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# Aerosolized Antibiotics for Treating Hospital-acquired and Ventilator-associated Pneumonia

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## Abstract and Introduction


### Abstract

Hospital-acquired pneumonia is a common complication that continues to have a poor cure rate in some patients with intravenous therapy alone. Aerosolized antibiotics are theoretically attractive in an attempt to optimize lung concentrations of antibiotics. Limited data suggest that aerosolized aminoglycosides or colistin in addition to intravenous therapy results in good response rates in patients with multidrug-resistant organisms or nonresponding pneumonia. Adverse events can occur, especially with colistin. When used, care should be taken to properly compound and administer aerosolized antibiotics to ensure tolerability and good drug delivery.


### Introduction

Hospital-acquired pneumonia (HAP) continues to be a common and often devastating complication of modern healthcare. Approximately 90% of HAP patients are mechanically ventilated and may also be referred to as having ventilator-associated pneumonia (VAP).[1] Approximately 9–27% of mechanically ventilated patients in the intensive care unit (ICU) develop HAP/VAP. This results in an increased attributable mortality of up to 50%, an increased length of stay by 7–9 days, and increased healthcare costs of up to US$40,000 per patient.[1] Despite the availability of modern ICU care and modern antibiotics, the overall clinical cure rate for HAP in randomized clinical trials is only 63%. The cure rate for *Pseudomonas aeruginosa* is even lower.[1,2] It is unclear why HAP/VAP cure rates are so low. A number of patient and pathogen-related factors could be involved including patients' underlying disease states, interpatient differences in the immuno-inflammatory response to illness and bacterial colonization, and pathogenic differences among bacteria including the potential to develop resistance during therapy. Compounding the problem is the lack of novel Gram-negative antibiotics in a time of increasing resistance from organisms such as *P. aeruginosa*, *Acinetobacter baumannii* and various Enterobacteriacae.

However, problems with antibiotic delivery may also be important. Many antibiotics used to treat HAP, including β-lactams, aminoglycosides and vancomycin, have poor penetration into the epithelial lining fluid (ELF) of the lungs.[3] The ELF concentrations for these antibiotics are usually less than 50% of the concentrations achieved in the serum.[3] Unfortunately, pharmacokinetic studies to determine optimal dosing of antibiotics are normally done in normal volunteers and not critically ill patients who can have markedly different pharmacokinetics.[4] Even fewer formal pharmacokinetic studies are done to assess lung ELF penetration of antibiotics in actual patients. As such, relatively little is known about the optimal dosing of most antibiotics for HAP. Many antibiotics have doses specific to treating HAP or life-threatening infections; however, correct doses may not be used.[1] It is clear that antibiotic therapy needs to be optimized in HAP.

One method of improving antibiotic delivery to the lung ELF, and potentially improving outcomes, is aerosolized delivery into the lungs. Since the 1960s there have been a number of reports using aminoglycosides, colistin and β-lactams for treating HAP. However, there has been a sharp increase in these reports over the last decade largely in an effort to treat emerging multidrug-resistant (MDR) strains of Gram-negative bacilli such as *P. aeruginosa* and *A. baumannii*. This article will summarize the available literature on the use of aerosolized antibiotics for treating HAP in adult patients.

## Aminoglycosides

Until the 2000s, aminoglycosides were the most widely studied aerosolized agents for treating HAP (Table 1). Pines *et al.* initially reported two observational case series with aerosolized gentamicin.[5,6] The first series included patients that had not responded to intravenous therapy for chronic bronchial infections.[5] The clinical improvement rate after

4–8 weeks of therapy was rather dismal (18%) regardless of whether systemic therapy was continued or not. However, in the second series 12 patients undergoing initial treatment for HAP had aerosolized therapy added to carbenicillin.[6] A more typical response rate of 67% was reported after 7–10 days of therapy.

**Table 1. Use of aerosolized aminoglycosides for treating hospital-acquired pneumonia.**

| Study (year) | Patients (n, % ventilated) | Dose | Systemic therapy | Duration | Outcome (%) | Adverse events | Ref. |
|---|---|---|---|---|---|---|---|
| Pines *et al.* (1967) | 11 (NR) | Gentamicin 80–120 mg b.i.d.–t.i.d. | Gentamicin (n = 6) | 4–8 weeks | 18 improved | Dizziness (n = 3) | [5] |
| Pines *et al.* (1970) | 12 (NR) | Gentamicin 40 mg q.i.d. | Carbenicillin | 7–10 days | 67 improved | None | [6] |
| Klastersky *et al.* (1972) | 15 (NR) | Gentamicin 40 mg every 3 h | None | NR | 100 vs 25 cured† | NR | [7] |
| Klastersky *et al.* (1979) | 38 (45) | Sisomicin 25 mg every 8 h | Carbenicillin/sisomicin | 7 days | 77 vs 45 cured‡ | None | [8] |
| Sorenson *et al.* (1986) | 5 (100) | Tobramycin 40 mg or amikacin 200 mg every 4 h | Varied | 7 days | 100 cured | NR | [9] |
| Stillwell *et al.* (1988) | 1 (100) | Tobramycin 2 mg/kg every 8 h | Ticarcillin/tobramycin | 14 days | 100 cured | Transient coughing | [10] |
| McCall *et al.* (1989) | 1 (100) | Tobramycin 100 mg every 8 h | None | 16 days | 100 cured | NR | [11] |
| Hallal *et al.* (2007) | 10 (100) | Tobramycin 300 mg every 12 h | Varied | 10–14 days | 100 vs 60 cured§ | None | [12] |
| Mohr *et al.* (2008) | 22 (100) | Tobramycin 300 mg every 12 h or amikacin 400 mg every 8 h | Varied | 7 days (mean) | 59 cured | None | [13] |
| Czosnowski *et al.* (2009) | 53 (100) | Tobramycin 300 mg every 12 h or amikacin 1000 mg every 12 h | Varied | 9–10 days (mean) | 73 cured | None | [14] |

†Endotracheally instilled (ET) therapy alone vs intravenous therapy alone.
‡ET sisomicin vs ET placebo.
§Aerosolized tobramycin vs no aerosolized therapy.
b.i.d.: Two times per day; NR: Not reported; q.i.d.: Four times per day; t.i.d.: Three times per day.

Subsequently, Klastersky *et al.* increased the rigor of study design with two randomized trials.[7,8] It is important to note that antibiotics were endotracheally instilled (ET) as a solution in these two studies rather than aerosolized. In the first, 15 patients were randomized to receive either ET or systemic gentamicin.[7] The cure rate was significantly better in the patients in the ET group (100 vs 25%). In the second study, 38 patients were randomized to receive either ET sisomicin or placebo added to systemic β-lactam/aminoglycoside therapy.[8] Again, the cure rate was significantly better in the ET group (77 vs 45%). Incredibly, this study from 1979 remains the largest randomized, placebo-controlled trial of aerosolized antibiotics for treating HAP.[8] In the 1980s, three case reports totaling eight patients showed a cure rate of 100% with ET or aerosolized therapy for 7–16 days.[9–11] Seven of the eight cases also received intravenous

antibiotics. Importantly, five of the patients had previously not responded well to intravenous antibiotics alone.

After years without new data, since 2007 there have been four new publications. All four reports used increased rigor in that they all used aerosolization, included only patients with VAP, and required bacteriologic confirmation of infection. A small trial randomized ten patients to receive either aersosolized or intravenous tobramycin for *P. aeruginosa* or *A. baumannii*.[12] The two treatment failures were in the intravenous group. A retrospective observational study of 22 patients receiving either aerosolized tobramycin or amikacin for a mean of 7 days added to intravenous therapy reported a 41% recurrence rate (i.e., 59% cure rate).[13] This cure rate is not impressive; however, many of the treatment failures were in patients with difficult-to-treat situations such as previous episodes of VAP or MDR organisms. In the largest observational study to date, Czosnowski *et al.* reported the outcomes of 53 trauma ICU patients treated with aerosolized tobramycin or amikacin added to intravenous therapy for approximately 10 days.[14] The clinical cure rate was a reasonable 73% despite a high rate of patients with previous treatment failure with intravenous therapy alone or the presence of MDR organisms. This study is also the only one with microbiologic confirmation of outcomes in a large percentage of patients. Lastly, there was an observational study in 16 cancer patients treated with aerosolized aminoglycosides and/or aerosolized colistin. The overall clinical response rate was 100% compared with 55% in a matched group of patients who did not receive aerosolized therapy. However, the outcomes for colistin and aminoglycosides were not reported separately.[15]

## Colistin

Similar to aminoglycosides, reports with aerosolized colistin date from the 1960s (Table 2). Pines *et al.* again reported poor outcomes (clinical improvement 24%) when adding aerosolized colistin to intravenous colistin in 17 patients treated for 7–10 days.[5] However, the use of systemic and aerosolized colistin has reemerged over the past decade owing to the emergence of MDR *P. aeruginosa* and *A. baumannii*, which are resistant to all other antibiotic choices such as carbapenems, aminoglycosides and floroquinolones. Hamer reported a 100% cure rate in three patients with MDR *P. aeruginosa* HAP treated for 11–14 days with aerosolized colistin added to intravenous therapy.[16] Similarly, 16 patients with MDR *A. baumannii* VAP in another report also had a 100% cure rate after 15 days of therapy.[17] Interestingly, rifampicin was the systemic therapy used rather than intravenous colistin.

**Table 2. Use of aerosolized colistin or β-lactams for treating hospital-acquired pneumonia.**

| Study (year) | Patients (n, % ventilated) | Dose† | Systemic therapy | Duration (days) | Outcome (%) | Adverse events | Ref. |
|---|---|---|---|---|---|---|---|
| *Colistin* | | | | | | | |
| Pines *et al.* (1967) | 17 (NR) | 33–132 mg/day divided t.i.d.–q.i.d. | Colistin | 7–10 | 24 improved | Badly tolerated (n = 3) | [5] |
| Hamer (2000) | 3 (67) | 100–150 mg b.i.d. | Varied | 11–14 | 100 cured | None | [16] |
| Motaouakkil *et al.* (2006) | 16 (100) | 33 mg t.i.d. | Rifampicin | 15 | 100 cured | None | [17] |
| Sobieszczyk *et al.* (2004) | 8 (NR) | 2.5 mg/kg/day divided every 6 h | Varied | Mean: 19 | 76 cured/improved | Possible nephrotoxicity (n = 2) | [18] |
| Michalopoulos *et al.* (2005) | 8 (100) | 33–198 mg/day | Varied (7/8) | Mean: 10 | 88 cured/improved | None | [19] |
| Kwa *et al.* (2005) | 21 (14) | 33 mg b.i.d. | Varied | Mean: 14 | 86 cured/improved | NR | [20] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pereira *et al.* (2007) | 14 (79) | 16.5 mg b.i.d.‡ | Polymyxin B | Mean: 14 | 93 cured/improved | Cough/bronchospasm (n = 4) | [23] |
| Czosnowski *et al.* (2009) | 9 (100) | 150 mg b.i.d. | Varied | Mean: 7 | 73 cured | None | [14] |
| Michalopoulos *et al.* (2008) | 60 (100) | 33 mg t.i.d. divided t.i.d.–q.i.d. | Colistin | Mean: 16 | 83 cured | None | [21] |
| Lin *et al.* (2010) | 45 (100) | 66 mg/day | Varied | Mean: 10 | 58 cured | None | [22] |
| Kofteridis *et al.* (2010) | 86 (100) | 33 mg b.i.d. | Colistin | Mean: 10–13 | 74 vs 60 cured§ | None | [24] |
| *β-lactams* | | | | | | | |
| Pines *et al.* (1970) | 15 (NR) | Carbenicillin 1 g q.i.d. | Carbenicillin | 7–14 | 92 cured | None | [6] |
| Stoutenbeek *et al.* (1986) | 25 (100) | Cefotaxime or ceftazidime 50–100 mg/kg q.i.d. | Cefotaxime or ceftazidime plus tobramycin | NR | 96 cured | NR | [28] |

†Doses have been converted to active colistin. Some studies used colistimethate sodium which is 1 million units = 80 mg colistimethate sodium = approximately 33 mg active colistin.
‡Polymyxin B used instead of colistin (polymyxin E).
§Aerosolized colistin vs no aerosolized therapy.
b.i.d.: Two times per day; NR: Not reported; q.i.d.: Four times per day; t.i.d.: Three times per day.

Four other relatively small observational reports since 2004 involved a total of 46 patients with either MDR *P. aeruginosa* or *A. baumannii* HAP.[14,18–20] Various systemic antibiotic regimens were used in all but one patient and the mean treatment duration was 10–19 days. The clinical cure rates in these reports were rather consistent (73–88%) and seem reasonable for treating MDR organisms.

Fortunately, the most recent group of four studies had better study designs and/or increased numbers of patients. All of the patients in these studies were mechanically ventilated and higher quality culture techniques were used. Michalopoulos *et al.* reported a prospective observational study of 60 patients with *P. aeruginosa*, *A. baumannii* or *Klebsiella pneumoniae* VAP treated for a mean of 16 days.[21] The vast majority also received intravenous therapy (57 out of 60) and half of the isolates were MDR. The clinical cure rate was 83% and the mortality rate attributable to VAP was 17%. Similarly, Lin *et al.* reported a retrospective observational study of 45 patients with MDR *A. baumannii* VAP treated for a mean of 10 days.[22] All patients also received intravenous therapy; however, the clinical cure rate was lower than most other reports (58%). The overall mortality rate was high at 42%, but the VAP-related mortality was not reported. Pereira *et al.* also reported an observational case series of 14 patients; mostly with *P. aeruginosa*. The combined cure or improvement rate was 93%.[23]

The largest and most well-designed study was a retrospective matched case–control study of 43 VAP patients who received aerosolized and intravenous colistin compared with 43 patients treated with intravenous colistin monotherapy.[24] Patients were matched based on age and APACHE II score and the mean treatment duration was 10–13 days. Approximately 75% of patients had *A. baumanii* and the remaining patients had *K. pneumoniae* or *P. aeruginosa*. Unfortunately, there were no significant differences between the aerosolized group and the control group in the combined clinical cure or improvement rate (74 vs 60%) or VAP-related mortality (16 vs 26%). However, there was a statistical trend towards decreased mortality in the aerosolized group (23 vs 42%; p = 0.066). Three important limitations of the study are the retrospective design, the possibility of a type II error because of the small study size, and a lack of reporting of antibiotic therapy prior to initiating colistin that could have affected patient outcomes.

Nonetheless, this is an important study because of the case-matched design.

Three other reports deserve mention. A case series of five patients with chronic *P. aeruginosa* pulmonary colonization were treated with 4–8 days of aerosolized colistin alone.[25] All patients had eradication of the organism. A larger observational study reported on a mixed group of 71 patients with either HAP or pulmonary colonization with *P. aeruginosa* or *A. baumannii*.[26] Most patients received intravenous therapy, and the mean duration was 11 days. The eradication rate was 92%. These two reports are less important because it wasn't clear which patients actually had HAP versus colonization. Last, a case report showed successful treatment of *Stenotrophomonas maltophilia* VAP with aerosolized colistin added to intravenous doxycycline in one patient who failed trimethoprim/sulfamethoxazole therapy.[27]

## β-lactams

Pines *et al.* again provided an early report, this time with aerosolized carbenicillin added to intravenous in 15 patients with *P. aeruginosa* HAP (Box 1).[6] Only 47% of patients responded well to 7–14 days of therapy. Other researchers in the 1980s added aerosolized cefotaxime or ceftazidime to the same antibiotic given intravenous for HAP caused by various Gram-negative organisms.[28] The cure rate was 96% in 25 patients.

**Box 1. Recommendations for improving patient tolerance and aerosol delivery in mechanically ventilated patients.**

| **Improving delivery** |
|---|
| • Use a ventilator with a flow rate of at least 6 l/min<br>• Use a ventilator that nebulizes only during inspiration<br>• Use a jet nebulizer with a MMAD 1–5 μm<br>• Compound doses to fill the nebulizer chamber prior to administration<br>• Place nebulizer in inspiratory loop 30 cm from endotracheal tube<br>• Discontinue humidification during nebulization |
| **Improving tolerance** |
| • Consider pretreating patients with albuterol if they had a previous adverse reaction to a dose or if they have chronic lung disease<br>• Ensure pH of drug is 4.0–8.0<br>• Ensure osmolarity of drug is 150–1200 mOsm/l<br>• Use normal saline for drug dilution<br>• Consider use of tobramycin for inhalation if adverse reactions occur to intravenous tobramycin product<br>• Use colistin immediately after preparation |

MMAD: Median mass aerodynamic diameter.
Data taken from [29,32,101].

## Administration Considerations in Mechanically Ventilated Patients

Because 90% of HAP patients have VAP, this article will focus on administration issues only in mechanically ventilated patients. Also, there are a number of unique issues in delivery of aerosolized medications in mechanically ventilated patients. Outpatient administration of aerosolized tobramycin results in delivery of approximately 10–20% of the dose to the lung.[29] However, initial data examining the lung delivery of aerosolized medications in mechanically ventilated patients showed that less than 3% of a dose reached the lung.[30] Not only was drug delivery poor, but it was highly variable with over a tenfold difference in delivery depending on the administration techniques used.[31] It is unclear why delivery is so poor during mechanical ventilation, but some potential problems include deposition of drug in the tubing, the distance from the site of aerosolization to the lung, the inability of patients to control their breathing and the nonphysiologic nature of mechanical ventilation. Other patient-related factors that may impair drug delivery include

atelectasis, mucus production, or possibly preexisting lung diseases such as asthma or chronic obstructive pulmonary disease.

Thus, a series of laboratory and clinical studies were performed to determine how to improve aerosol drug delivery during mechanical ventilation.[29,32] It has subsequently been shown that using optimal technique can increase lung delivery by as much as 650%.[31] Factors related to optimal aerosol delivery in mechanically ventilated patients are listed in Box 1. Ideally, hospitals would only use ventilators for which good aerosolized delivery has been confirmed in studies. One study showed a high degree of variability between four ventilators in aerosol delivery.[32] However, very few comparative data are available. A reasonable alternative is to ensure that ventilators used for antibiotic delivery should have a flow rate greater than 6 l/min and that they only nebulize during inspiration rather than continuously.[32]

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| --- |
| • Use a ventilator with a flow rate of at least 6 l/min<br>• Use a ventilator that nebulizes only during inspiration<br>• Use a jet nebulizer with a MMAD 1–5 µm<br>• Compound doses to fill the nebulizer chamber prior to administration<br>• Place nebulizer in inspiratory loop 30 cm from endotracheal tube<br>• Discontinue humidification during nebulization |
| **Improving tolerance** |
| • Consider pretreating patients with albuterol if they had a previous adverse reaction to a dose or if they have chronic lung disease<br>• Ensure pH of drug is 4.0–8.0<br>• Ensure osmolarity of drug is 150–1200 mOsm/l<br>• Use normal saline for drug dilution<br>• Consider use of tobramycin for inhalation if adverse reactions occur to intravenous tobramycin product<br>• Use colistin immediately after preparation |

MMAD: Median mass aerodynamic diameter.
Data taken from [29,32,101].

The choice of nebulizer can also be important. One of the primary determinants of lung deposition is the median mass aerodynamic diameter (MMAD) of the particles generated. Lung deposition is optimized at a MMAD of 1–5 µm. Larger particles tend to deposit in the upper airways and smaller particles tend to be exhaled.[29,32] Jet nebulizers are the most widely used in ICUs. They are inexpensive, disposable and generally produce acceptable particle size. The aforementioned studies almost universally used jet nebulizers. Ultrasonic nebulizers can perform better than jet nebulizers in producing better particle size and shorter administration times. However, they require a specialized power supply at the bedside, must be cleaned, and are more expensive.[32] Also, some large drug molecules may be broken down during ultrasonic nebulization.[32] As such, jet nebulizers are preferred for aerosolized antibiotic use in HAP. There is no preferred model of jet nebulizer for HAP. Clinicians should ensure that the nebulizer model being used creates a MMAD of 1–5 µm based on the manufacturer's information.

Clinicians should also know the maximum fill volume for the nebulizer being used. Starting administration with a full nebulizer results in improved drug delivery.[32] Aerosolized doses should be compounded to a total volume equivalent to the fill volume.[29,32] The placement of the nebulizer in the ventilator circuit also affects delivery. The optimal site for placement is 30 cm from the endotracheal tube in the inspiratory loop.[29,32] There are also data showing that drug delivery is improved when the ventilator humidification is turned off during nebulization.[29,32] Obviously, it is important that humidification be resumed after the dose is administered. Implementing this into practice will require more training and vigilance than the other methods described here.

## Safety & Tolerability

A number of pulmonary adverse events such as coughing and bronchospasm can occur with outpatient use of aerosolized antibiotics. The only adverse events reported in the aminoglycoside HAP studies were coughing and dizziness in four patients.[5,10] No other adverse events were reported. The vast majority of aminoglycoside HAP reports used the intravenous formulation. A preservative-free formulation of tobramycin for inhalation used in cystic fibrosis may theoretically provide a better safety profile, but this has not been studied widely in HAP patients. There are fewer data on the safety of aerosolized β-lactams; however, no adverse events were reported in the HAP treatment studies or when ceftazidime was used in trials of VAP prevention.[6,28,33,34]

Compared to aminoglycosides, aerosolized colistin may have a worse adverse event profile. It was 'badly tolerated' in an earlier report but a number of more recent studies reported that there were no adverse events.[14,17,19,24] Hypotension was reported in one patient treated and cough or bronchospasm was reported in four others.[23,33,35] This did not occur with intravenous colistin in this patient. Another case report showed hypersensitivity pneumonitis and fibrosis from aerosolized colistin used to treat HAP.[36] Most worrying is the report of death in a patient treated as an outpatient with aerosolized colistin.[101] It is thought that this patient suffered from a reaction to a toxic breakdown product of colistin that occurred because the doses were prepared more than 24 h prior to administration. Subsequently, the US FDA issued a public health advisory that colistin be administered promptly after preparation.

Clinicians should be aware of several factors that can improve tolerability of aerosolized antibiotics.[29,32] Doses should be diluted in normal saline when dilution is needed to QS to the maximum fill volume of the nebulizer being used. A sodium concentration of 77–154 mEq/l is associated with better tolerability. The pH of the dose should also be roughly physiologic (4.0–8.0). There is a wide range of tolerable osmolarity (150–1200 mOsm/l), but hypotonic solutions should be avoided. For patients with chronic lung disease or who have had previous adverse events from an aerosolized dose, pretreatment with albuterol should be considered (Box 1). Another option may be to switch to the preservative-free tobramycin if the organism is sensitive to it.

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One of the potential benefits of aerosolized administration is the potential for lower systemic concentrations and thus fewer adverse events such as nephrotoxicity. It appears that aerosolized aminoglycosides do not generate detectable

serum concentrations in patients with normal renal function.[29,32] A recent study of nine critically ill HAP patients showed that the only patient with a detectable tobramycin serum concentration (0.80 µg/ml) during aerosolized therapy also had moderate renal dysfunction.[37] Similarly, a lack of detectable serum concentrations was seen with aerosolized ceftazidime.[33] However, accumulation has been rarely reported, especially in patients with renal dysfunction.[10,37] Thus, assessing systemic accumulation in patients with renal dysfunction may be prudent.

## Expert Commentary

Despite the fact that adjunctive aerosolized antibiotics are commonly used in HAP, there is a disappointing amount of data in the medical literature. Almost all of the studies were observational and did not have control groups. Nonetheless, the relatively poor response rates seen with intravenous therapy of HAP and the emergence of MDR organisms makes new treatment options desirable. The ATS/IDSA HAP guidelines recommend that "adjunctive therapy with an inhaled aminoglycoside or polymyxin (colistin) for MDR Gram-negative pneumonia should be considered, especially in patients who are not improving.[1] " The recommendations by the Society of Infectious Diseases Pharmacists are similar.[38]

However, is it still unclear from the literature if aerosolized antibiotics provide an additional benefit in HAP. If one discounts the universally poor results seen by the early studies by Pines *et al.*, aminoglycoside cure rates were 67–100% in a total of over 165 patients[6–14] and colistin cure rates were 58–100% in a total of over 200 patients.[14,16–24] Given than many of these patients had MDR organisms or had failed intravenous therapy alone, these cure rates seem to compare favorably to the baseline cure rate of 63% for VAP seen in clinical trials. The only randomized study did show a benefit; but that study is from the 1970s.[8] Unfortunately, the most recent and best designed study with colistin failed to show a benefit.[24]

There are also questions regarding the quality of the data. There could have been publication bias over time such that clinicians only reported positive experiences. Obviously, there is a lack of controlled studies and the numbers are low. Perhaps more concerning are the vast differences in ICU care over the decades between the early reports and today in any number of areas. Many of the early reports included nonmechanically ventilated patients or did not report whether patients were mechanically ventilated. It is also difficult to determine the severity of illness of those patients. The culture techniques were also not well described in earlier studies. Thus, it is not clear if those patients truly had HAP. Some patients were treated with aminoglycoside monotherapy for HAP which is not acceptable in the modern context based on poor cure rates.[1] Fortunately, reports from the 2000s have generally become larger and more rigorous in important aspects of HAP care. For instance, the recent reports focused only on VAP patients, used far better microbiologic techniques for diagnosis and were likely to have used better administration techniques. Although most studies did a very poor job of describing drug administration in detail.

Ultimately, the risk versus benefit analysis seems to be somewhat in favor of using aerosolized antibiotics in selected patients. Such patients might include those:

- Not responding to intravenous therapy alone;
- Who are being treated for a recurrence of the same organism;
- Who have MDR organisms.

This recommendation is based on what seems to be good cure rates in difficult-to-treat cases. This is balanced by a rather benign adverse event profile based on limited data – at least for aminoglycosides. Aminoglycosides should be the drug of choice when they can be used based on *in vitro* sensitivity. Colistin should only be used for aminoglycoside-resistant isolates based on what seems to be a higher risk of adverse events. Clinicians should also take care that doses are optimally compounded and administered to ensure the best drug delivery possible.

Regarding dosing, a wide range of doses were used clinically in the reports described. The Society of Infectious Diseases Pharmacists statement also provides dosing recommendations.[38] A reasonable approach when using gentamicin or tobramycin is to use 300 mg every 12 h. This is the FDA-approved dose in cystic fibrosis. There are very few data to guide amikacin dosing, but the drug is typically dosed approximately three times higher than gentamicin and tobramycin when administered systemically, so a dose of 500–1000 mg every 12 h seems reasonable. A colistin dose of 150 mg every 12 h is reasonable based on recent reports. Although the prescribing information recommends 25–50 mg two to three times per day. Note that these doses are based on the Coly-Mycin M product (Monarch Pharmaceuticals, TN, USA) in the USA, which is dosed in mg of active colistin. The Colomycin product (Forest

Laboratories UK, Dartford, UK) has 30–33 mg of active colistin per 80 of colistimethate sodium (equivalent to 1 million units).

## Five-year View

### Current Research

In 5 years from now, the first large randomized, placebo-controlled clinical trial of aerosolized antibiotics in HAP might have been completed.[102] This will be a clear landmark in this area for two reasons. First, this will be by far the largest and most rigorous study to date. Second, the study will use a new generation of nebulizer technology: vibrating mesh plate nebulizers. These nebulizers seem to provide much better drug delivery than jet nebulizers.[38] A pharmacokinetic trial of a new aerosolized amikacin product in VAP patients showed excellent drug delivery to the lung.[39] If this study is successful at showing that adding the aerosolized plus intravenous therapy is superior to intravenous therapy alone, then it could potentially create a dramatic shift in the treatment of HAP. One could also envision a middle ground where aerosolized therapy only adds a benefit in certain situations based on patient- or organism-related factors. Although such an outcome would likely not result in FDA approval. If the study shows no benefit for aerosolized therapy, then it will cast a very negative light on this therapy.

### Future Research

With a lack of any other currently registered clinical trials under development, it appears that clinician-investigators will have to continue to report on their experiences with aerosolized antibiotics. Hopefully, some will use the higher-level techniques, as seen in the recent case-matched study, to better determine if there is a beneficial effect. Ideally, more prospective, randomized, double-blinded trials will be performed. However, the funding challenges for such a trial are clear. Funding would have to come from the federal government or from a manufacturer developing an aerosolized drug formulation. A welcome advance would be more data on the use of β-lactams, which appear to be well tolerated. Data on aerosolized quinolones may also be available in 5 years, although more likely in other indications than HAP. Even more on the cutting edge are potential advances in drug formulations using lipid-based products, or new-generation dry powder delivery that could improve lung deposition.

## Sidebar

### Key Issues

- Hospital-acquired pneumonia is a common complication that results in poor patient outcomes and only responds well to intravenous antibiotics in approximately two-thirds of cases.
- Aerosolized antibiotics may be an adjunctive way to improve lung concentrations of antibiotics.
- Mostly uncontrolled, observational data with aminoglycosides and colistin (and to a lesser extent β-lactams) suggest that adding aerosolized therapy to intravenous therapy results in reasonable cure rates in patients with difficult clinical situations such as multidrug-resistant organisms.
- Adverse events can occur and seem to be more common with colistin than aminoglycosides.
- Attention must be paid to optimizing administration technique in mechanically ventilated patients and optimal compounding to improve tolerability.

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