REVIEW ARTICLE

Drugs 2007; 67 (6): 903-914
0012-6667/07/0006-0903/$49.95/0

Aerosolised Antibacterials for the Prevention and Treatment of Hospital-Acquired Pneumonia

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Abstract

Aerosolised administration of antibacterials remains theoretically attractive for the prevention and treatment of hospital-acquired pneumonia (HAP) because of the ability to generate high drug concentrations at the site of infection. There is renewed interest in this area because of the shortcomings of current therapies and increasing multidrug resistance in Gram-negative organisms. Clinical trials of aerosolised or endotracheally administered antibacterials for HAP prevention have generally been positive; however, early trials were hampered by the development of resistance related to indiscriminate use. More recent trials have shown efficacy at HAP prevention without adverse effects on microflora as a result of more limited usage. However, prophylactic aerosolised antibacterials still need to be studied in large randomised trials before they could enter widespread use.

The treatment of HAP with aerosolised antibacterials has mostly been reported in case series without control groups. Both early reports with aminoglycosides and the more recent use of colistin have reported very good response rates; even with organisms such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Aerosolised antibacterials were almost always added to intravenous therapy. On the basis of these reports, the current HAP guidelines allow the addition of aerosolised antibacterials in selected patients with multidrug-resistant organisms. This seems to be a reasonable recommendation until large trials are performed.

Overall, toxicity was relatively low in the publications reviewed. Aerosolised drug administration in mechanically ventilated patients requires attention to a number of factors in order to maximise drug deposition in the lung.

Hospital-acquired pneumonia (HAP) is the most common serious hospital-acquired infection.[1] Ninety percent of HAP occurs in mechanically ventilated patients. So-called ventilator-associated pneumonia (VAP) results in significant increases in morbidity, mortality and healthcare costs.[1] Unfortunately, current prevention and treatment of VAP are far from optimal despite modern antibacterials and decades of research. Therapy is likely to become more difficult in the future as a result of increasing bacterial resistance. Thus, the use of aerosolised antibacterials continues to be theoretically attractive for VAP prevention and treatment primarily because of the high drug concentrations achieved at site of action. This is important because poor pulmonary penetration of commonly used drugs such as β-lactams, aminoglycosides and vancomycin may contribute to treatment failure.[1] A secondary benefit of aerosolisation is the potential for decreased adverse drug events and bacterial resistance by limiting drug exposure. This is especially important because the most commonly used aerosolised antibacterials in the intensive care unit (ICU), aminoglycosides and colistin, are nephrotoxic.

Over the past 10–15 years, this area of research has undergone somewhat of a renaissance. This is due to the continuing emergence of multidrug-resistant Gram-negative organisms as VAP pathogens, the need to improve VAP prevention and treatment, new data on optimising aerosol drug delivery during mechanical ventilation, and the success of aerosolised antibacterials in other diseases such as cystic fibrosis.[2] The primary focus of this article is on the use of aerosolised antibacterials for the prevention and treatment of HAP/VAP in immunocompetent critically ill patients. A secondary focus is reviewing key factors for optimising aerosolised drug administration in mechanically ventilated patients. This is important because optimal delivery of aerosolised drugs to the lungs of mechanically ventilated patients is difficult to achieve, and aerosolised antibacterials for HAP are used almost exclusively in mechanically ventilated patients. Publications were identified using PubMed and the reference lists of identified papers. Search terms included various combinations of 'aerosolised', 'nebulised', 'antibiotics', 'pneumonia' and individual names of antibacterials.

1. Prevention of Hospital-Acquired/ Ventilator-Associated Pneumonia (HAP/ VAP)

The development of a widely accepted pharmacological regimen to prevent VAP continues to be a difficult process. Current VAP prevention is achieved by indirect methods, such as raising the head of the bed, minimising sedation and paralytic drug use, intensive insulin therapy and good infection-control practices.[1] Despite these efforts, 9–27% of all mechanically ventilated patients develop VAP; with an incidence >50% in the most severely ill.[1,3,4] An effective regimen to prevent VAP could have enormous impacts on patient care.

By far the most studied type of pharmacological therapy has been selective decontamination of the digestive tract (SDD) using non-absorbed antibacterials with or without short-term intravenous antibacterials. SDD decreases VAP by ≈50%, but has not been universally adopted primarily because of fears of resistance with long-term prophylaxis and questions over the optimal patient selection.[1,5] SDD can also be labour intensive. Thus, the current American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) HAP guidelines do not recommend SDD for general use.[1]

1.1 Early Trials: 1970s–80s

The next most studied method of pharmacological HAP prophylaxis has been aerosolisation or instillation of antibacterials into the endotracheal tube (table I). The first set of clinical trials was published in the 1970s. Klastersky et al.[6,7] conducted two small studies of endotracheally instilled (ET) aminoglycosides in neurosurgical ICU patients. The first study showed a 71% reduction in HAP for

Table I. Prevention of hospital-acquired pneumonia (HAP) with aerosolised (Aero) or endotracheally instilled (ET) antibacterials

Study	No. of patients (%MV)	Study design	Treatments compared	Route	Duration	Incidence of HAP (%)	Mortality (%)	Mean ICU LOS (days)	Adverse events	Resistance
Early studies: aminoglycosides										
Klastersky et al.[6]	85 (24)	r, db	Gentamicin 80mg tid vs placebo	ET	Entire ICU stay	12 vs 41[a]	54 vs 38	19.9 vs 14.7	NR	↑ Gentamicin resistance
Klastersky et al.[7]	47 (30)	r	Gentamicin 80mg tid vs aminosidin[b] 250 mg/ polymyxin 50mg tid	ET	Entire ICU stay	20 vs 27	36 vs 27	17.6 vs 16	Cough (% NR)	↑ Gentamicin resistance
Levine et al.[8]	30 (63)	r, db	Gentamicin 80mg tid vs placebo	Aero	10d	67 vs 67	50 vs 67	4.5 vs 5.4 (MV)	None	↑ Gentamicin resistance
Vogel et al.[9]	40 (100)	NR	Gentamicin 40mg q6h vs no therapy	ET	NR	'Decreased' with gentamicin	NR	NR	NR	NR
Early studies: polymyxin										
Greenfield et al.[10]	58 (100)	r	Polymyxin 2.5 mg/kg/d (divided q4h) vs no therapy	ET	Entire ICU stay	10 vs 8; (*Pseudomonas* colonisation 0 vs 12)	12 vs 24	9 vs 7.6	None	NR
Klick et al.[11]	744 (NR)	db	Polymyxin 2.5 mg/kg/d (divided q4h) vs placebo (alternating every 8wk)	ET	Entire ICU stay	4.8 vs 8.1 (*Pseudomonas* HAP 0.8 vs 4.5)[a]	12 vs 12	5.1 vs 5.3	NR	↔
Feeley et al.[12]	292 (NR)	o, rcg	Polymyxin 2.5 mg/kg/d (divided q4h) vs retrospective group	ET	Entire ICU stay	3.8 vs 8.1	12 vs 12 (HAP associated: 64 vs 48)[a]	5 vs 5.3	NR	↑ Polymyxin-resistant organisms
Later studies										
Lode et al.[13]	199 (100)	r, db	Gentamicin 40mg q6h vs placebo	ET	Until extubated	34 vs 32	27 vs 39	NR	NR	NR
Rathgeber et al.[14]	69 (100)	r	Tobramycin 80mg qid vs no therapy	Aero	14d	17.5 vs 42[a]	14 vs 20	17 vs 13 (MV)	None	No clinically significant change
Rouby et al.[15]	598 (100)	o, rcg	Polymyxin 200 000U q3h vs retrospective group	ET	14d	28 vs 40[a]	14 vs 14	18 vs 12	NR	↔
Wood et al.[3]	40 (100)	r, db	Ceftazidime 250mg q12h vs placebo	Aero	7d	30 vs 65[a]	15 vs 30	19 vs 21	None	↔

a $p < 0.05$.

b Paromomycin.

db = double-blind; **ICU** = intensive care unit; **LOS** = length of stay; **MV** = mechanically ventilated; **NR** = not reported; **o** = observational; **qid** = four times daily; **q*x*h** = every *x* hours; **r** = randomised; **rcg** = retrospective control group; **tid** = three times daily; ↑ indicates increased; ↔ indicates no change.

gentamicin compared with placebo,[6] while the second study showed no additional benefit of an aminoglycoside/polymyxin combination compared with gentamicin alone.[7] Two later studies with aerosolised gentamicin in burn and medical ICU patients showed no reduction in VAP compared with placebo.[8,9] More importantly, three of these four studies with gentamicin showed the development of bacterial resistance to gentamicin.[6-8]

Meanwhile, groups led by Greenfield, Klick and Feeley[10-12] studied prophylactic polymyxin in mixed respiratory/surgical ICU populations. None of these studies showed statistically significant reductions in overall HAP rates. However, Klick et al.[11] did report a significant reduction in HAP caused by *Pseudomonas* spp. This overall lack of efficacy was especially concerning because the Klick and Feeley trials were the largest to date with >1000 patients enrolled between them.[11,12] More ominously, the study by Feeley et al.[12] reported *increased* pneumonia-related mortality in the treatment group and the emergence of atypical organisms causing HAP. Another group reported an outbreak of atypical organisms associated with prophylactic aerosolised polymyxin.[16] These very negative findings essentially ended research in prophylactic aerosolised or ET antibacterials for more than a decade.

In hindsight, the poor results of these studies might have been predicted because of major methodological shortcomings. First, the techniques for diagnosing HAP were poor in that no invasive quantitative cultures were used. Second, most studies used instillation of antibiotic solutions into the endotracheal tubes rather than aerosolisation. This is likely to create a less uniform distribution of drug in the lung.[17] Third, these studies included all patients in the ICU and, thus, included non-mechanically ventilated patients at low risk for HAP. Fourth, patients were treated for the entire duration of their ICU stay. Overall, it is likely that the lack of efficacy was due to suboptimal drug delivery and long-term, widespread use in low-risk patients.

Similarly, the indiscriminate use in all patients for the duration of stay most probably caused the increased bacterial resistance in most studies. This is highlighted in two sequential studies from the same centre.[11,12] Initially, polymyxin and placebo were alternated in all patients every 2 months.[11] This form of antibacterial cycling resulted in shorter duration of prophylaxis compared with other studies and no increased resistance. However, when aerosolised polymyxin was given as the standard of practice to all patients, increased resistance and increased mortality followed.[12] In addition, the only gentamicin study that did not report increased resistance is the study that limited the duration of therapy to 14 days.[9] These two studies suggest that some limitations on therapy (i.e. limited duration or cycling) are needed to avoid the development of resistance.

1.2 Later Trials: 1990s–Present

Later studies in the early 1990s focused on limiting the duration of therapy and limiting enrolment to patients at high risk for HAP. Lode et al.[13] limited enrolment to mechanically ventilated patients and discontinued therapy upon extubation. However, the ET gentamicin regimen was not effective. In a similarly designed study, Rathgeber et al.[14] used aerosolised tobramycin in mechanically ventilated patients until extubation and reported a 58% decrease in VAP. The primary difference between these two studies is that Rathgeber et al.[14] used aerosolised administration. Later, Rouby et al.[15] limited ET colistin therapy to mechanically ventilated patients for a maximum of 14 days. The incidence of VAP was significantly decreased by 30% compared with a retrospective control group. This study is noteworthy because of its large size (≈600 patients); however, the results are weakened somewhat by the use of an historical control group and the use of SDD in all patients.

Subsequently, Wood et al.[3] conducted a trial of prophylactic aerosolised ceftazidime in critically ill trauma patients that continued to improve on previous study designs in several ways. This study continued the theme of limiting therapy to mechanically ventilated patients; however, the duration was further limited to 7 days. It also used a well designed administration technique based on newly published data, an optimal diagnosis for VAP based on quantitative bronchoalveolar lavage cultures, and pulmonary ceftazidime concentrations were measured to ensure adequate delivery. This study showed a 54% reduction in VAP compared with placebo and no adverse changes in microflora. The study was also

unique in that is was the only study limited solely to trauma patients (the ICU population at highest risk for VAP) and it used ceftazidime. Interestingly, prophylaxis failure seemed to be related to low ceftazidime concentrations in the lung and indicates the importance of using good aerosolisation techniques.[3]

1.3 Discussion

As a group, the studies by Rathgeber et al.,[14] Rouby et al.[15] and Wood et al.[3] were much more positive than earlier studies. They showed that limited prophylactic therapy significantly decreased the incidence of VAP without the emergence of atypical organisms or bacterial resistance. However, the small size of the studies by Rathgeber et al.[14] and Wood et al.[3] and the design of the study by Rouby et al.[15] limit their applicability to general use. Despite the existence of this moderately sized body of work (>2000 total patients), the current ATS/IDSA HAP guidelines do not discuss this issue.[1] As such, we recommend that the use of prophylactic aerosolised antibacterials be limited to clinical trials at this time because of the lack of large, well designed trials. This is primarily because of the risk of the development of resistance that could accompany uncontrolled use, and questions regarding the optimal patient mix and regimen. Key components of future studies should include limiting patient enrolment to mechanically ventilated patients at high risk of VAP, limiting the duration of therapy, selecting drugs based on known antibiograms, using optimal techniques for administration and VAP diagnosis, and careful analysis of bacterial resistance.

2. Treatment of HAP/VAP

Similar to VAP prevention, current pharmacotherapy of VAP is often suboptimal. Cure rates vary and are typically no better than 75% despite aggressive antibacterial therapy. Cure rates for resistant organisms such as *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* (MRSA) can be <50%,[18,19] and are further impaired by poor lung penetration of many antibacterials. There are a number of observational case series of aerosolised antibacterials for treating HAP; typically in patients with highly resistant organisms or who did not respond to systemic therapy alone (table II). However, compared with the prophylaxis data, there are fewer controlled trials and a much smaller number of total patients studied (~275). Colistin and aminoglycosides have been the most studied agents.

2.1 Aminoglycosides

Pines et al.[20,21] published two early case series of aerosolised gentamicin with or without systemic antibacterials in hospitalised patients with chronic bronchitis caused mostly by *Pseudomonas* spp. and *Klebsiella pneumoniae*. An acceptable cure rate was reported only when aerosolised gentamicin was added to intravenous carbenicillin. Soon afterwards, Klastersky et al.[22,23] conducted two studies in neurosurgical patients with pneumonia caused primarily by *P. aeruginosa*. These studies are noteworthy because they are the only randomised, controlled trials of aerosolised antibacterials in HAP. In the first trial, ET gentamicin monotherapy was reported to be superior to systemic gentamicin monotherapy.[22] However, the modern relevance of this study is questionable because gentamicin monotherapy is not considered to be an acceptable therapy for treating HAP. The second study reported that adding an ET aminoglycoside to systemic therapy for 7 days resulted in superior cure rates compared with intravenous therapy alone.[23] Lastly, three case series totalling seven patients reported a 100% cure rate in patients who had not previously responded to systemic therapy for Gram-negative bacilli such as *P. aeruginosa* and *Enterobacter* spp.[24-26]

Overall, six of the seven publications with aerosolised or ET aminoglycosides reported positive outcomes. Importantly, the larger randomised trial showed a benefit to adding ET gentamicin to systemic therapy.[23] Even though most reports did not have control groups *per se*, achieving positive responses in previously nonresponding patients is a desirable result.

2.2 Colistin

Colistin has undergone a recent revival as an intravenous therapy for multidrug resistant (MDR) *P. aeruginosa* and *Acinetobacter baumannii*. Similarly, all of the recent data with aerosolised therapy of HAP involves colistin. Pines et al.[21] initially

Table II. Treatment of hospital-acquired pneumonia (HAP) with aerosolised (Aero) or endotracheally instilled (ET) antibacterials

Study	No. of patients (%MV)	Study design	Aerosolised therapy	Systemic therapy added to aerosol	Control group	Route	Duration	Clinical outcomes	Mortality (%)	Adverse events	Comment
Aminoglycosides											
Pines et al.[20]	11 (NR)	o	Gentamicin 80–120mg bid–tid	None (5), gentamicin (6)	None	Aero	4–8wk	18% improved (both therapies)	NR	Dizziness (3/11)	Had not responded to systemic therapy
Pines et al.[21]	12 (NR)	o	Gentamicin 40mg qid	Carbenicillin	None	Aero	7–10d	67% improved	NR	None	Mixed GNB
Klastersky et al.[22]	15 (NR)	r	Gentamicin 40mg q3h	None	IM gentamicin	ET	NR	Cure rate: 100% vs 25%[a]	NR	NR	Mixed GNB
Klastersky et al.[23]	38 (45)	r, db	Sisomicin 25mg q8h	Carbenicillin and sisomicin	Placebo	ET	7d	Cure rate: 77% vs 45%[a]	28 vs 20	None	Mixed GNB
Sorenson et al.[24]	5 (100)	o	Tobramycin 40mg or amikacin 200mg q4h	Yes (varied regimens)	None	ET	7d	Cure rate: 100%	60 (0 due to HAP)	NR	Mixed GNB, had not responded to systemic therapy
Stillwell et al.[25]	1 (100)	o	Tobramycin 2 mg/kg q8h	Ticarcillin and tobramycin	None	ET	14d	Cured	0	'Transient coughing'	Systemic accumulation
McCall et al.[26]	1 (100)	o	Tobramycin 100mg q8h	None (failed systemic therapy)	None	Aero	16d	Cured	0	NR	SCr 4.0, no accumulation
Colistin (1mg = 10 000U)											
Pines et al.[20]	17 (NR)	o	2–4 MU/d divided tid–qid	Colistin	None	Aero	7–10d	24% improved	NR	'Badly tolerated' (3/17)	Mixed GNB
Hamer[27]	3 (67)	o	100–150mg bid	Varied regimens	None	Aero	11–14d	100% cured	0	None	MDR PA
Sobieszczyk et al.[28]	8 (NR)	o	2.5 mg/kg/d divided q6h	Varied regimens	None	Aero	2–57d (mean 19)	76% cured or improved	21 (end of treatment)	Questionable nephrotoxicity (2/8)	MDR PA and AB
Michalopoulos et al.[29]	8 (100)	o	1.5–6 MU/d divided tid–qid	Varied regimens (7/8 patients)	None	Aero	3–19d (mean 10)	88% cured or improved	12	None	MDR PA and AB
Horianopoulou et al.[30]	5 (100)	o	1 MU q8h	None	None	Aero	4–8d	100% eradication	0	None	Colonisation only, not HAP
Kwa et al.[31]	21 (14)	o	1 MU bid	Varied regimens	None	Aero	2–36d (mean 14)	86% cured or improved	14	NR	MDR PA, AB

Continued next page

Table II. Contd

Study	No. of patients (%MV)	Study design	Aerosolised therapy	Systemic therapy added to aerosol	Control group	Route	Duration	Clinical outcomes	Mortality (%)	Adverse events	Comment
Berlana et al.[32]	71 (NR)	o	500 000U–1MU q6–8h	Varied regimens (87% of patients)	None	Aero	2–21d (mean 11)	92% eradication	18	NR	Only 69% had HAP; PA, AB
Motaouakkil et al.[33]	16 (100)	o	1MU tid	Rifampicin	None	Aero	15d	100% cured	0	None	All AB
β-Lactams											
Pines et al.[21]	15 (NR)	o	Carbenicillin 1g qid	Carbenicillin	None	Aero	7–14d	47% improved	NR	None	PA
Stoutenbeek et al.[34]	25 (100)	o	Cefotaxime or ceftazidime 50–100 mg/kg qid	Cefotaxime or ceftazidime plus tobramycin	None	Aero	NR	97% cured	12	NR	Mixed GNB

a $p < 0.05$.

AB = *Acinetobacter baumannii*; **bid** = twice daily; **db** = double-blind; **GNB** = Gram-negative bacilli; **IM** = intramuscular; **MDR** = multidrug resistant; **MV** = mechanically ventilated; **NR** = not reported; **o** = observational; **PA** = *Pseudomonas aeruginosa*; **qid** = four times daily; **qxh** = every *x* hours; **r** = randomised; **SCr** = serum creatinine; **tid** = three times daily.

reported a poor response rate for aerosolised colistin in patients with chronic bronchitis caused mostly by *Pseudomonas* spp. and *Klebsiella pneumoniae*. However, in this decade there are a number of case series with very good response rates of 76–100%.[27-33] In most cases, aerosolised colistin was added to a variety of systemic therapies for 10–14 days for MDR *P. aeruginosa* or *A. baumannii*. The largest report (n = 71) reported microbiological eradication in 92% of patients with *P. aeruginosa* or *A. baumannii*; however, the results are limited somewhat because one-third of the patients were merely colonised and did not have HAP.[32]

Nonetheless, the high response rates in these reports are encouraging because *P. aeruginosa* infection is notoriously difficult to treat and is associated with a high mortality rate.[1] While the lethality of *A. baumannii* may be debatable, infection with this pathogen is also difficult to treat because of a high level of intrinsic resistance.[1] Aside from the one large series, the major limitation of these results is the small size of most reports (mean n = 11).[20,26-33]

2.3 Other Antibacterials

Two studies have reported the use of aerosolised β-lactams. Pines et al.[21] had an unimpressive response rate with a combination of aerosolised and intravenous carbenicillin; albeit they were treating mostly *P. aeruginosa*. Later, Stoutenbeek et al.[34] reported an excellent cure rate by adding aerosolised cefotaxime or ceftazidime to intravenous therapy for common Gram-negative bacilli including *P. aeruginosa*, *K. pneumoniae*, *Escherichia coli*, *Proteus mirabilis* and *Serratia marcescens*. The later study may have been more positive because broader spectrum antibacterials were being used as combination and intravenous therapy. Even though there are only two studies with β-lactams, the Stoutenbeek series is significant because it is larger than all but two of the aminoglycoside and colistin reports.

Aerosolised vancomycin is theoretically appealing because of the difficulty in treating VAP involving MRSA. However, there are no such data. The only data with aerosolised vancomycin are in non-acute settings to eradicate MRSA colonisation.[35,36]

2.4 Discussion

The major limitations of these reports are the small size and lack of control groups that severely limits the ability to determine their clinical significance. Nonetheless, the clinical response rates are generally high regardless of the agent. Typical response rates in clinical trials of HAP are ≈60–75% and most reports using aerosolised antibacterials fall in that range or better. Indeed, the two randomised trials and the large case series seem to be highly positive.[22,23,32] Colistin would appear to be the drug of choice merely because the data with this drug are much newer. However, two factors may favour aminoglycosides or β-lactams. First, colistin may have more potential for pulmonary adverse effects (see section 3.1). Second, it may be preferable to reserve colistin for organisms that are resistant to all other drugs, especially since this is how it was used in the recent reports.[27-33]

Despite the paucity of data, the current ATS/IDSA guidelines recommend that clinicians consider adding aerosolised antibacterials to intravenous therapy in patients with MDR Gram-negative organisms that are not responding to therapy.[1] This recommendation has the potential to dramatically increase usage. It would be preferable to see well designed, randomised clinical trials of aerosolised antibacterials compared with placebo before they enter widespread use. Nonetheless, the guideline recommendation seems reasonable because of a lack of therapeutic options in such patients. As such, we agree with this recommendation. Regarding drug selection, we prefer that aminoglycosides be used first line with colistin reserved for aminoglycoside-resistant isolates. Clinicians are also encouraged to continue to publish their experiences with aerosolised antibacterials in HAP.

3. Administration Issues

3.1 Toxicity

One of the theoretical advantages of aerosolised administration is a decrease in adverse events compared with systemic therapy. This is particularly desirable with aminoglycosides and colistin because both drugs can be nephro- and ototoxic. A direct comparison of adverse events between aerosolisation and intravenous administration is not available. However, it appears that the incidence of tobramycin-induced nephrotoxicity is lower for aerosolisation (3% vs 10%), while ototoxicity appears to be similar (3% vs 5.5%).[2,37] For colistin, the incidence of nephrotoxicity with intravenous administration in more recent trials is ≈ 8–15% compared with a nonquantified, but apparently low, incidence in aerosolised studies.[28,38]

However, unique adverse effects of aerosolised antibacterials can occur because of the drug or the delivery vehicle. Cough, bad taste and bronchospasm are the most common adverse events reported in the general literature.[39-41] Colistin may have a higher incidence of adverse events than aminoglycosides, and may cause more severe pulmonary reactions or hypotension.[41-45] Preservatives and extremes in osmolarity, sodium content and pH can also affect tolerability.[46-51] A preservative-free formulation of tobramycin (TOBI®, Chiron Corporation)[1] is used in cystic fibrosis in an attempt to minimise adverse reactions. Recommendations for drug preparation to maximise tolerability are presented in table III. Pretreatment with salbutamol (albuterol) may improve the tolerability in patients with known tolerance problems or chronic lung disease; although most of these data are from aerosolised pentamadine studies.[39,44]

Interestingly, adverse events were either not reported or did not occur in the majority of patients covered in this review. Only 4 of 13 studies that included adverse event data reported any occurrences.[7,20,25,28] Cough or dizziness was reported in some patients receiving aminoglycosides.[7,20] One study of colistin reported that is was 'badly tolerated' in some patients.[20] Another potential adverse event is nephrotoxicity with systemic absorption of colistin and aminoglycosides from the lung into the bloodstream. One study reported nephrotoxicity with aerosolised colistin, but the relationship was questionable.[28] However, a number of studies have shown very low or undetectable systemic antibacterial concentrations with aerosolised therapy.[3,20,22,23,26,60-64] ET therapy[22,23,25,62,65,66] seems

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table III. Factors for optimising aerosolised drug delivery during mechanical ventilation

Factors	References
Drug factors	
pH between 4.0 and 8.0	48
Sodium concentration between 1/2 normal saline and normal saline (77–154 mEq/L) [dilute drug in normal saline when possible]	46-48
Osmolarity 150–1200 mOsm/L	46-48
Compound the drug in a volume of fluid that completely fills the nebuliser (typically ≈5mL)	52-55
Administration factors	
Use a nebuliser that produces a mean mass aerodynamic diameter between 1–5μm (data available from manufacturer)	53,54,56
Fill the nebuliser reservoir to full capacity with drug solution	52-55
Use ventilators that nebulise only during inspiration	57
Use high air flow rates for nebulisation (>6 L/min)	54
Position the nebuliser 30cm from the endotracheal tube in the inspiratory loop	57,58
Discontinue humidification during nebulisation	53,59
For patients with known intolerance or chronic lung disease, consider pretreating with salbutamol (albuterol) and/or using a preservative-free product	39,44,51

to result in higher systemic absorption than aerosolisation and, unlike aerosolisation, there are no data documenting homogenous distribution in the lung. Because of the potential for accumulation during renal failure, monitoring of serum concentrations in such patients who receive aerosolised aminoglycosides may be prudent.[66,67]

3.2 Optimising Administration During Mechanical Ventilation

A key issue in using aerosolised antibacterials is proper drug administration. Compared with oral or intravenous administration, aerosolised drug delivery is far less consistent and can be dramatically affected by a number of factors. Obviously, suboptimal drug delivery to the distal lung fields will compromise the efficacy of the drug. Data from outpatient use of aerosolised tobramycin in cystic fibrosis shows that only 10–20% of an aerosolised dose reaches the lung, even when optimal techniques are used.[2] However, it was recognised that lung deposition of an aerosolised dose in mechanically ventilated patients can be far worse (<3%).[68] This realisation spawned a number of *in vitro* and *in vivo* studies in the 1990s and 2000s that shed light on optimising aerosol delivery to mechanically ventilated patients.

A recent study during mechanical ventilation showed that differences in delivery techniques can result in as much as a 650% increase in the amount of salbutamol delivered to the lung.[69] However, drug delivery is also highly variable with >10-fold variation in aerosolised drug delivery depending on the administration technique.[69] Another recent clinical trial confirmed that an optimal technique results in high pulmonary drug concentrations for most patients; nonetheless, a few patients had poor concentrations.[3] Thus, it is clearly important that aerosolised drug administration in mechanically ventilated patients is highly variable and must be carried out in an optimal fashion.

Factors that will maximise delivery in mechanically ventilated patients are summarised in table III. Prescribing clinicians should work with pharmacists to ensure that doses are compounded in a volume that completely fills the nebuliser reservoir being used.[52-55] For maximum tolerability, normal saline is the preferred diluent and the pH of final solutions should be approximately physiological.[46-48] Osmolarity is less alterable as it will be a function of the final volume needed for the nebuliser.[46-48] Nebulisers that produce mean droplet sizes with an optimal diameter (1–5μm) have the best chance to deposit drug in the distal airways.[53,54,56] Larger droplets tend to impact on the upper airways and smaller droplets tend to be exhaled. Proper location of the nebuliser in the circuit and discontinuing ventilator humidification during nebulisation may also in-

crease drug delivery.[53,57-59] Clinicians should ensure nebulisers used in their institutions meet this requirement and that respiratory therapists are aware of proper technique. Ventilator issues such as adequate air flow rates and breath-actuated nebulisation are also important, but less amenable to change.[54,57]

ET administration of antibacterials is not recommended as a replacement for aerosolised administration. Certainly, some studies did show a positive response using ET administration,[15,22,23] and ET administration is easier than proper aerosolisation. However, there are two major reasons why ET administration should not be used. First, there is a body of recent literature on optimising aerosolisation in mechanically ventilated patients (table III). Most recent clinical trials and case reports have used aerosolisation rather than ET administration including a clinical trial demonstrating good drug delivery to the alveolar epithelial lining fluid when modern optimised administration was used.[3] Aerosolisation is more likely to deliver drug to the distal airways in a more homogenous fashion.[17] There are no such data supporting ET administration. Second, ET administration results in higher systemic antibacterial absorption than aerosolisation; presumably from the high concentration gradient of the antibacterial solution meeting the respiratory endothelium.[22,23,25,62,65,66] This is undesirable from a toxicity standpoint.

Another factor affecting drug deposition in the lung is the suitability of a drug product to undergo aerosolisation. Colistin, aminoglycosides and cephalosporins undergo aerosolisation well.[2,3,70] However, imipenem/cilastatin does not achieve adequate lung concentrations when aerosolised and should not be used in this fashion.[67] This is probably because the product does not go into a true solution when diluted and thus remains in the nebuliser.

In the near future, significant advances in dry powder and lipid-associated administration techniques may result in even better, and more consistent, drug delivery to the lung.[71,72] However, the current state of knowledge is such that physicians choosing to use aerosolised antibacterials for HAP should collaborate with respiratory therapists and pharmacists to design an optimal drug delivery regimen according to the recommendations of this review.

4. Conclusions

There are no large randomised clinical trials to evaluate the use of aerosolised antibacterials for the prevention or treatment of HAP. While the more modern prophylaxis studies were successful at preventing HAP without adversely affecting microflora, the general use of prophylactic aerosolised antibacterials is not recommended until large definitive trials can be performed. Regarding HAP treatment, current US guidelines allow aerosolised therapy in selected patients. We agree with that recommendation based on the general success reported and the lack of options in treating resistant organisms, but also caution against overuse because of a lack of large trials. Clinicians should be aware of unique toxicities of aerosolised antibacterials and pay careful attention to administration techniques to ensure good drug delivery. Ultimately, large randomised clinical trials should be conducted to better define the role of aerosolised antibacterials in preventing and treating HAP.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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