanamivir**

Zanamivir is a new antiviral agent that is specific for influenza A and B. The mechanism of action of zanamivir is inhibition of neuraminidase, an enzyme that is important for releasing newly formed influenza viral particles from the surface of the infected cell. Inhibition of this enzyme effectively disrupts viral replication. The drug is well tolerated, with a pattern of adverse effects similar to that of placebo. Zanamivir is delivered as a powder from a multi-

![Fig. 4. Response to treatment with zanamivir (inhaled), zanamivir (inhaled plus intranasal), or placebo, as assessed by the persistence of symptoms. (From Reference 45, with permission.)](image-url)
dose inhaler called the Diskhaler. The drug has low oral bioavailability and is renally excreted.

Influenza affects about a hundred million Americans in a given year and is associated with about 40,000 deaths per year. There are generally three courses for influenza infection:

1. An uncomplicated illness of approximately one week’s duration. This usually occurs in previously healthy patients, and it is in this group that zanamivir has been extensively tested. Studies demonstrate that the use of zanamivir can significantly shorten the duration of influenza symptoms (Fig. 4). Studies of its possible prophylactic role in subjects at risk of contracting the illness (e.g., household contacts of patients with influenza) are in progress.

2. Influenza infection may progress rapidly to viral pneumonia. There are no data on the role of Zanamivir in this group.

3. After an initial improvement the patient deteriorates, with evidence of a secondary bacterial pneumonia or purulent tracheobronchitis. Many of these patients have preexisting chronic respiratory disease. The drug has not been widely tested in asthma or bronchitis patients. Because of some reports of cough and bronchospasm, the drug should be used with caution in such patients. It should be emphasized that if patients with clinical evidence of bacterial superinfection are given zanamivir, that they should also receive broad spectrum antibiotic therapy. Though there is some preliminary data that zanamivir therapy may reduce the likelihood of needing antibiotic therapy in patients that are immunocompromised because of a pre-existing respiratory disease (see Table 2 and Fig. 5), these data are limited, and additional studies are needed in compromised patients.

**Summary**

Recent controlled clinical trials have confirmed the usefulness of aerosolized tobramycin in cystic fibrosis and have emphasized the importance of ensuring adequate lung delivery of inhaled antimicrobials. For purulent tracheobronchitis associated with prolonged mechanical ventilation it has recently been established that it is possible to deliver substantial and measurable doses of medications to the airway via aerosolization, but controlled studies are needed to determine the efficacy and safety of inhaled antibiotic therapy in this setting. However, prophylactic aerosolized antibiotic therapy in an intensive care unit setting may be counterproductive. Aerosolized pentamidine continues to provide prophylaxis against PCP in a substantial minority of subjects with human immunodeficiency virus infection who are intolerant of oral agents. The effectiveness of aerosolized amphotericin B as prophylaxis against aspergillosis in neutropenic patients needs to be evaluated in a large clinical trial. Zanamivir, an inhibitor of neuraminidase, delivered via inhalation, shows promise in the treatment of uncomplicated influenza infection, but more data are needed on its effectiveness and safety in patients with preexisting respiratory disease. The development of new chemical entities, more efficient delivery systems, and more precise measurement of dose-response and regional pulmonary drug distribution of inhaled antimicrobials suggest that this somewhat neglected topic in therapeutics may be about to receive an increased degree of attention.

**REFERENCES**