

REVIEWS OF THERAPEUTICS

Consensus Summary of Aerosolized Antimicrobial Agents: Application of Guideline Criteria

Insights from the Society of Infectious Diseases Pharmacists

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Appendix 1

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Appendix 1. Summary of Clinical Studies on Aerosolized Antimicrobial Agents

Condition	Antimicrobial Dosing Regimen	Study Design	Sample Size and Population
Cystic fibrosis, chronic suppressive therapy	Tobramycin 300 mg nebulized b.i.d. for 28 days ⁴¹	Randomized, double-blind, placebo-controlled, multicenter	21 children, 6 mo–6 yrs of age with early <i>P. aeruginosa</i> pulmonary colonization (average of 1–2 yrs prior to study entry)
	Tobramycin 80 mg b.i.d. for 12 mo using Pari Boy jet nebulizer ⁴²	Randomized, double-blind, placebo-controlled, multicenter	22 pediatric patients 4–18 yrs old within 7–12 wks of initial <i>P. aeruginosa</i> colonization
	Colistin 1 million units nebulized b.i.d. with oral ciprofloxacin 250–750 mg b.i.d. for 3 wks ⁴³	Randomized, placebo-controlled	26 children aged 2–9 yrs with early <i>P. aeruginosa</i> colonization
	Colistin 1–2 million units nebulized b.i.d. with oral ciprofloxacin 30 mg/kg/day for 3 wks ⁴⁴	Age- and sex-matched controlled to patients with chronic <i>P. aeruginosa</i> infection	47 patients with early <i>P. aeruginosa</i> colonization (average age of 8.9 yrs at time of first colonization)
	Jet nebulized colistin 1 million units b.i.d.–2 million units t.i.d. with oral ciprofloxacin 25–50 mg/kg/day divided b.i.d. for 3 wks–3 mo depending on colonization length ⁴⁵	Historical-controlled	91 patients aged 10 mo–18 yrs with early <i>P. aeruginosa</i> colonization or improved FEV ₁ and FVC
	Tobramycin 300 mg b.i.d. 28 days on and 28 days off for 56 wks using Pari LC Plus jet nebulizer and Pulmo-Aide compressor ⁴⁶	Randomized, open-label, parallel-group, multicenter	63 pediatric patients 6–15 yrs old who were asymptomatic or with mild lung disease and colonized with <i>P. aeruginosa</i>
	Tobramycin 300 mg b.i.d. 28 days on and 28 days off for 24 wks using Pari LC Plus jet nebulizer with Pulmo-Aide compressor ⁴⁷	Randomized, double-blind, placebo-controlled, multicenter	520 patients aged ≥ 6 yrs with moderate-to-severe airway disease and <i>P. aeruginosa</i> colonization
	Tobramycin 80 mg solution nebulized t.i.d. for 32 mo (mean duration) using Hodson 1730 or Intec 3010 nebulizer ⁴⁸	Randomized, physician-blinded, placebo-controlled	27 patients 7–24 yrs old (average age 14 yrs) with <i>P. aeruginosa</i> colonization
	Tobramycin 600 mg aerosolized t.i.d. 28 days on and 2 x 28 days off (or 28 days off and 2 x 28 days on) using Ultraneb 100/99 ultrasonic nebulizer ⁴⁹	Randomized, double-blind, placebo-controlled, three-period crossover, multicenter	71 patients (average age 16–18 yrs old) with <i>P. aeruginosa</i> colonization
	Tobramycin 40 mg nebulized (gentamicin in 1 patient) with oral flucloxacillin 25 mg/kg/dose b.i.d. for 1 mo using Bard nebulizer ⁵⁰	Double-blind, placebo-controlled, crossover	6 children 7–16 yrs old (average 11.7 yrs) with persistent respiratory isolation of <i>P. aeruginosa</i>

Appendix 1. (continued)

Outcomes	Comments
Eradication of colonization occurred in 8/8 treated patients (5 with mucoid isolates) and 1/13 patients in placebo group; no difference in clinical indices or markers of inflammation	Study was terminated before reaching target sample size of 98 because of statistically significant difference favoring treatment group
Significant reduction ($p < 0.05$) in positive cultures at 3, 6 and 12 mo in the treatment group ($n = 16$) compared with placebo ($n = 8$); no difference in lung function or inflammatory markers	8 lost to follow-up
Treated patients were 88% less likely to be colonized with <i>Pseudomonas</i> at 24 mo posttreatment (not observed at earlier intervals); clinical outcomes were not measured	
Median time to recolonization was 18 mo (range 4–80 mo) after eradication; lung function declined significantly less than in patients with chronic infection ($p < 0.05$)	Lung function comparisons only performed in 18 treatment patients and 18 controls
Treatment ($n = 48$) prevented or delayed chronic infection by 78% over 3.5 yrs, and significantly maintained compared with controls ($n = 43$) over 2 yrs ($p < 0.05$)	
Significant reduction in hospitalization and antibiotic use with nebulized tobramycin ($n = 30$) compared with standard treatment ($n = 33$); no difference in lung function	Study terminated early because of logistical enrollment challenges; large dropout rate
Significant improvement in pulmonary function ($p < 0.001$); decreases in density of <i>P. aeruginosa</i> ($p < 0.001$), hospitalizations ($p < 0.05$), and need for intravenous antibiotics ($p < 0.05$) in treatment group ($n = 258$) compared with placebo ($n = 262$)	
Lung function deterioration occurred in 6/15 in the treatment group and 11/12 in the control group; tobramycin resistance developed in 4/12 in the treatment group and none in the placebo group with susceptible <i>P. aeruginosa</i> at baseline	
Significant increase in FEV ₁ by 9.7% ($p < 0.001$) and decrease in sputum density of <i>P. aeruginosa</i> by factor of 100 ($p < 0.001$) during treatment ($n = 36$) compared with placebo ($n = 35$)	
Improved FEV ₁ by approximately 6% at end of treatment phase compared with end of placebo phase	3 of 9 enrolled patients withdrew because of noncompliance

Appendix 1. Summary of Clinical Studies on Aerosolized Antimicrobial Agents (continued)

Condition	Antimicrobial Dosing Regimen	Study Design	Sample Size and Population
Cystic fibrosis, chronic suppressive therapy (continued)	Tobramycin 300 mg b.i.d. using Pari LC Plus nebulizer and CR50 compressor, or colistin (colistin sulphomethate sodium) 80 mg b.i.d. using Ventstream nebulizer and CR50 compressor for 4 wks ⁵¹	Randomized, controlled, open-label, multicenter	115 patients aged 7–50 yrs airway disease and colonized with <i>P. aeruginosa</i> ; > 80% had pretreatment with nebulized aminoglycosides or colistin in previous 6 mo
	Tobramycin 80 mg nebulized b.i.d. with oral ciprofloxacin 10 mg/kg b.i.d for 1 mo ⁵²	Open-label, single center	26 children aged 3 mo–6 yrs infected with <i>P. aeruginosa</i> ; patients treated with 14-day course of intravenous antibiotics before initiation of aerosolized therapy
	Colistin (as colistin sodium methansulphonate) 1 million units nebulized b.i.d. using Raindrop nebulizer for 90 days ⁵³	Randomized, double-blind, placebo-controlled	40 patients aged 7–35 yrs (average 14.2 yrs) with chronic <i>P. aeruginosa</i> bronchopulmonary infection and moderate airway disease
	Aztreonam lysine 75 mg b.i.d.–t.i.d. using eFlow nebulizer + open-label tobramycin 300 mg nebulized b.i.d. ⁵⁴	Randomized, double-blind, placebo-controlled, multicenter	211 patients at least 6 yrs old with moderate-to-severe airway disease and positive <i>P. aeruginosa</i> from sputum or throat cultures
	Aztreonam lysine 75 mg t.i.d. using eFlow nebulizer + β_2 -agonist for 28 days ⁵⁵	Randomized, double-blind, placebo-controlled, international	164 patients at least 6 yrs of age with moderate-to-severe airway disease and colonized with <i>P. aeruginosa</i>
Cystic fibrosis, treatment of acute exacerbation	Amikacin 100 mg nebulized b.i.d. using Pari LC Plus with i.v. ceftazidime + amikacin vs i.v. agents alone for average of 15 days ⁵⁶	Randomized, controlled, open-label	62 patients aged 3–24 yrs with acute exacerbation and <i>P. aeruginosa</i> in sputum on admission (87 courses)
	Nebulized tobramycin 80 mg t.i.d. using Bennet twin jet nebulizer with i.v. ticarcillin + tobramycin vs i.v. agents alone for 14 days ⁵⁷	Randomized, controlled, open-label	28 patients aged 7–22 yrs with acute exacerbation and hospital admission
Non-cystic fibrosis bronchiectasis, suppression and prevention	Tobramycin 300 mg nebulized b.i.d. using Pari LC Plus jet nebulizer for 28 days ⁵⁸	Randomized, double-blind, placebo-controlled	74 adult patients with bronchiectasis and <i>P. aeruginosa</i> (powered only to address changes in sputum concentration of <i>P. aeruginosa</i>)

Appendix 1. (continued)

	Outcomes	Comments
Tobramycin (n=53) was significantly more effective at increasing %FEV ₁ predicted from baseline compared with colistin (n=62) (+6.7% vs +0.37%, p=0.008) after 4 wks; tobramycin most beneficial for patients 6–17 yrs of age; both treatments led to significant reductions in <i>P. aeruginosa</i> sputum density	Did not reach target sample size of 60 per group; 7 patients withdrew before end of study (5 due to adverse events, 1 lost to follow-up, 1 death); small increase in tobramycin MIC values for those treated with tobramycin	
<i>P. aeruginosa</i> eradication achieved in 77% of patients (88% with two cycles of aerosolized therapy); significant decrease in neutrophil elastase and interleukin-1 β in BAL fluid	No adverse events were reported	
Significant reduction in %predicted FVC at 90 days with treatment (7 vs 18, p<0.05); no difference in FEV ₁ between groups; <i>Pseudomonas</i> eradication not achieved in any patient	All patients received 2 wks of i.v. tobramycin + antipseudomonal β -lactam prior to study entry; only 29 patients completed study with more dropouts in placebo group from deterioration or lack of benefit; no bronchospasm reported with colistin; colistin MIC values did not change during trial, and no isolates developed resistance to colistin	
Significant improvement in patient-reported respiratory symptoms (5.0 points; 95% CI 0.8–9.21, p=0.02), FEV ₁ (6.3%; 95% CI 2.5–10.1, p=0.001), sputum density (–0.66 log ₁₀ cfu/g; 95% CI –1.13 to –0.19, p=0.006); time to need for more nebulized or i.v. antibiotics was 21 days longer for treated patients (92 vs 71 days, p=0.007)	Comparable incidence of adverse effects reported	
Significant improvement in patient-reported respiratory symptoms (9.7 points; 95% CI 4.3–15.1, p<0.001), FEV ₁ (10.3%; 95% CI 6.3–14.3, p<0.001), sputum density (–1.45 log ₁₀ cfu/g; 95% CI –2.1 to –0.8, p<0.001); trend toward fewer hospitalized patients and hospital stay	Incidence of adverse effects similar, except significantly more productive cough reported with nebulized aztreonam (25% vs 12.5%, p=0.047)	
No differences in clinical improvement; <i>Pseudomonas</i> eradication at end of treatment was higher with inhaled amikacin than systemic therapy alone (70% vs 41%, p<0.02) but most were recolonized 4–6 wks later	No differences in adverse effects between groups	
No differences between groups for clinical improvement; <i>Pseudomonas</i> eradication was higher in nebulized tobramycin group than control group (63% vs 25%, p=0.03) after 10–14 days of therapy; all children recolonized within 1–2 mo	No differences in adverse effects between groups	
Improved medical condition was reported in 62% of 37 treated patients compared with 38% of 37 patients who received placebo; treated patients were 2.7 times more likely to improve (OR = 2.7, 95% CI 1.1–6.9); no significant differences in pulmonary function or hospitalizations for acute exacerbations were observed	84% of patients reported at least one adverse event; dyspnea, chest pain, and wheezing were significantly more frequent in the nebulized tobramycin group versus placebo (p=0.01)	

Appendix 1. Summary of Clinical Studies on Aerosolized Antimicrobial Agents (continued)

Condition	Antimicrobial Dosing Regimen	Study Design	Sample Size and Population
Non-cystic fibrosis bronchiectasis, suppression and prevention (continued)	Tobramycin 300 mg nebulized b.i.d. using System 22 Acorn nebulizer for 6 mo ⁵⁹	Randomized, double-blind, placebo-controlled, crossover	20 patients with chronic <i>P. aeruginosa</i> lung infection
	Tobramycin 300 mg nebulized b.i.d. via Pari LC Plus jet nebulizer for 14 days for 3 cycles (with 14-day washout between each cycle) ⁶⁰	Open-label, multicenter	41 adult patients with diffuse bronchiectasis, purulent sputum production, history of <i>P. aeruginosa</i> from sputum and ≥ 4 courses of antibiotics for respiratory symptoms in yr before enrollment
	Ceftazidime 1000 mg nebulized b.i.d. + tobramycin 100 mg nebulized b.i.d. (both using System 22 Acorn nebulizer) for 12 mo ⁶¹	Randomized, unblinded	17 patients with chronic bronchial infection with <i>P. aeruginosa</i>
	Gentamicin 40 mg nebulized b.i.d. for 3 days ⁶²	Randomized, double-blind, controlled	28 patients with bronchiectasis and mucus hypersecretion despite chest care and hydration
	Colistin 30 mg nebulized daily added to treatment regimen ⁶³	Prospective	18 patients with bronchiectasis, severe chronic obstructive pulmonary disease and recurrent multidrug-resistant gram-negative infections
Non-cystic fibrosis bronchiectasis, treatment	Amoxicillin 500 mg nebulized b.i.d. using Incenti Neb nebulizer for 4 mo ⁶⁴	Case series	6 patients with bronchiectasis who failed 2-wk course of high-dose oral amoxicillin twice
	Tobramycin 300 mg nebulized b.i.d. via Pari LC Plus jet nebulizer with oral ciprofloxacin b.i.d. for 14 days ⁶⁶	Randomized, double-blind, active comparator, parallel-design, multinational	53 adults with bronchiectasis confirmed by high-resolution CT and a history of chronic <i>P. aeruginosa</i> infection within 12 mo before the time of screening; active comparator consisted of nebulized placebo with oral ciprofloxacin
bronchiectasis,	Gentamicin or tobramycin 80 mg nebulized b.i.d., or amikacin 1000 mg nebulized q8h, or ceftazidime 1000 mg nebulized q8h + systemic antibiotics for 7 days ⁶⁷	Prospective, nonrandomized	40 patients with non-cystic fibrosis bronchiectasis, chronic lung abscess, or chronic bronchitis; patients received systemic antibiotics + nebulized antibiotics (group 1) or systemic antibiotics alone (group 2)

Appendix 1. (continued)

Outcomes	Comments
No significant differences in acute exacerbations, changes in PFTs and quality of life; significantly more exacerbations requiring hospitalization occurred during placebo cycle compared with treatment cycle (0.75 ± 1.16 vs 0.15 ± 0.37 , $p=0.038$); length of hospitalization was significantly longer in placebo group compared with treatment group (12.65 ± 21.8 vs 2.05 ± 5.03 , $p=0.047$)	Patients were admitted to the hospital and given 2 wks of i.v. antibiotics with two <i>P. aeruginosa</i> -susceptible antibiotics before starting aerosolized portion of study; 3 of original 30 enrolled patients discontinued due to bronchospasm; 1 of the 20 patients who completed treatment developed dyspnea and wheezing
Mean pulmonary symptom severity scores decreased by a mean of 1.5 ± 3.4 points ($p=0.006$); health-related quality of life was significantly improved; of the 27 patients evaluable for microbiologic response, 22% had eradication of <i>P. aeruginosa</i>	Nearly 27% of patients received antipseudomonal antibiotics other than tobramycin during the treatment phase due to symptoms of pulmonary infection; high rate of adverse events were reported: 85% were considered to be possibly, probably, or definitely related; 10 withdrawals (24%) were due to adverse events
Treatment group ($n=7$), compared with control group ($n=8$), had significantly fewer hospitalizations (0.6 ± 1.5 vs 2.5 ± 2.1 , $p=0.023$) and days of hospitalization (13.1 ± 34.8 vs 57.9 ± 41.8 , $p=0.033$); no significant differences were reported with FVC, FEV ₁ , P _a O ₂ , P _a CO ₂ , oral antibiotic use and the emergence of antibiotic resistant organisms	Two patients did not complete study, one had bronchospasm (treatment group) and one died before completion of study (control group)
Daily sputum production decreased from 94.6 ± 21.6 ml to 58.1 ± 17.8 ml ($p<0.01$) with treatment ($n=13$) but significantly increased in the control group ($n=11$); treatment significantly decreased bacterial load in sputum from 2.2 ± 0.3 to 1.2 ± 0.2 ($p<0.05$) with no change observed in the control group; short-term improvement in nocturnal desaturation, 6-min walking distance, breathlessness was reported with treatment; no significant differences in pulmonary function tests	
Commencement of treatment significantly slowed decline of FEV ₁ (104 ml/yr to 44 ml/yr, $p=0.035$) and FVC (110 ml/yr to 48 ml/yr, $p=0.033$); quality of life assessed retrospectively also significantly improved	No isolates were resistant to colistin
2 patients reported marked improvement, 2 had gradual improvement, and 2 patients had no improvement; significant increase in PEFr ($p<0.05$), improvement in sputum color ($p<0.025$), and decrease in sputum volume ($p<0.05$) were reported	No significant adverse events were reported; continuation of this study with 3 additional patients showed that 2 of the 3 patients had sputum clearance maintained for 6 and 11 mo after cessation of treatment ⁶⁵
50% of patients in the treatment group were considered cured (OR 0.36; $p=0.091$, logistic regression); more patients in the treatment group had <i>P. aeruginosa</i> eradicated from sputum than those in comparator group (34.6% vs 18.5%, $p=NS$)	96% of patients in the comparator and 85% in the treatment group reported at least one adverse drug event; report of wheezing was higher in the treatment group (50% vs 15%)
PFTs were significantly improved after treatment, and group 1 had a greater improvement in PFTs compared with group 2; there was a statistically significant reduction in the amount of sputum in group 1 vs group 2 ($p<0.001$)	Although 27 of the patients had non-cystic fibrosis results were not disclosed specifically for this group

Appendix 1. Summary of Clinical Studies on Aerosolized Antimicrobial Agents (continued)

Condition	Antimicrobial Dosing Regimen	Study Design	Sample Size and Population
Hospital-acquired pneumonia, prevention	Gentamicin 80 mg ET t.i.d. for duration of ICU stay ⁶⁸	Randomized, double-blind, placebo-controlled	85 neurosurgical ICU patients (24% mechanically ventilated)
	Gentamicin 80 mg ET t.i.d. vs aminosidin 250 mg–colistin 50 mg t.i.d. for duration of ICU stay ⁶⁹	Randomized, open-label	47 neurosurgical ICU patients (30% mechanically ventilated)
	Gentamicin 80 mg aerosolized t.i.d. for 10 days ⁷⁰	Randomized, double-blind, placebo-controlled	30 burn ICU patients (63% mechanically ventilated)
	Gentamicin 40 mg ET q6h (duration NR) ⁷¹	NR	40 burn ICU patients (100% mechanically ventilated)
	Colistin 2.5 mg/kg/day ET divided q4h for duration of ICU stay ⁷²	Randomized, open-label	58 general ICU patients (100% mechanically ventilated)
	Colistin 2.5 mg/kg/day divided q4h ET for duration of ICU stay (all patients alternating q8wks) ⁷³	Double-blind, placebo-controlled	744 general ICU patients (percent mechanically ventilated unknown)
	Colistin 2.5 mg/kg/day divided q4h ET for duration of ICU stay ⁷⁴	Historical-controlled	292 general ICU patients (percent mechanically ventilated unknown)
	Gentamicin 40 mg ET q6h until extubated ⁷⁵	Randomized, double-blind, placebo-controlled	199 general ICU patients (100% mechanically ventilated)
	Tobramycin 80 mg aerosolized q.i.d. for 14 days ⁷⁶	Randomized, open-label	69 general ICU patients (100% mechanically ventilated)
	Colistin 200,000 units q3h ET for 14 days ⁷⁷	Historical-controlled	598 surgical ICU patients (100% mechanically ventilated)
	Ceftazidime 250 mg aerosolized q12h for 7 days ⁷⁸	Randomized, double-blind, placebo-controlled	40 trauma ICU patients (100% mechanically ventilated)
	Ceftazidime 250 mg aerosolized q12h for 7 days ⁷⁹	Randomized, double-blind, placebo-controlled	105 trauma ICU patients (100% mechanically ventilated)
Hospital-acquired pneumonia, treatment ^a	Gentamicin 40 mg aerosolized q.i.d. for 7–10 days with i.v. carbenicillin ⁸⁰	Observational	12 general medical patients (percent mechanically ventilated unknown) with mixed gram-negative bacilli
	Gentamicin 40 mg ET q3h (no systemic antibiotics) vs i.m. gentamicin (duration NR) ⁸¹	Randomized, open-label	15 neurosurgical ICU patients (percent mechanically ventilated unknown) with mixed gram-negative bacilli
	Sisomicin 25 mg ET q8h for 7 days with i.v. carbenicillin and sisomicin ⁸²	Randomized, double-blind	38 neurosurgical ICU patients (45% mechanically ventilated) with mixed gram-negative bacilli
	Tobramycin 300 mg q12h or 150 mg q8h, or amikacin 1 g q12h or 400 mg q8h aerosolized for 3–14 days with i.v. antibiotics ⁸³	Observational	22 surgery or trauma ICU patients (100% mechanically ventilated) with mostly <i>P. aeruginosa</i> or <i>A. baumannii</i>

Appendix 1. (continued)

Outcomes	Comments
Decreased development of HAP (12% vs 41%, $p < 0.05$) with treatment; no differences in mortality (54% vs 38%) and ICU stay (20 vs 14.7 days)	Increased gentamicin resistance; adverse effects were not addressed
No differences in HAP (20% vs 27%, $p = \text{NS}$), mortality (36% vs 27%) and ICU stay (17.6 vs 16 days)	Increased gentamicin resistance; cough was reported (no rate provided)
No differences in HAP (67% in each group) and mortality (50% vs 67%)	Increased gentamicin resistance; adverse effects were not addressed
“Decreased” HAP	Adverse effects and resistance were not addressed
No differences HAP (10% vs 8%), mortality (12% vs 24%), and ICU stay (9 vs 7.6 days)	No adverse effects experienced; resistance was not addressed
No differences in HAP (4.8% vs 8.1%) and mortality (12% in each group); HAP caused by <i>Pseudomonas</i> was significantly less in the treatment group (0.8% vs 4.6%, $p < 0.01$)	No change in resistance was reported; adverse effects were not addressed
No difference in HAP development (3.8% vs 8.1%); attributable mortality was significantly less in treatment group (64% vs 48%, $p < 0.05$)	Increased polymyxin resistance was observed; adverse effects were not addressed
No difference in HAP (34% vs 32%, $p = 0.57$) and mortality (27% vs 39%)	Resistance and adverse effects were not addressed
No difference in HAP (17.5% vs 42)	Resistance unchanged; adverse effects were not addressed
Significant reduction in HAP with treatment (28% vs 40%, $p < 0.05$); mortality was similar between groups (each 14%)	Resistance unchanged; adverse effects were not addressed
Significant reduction in HAP with treatment (30% vs 65%, $p < 0.022$); mortality (15% vs 30%) and ICU stay (19 vs 21 days) were not different	Resistance unchanged; adverse effects were not addressed
No differences in HAP (50% vs 49%), mortality (12% vs 13%), and ICU stay (30 vs 25 days)	Resistance unchanged; adverse effects were not addressed
67% of patients improved	No adverse effects reported
Cure rates were 100% vs 25% reported, and attributable mortality was 0% vs 38% (p values NR)	Adverse effects were not addressed
Significantly higher cure rates for treatment group (77% vs 45%, $p < 0.05$); similar mortality (28% vs 20%)	No adverse effects reported
Cure rate and mortality were 59% and 14%, respectively	No adverse effects reported

Appendix 1. Summary of Clinical Studies on Aerosolized Antimicrobial Agents (continued)

Condition	Antimicrobial Dosing Regimen	Study Design	Sample Size and Population
Hospital-acquired pneumonia, treatment (continued) ^a	Tobramycin 300 mg q12h or amikacin 1000 mg q12h ⁸⁴	Observational	44 trauma ICU patients (100% mechanically ventilated) with <i>P.aeruginosa</i> or <i>A. baumannii</i>
	Colistin 2–4 million units divided t.i.d.–q.i.d. aerosolized for 7–10 day with i.v. colistin ⁸⁵	Observational	17 chronic respiratory infection patients (percent mechanically ventilated unknown) with mixed gram-negative bacilli
	Colistin 1 million units b.i.d. aerosolized for 2–36 days with i.v. antibiotics ⁸⁶	Observational	21 general ICU patients (14% mechanically ventilated) with mostly <i>P.aeruginosa</i> or <i>A.baumannii</i>
	Colistin 500,000–1 million units q6–8h aerosolized for 2–21 days with i.v. antibiotics in 87% of patients ⁸⁷	Observational	71 general ICU and floor patients (percent NR) with <i>P.aeruginosa</i> or <i>A.baumannii</i>
	Colistin 1 million units t.i.d. aerosolized for 15 days with i.v. rifampin ⁸⁸	Observational	16 medical ICU patients (100% mechanically ventilated) with <i>A.baumannii</i>
	Colistin 500,000 units b.i.d. aerosolized for 4–25 days (mean 14) with i.v. colistin ⁸⁹	Observational	14 general ICU patients (93% mechanically ventilated) with mostly <i>P.aeruginosa</i>
	Colistin 1 million units t.i.d. aerosolized for 5–49 days with i.v. antibiotics in 95% of patients ⁹⁰	Observational	60 general ICU patients (100% mechanically ventilated)
	Cefotaxime or ceftazidime 50–100 mg/kg q.i.d. aerosolized with i.v. cefotaxime or ceftazidime + tobramycin (duration NR) ⁹¹	Observational	25 medical, surgical, trauma ICU patients (100% mechanically ventilated) with mixed gram-negative bacilli
Invasive aspergillosis, prophylaxis in patients with hematologic malignancies	Amphotericin B deoxycholate 5–20 mg nebulized b.i.d. ⁹²	Dose finding	18 stem-cell transplant recipients and 8 patients with leukemia
	Amphotericin B deoxycholate 5–10 mg nebulized t.i.d. ⁹³	Observational, dose finding	42 patients with granulocytopenia
	Amphotericin B deoxycholate 10 mg nebulized b.i.d. during neutropenia (median 27 days) ⁶	Randomized, unblinded, placebo-controlled, multicenter	382 patients with leukemias, relapsed non-Hodgkin's lymphomas, or solid tumors
	Liposomal amphotericin B 12.5 mg nebulized twice/wk on consecutive days ⁹⁵	Randomized, placebo-controlled	271 patients with hematologic disease with expected neutropenia for ≥ 10 days
Invasive aspergillosis, prophylaxis in patients with lung transplants	Amphotericin B deoxycholate 30 mg nebulized t.i.d. for 120 days after transplant, then 30 mg/day for life ⁹⁶	Prospective, nonrandomized, uncontrolled	55 lung transplant patients receiving immunosuppressive drugs based on multivariate analysis)

Appendix 1. (continued)

Outcomes	Comments
Cure rate 73%, VAP-related mortality 12%	No adverse events reported
24% of patients improved	“Badly tolerated” in 18% of patients
86% of patients improved or were cured; 14% mortality	Adverse effects were not addressed
Eradication occurred in 92% of patients; 18% mortality	Only 69% had HAP; adverse effects were not addressed
Cure rate was 100% with no mortality	No adverse effects reported
93% of patients improved or were cured	29% experienced cough or bronchospasm
83% of patients improved or were cured; attributable mortality was 17%	No adverse effects reported
Cure rate was 97% with 12% mortality	Adverse effects were not addressed; ceftazidime or cefotaxime 250 mg q12h–500 mg q6h nebulized most commonly used
54% of patients required i.v. amphotericin B deoxycholate	No adverse effects were observed at any doses
88% of patients tolerated 5 mg t.i.d.; 28% developed fungal infection with no difference in efficacy between various doses	
No significant decreases between groups in development of invasive aspergillosis (4% vs 7%, $p=0.37$) and infection-related mortality (8% vs 7%, $p=0.79$)	Preliminary results were reported in another study ⁹⁴
Using intent-to-treat analysis, 18 of 132 patients in placebo group vs 6 of 139 patients in treatment group developed invasive pulmonary aspergillosis (OR 0.26; 95% CI 0.09–0.72, $p=0.05$)	Cough occurred more frequently in treatment than placebo groups (16 vs 1, $p=0.002$); significantly more patients discontinued therapy in treatment group (45% vs 30%, $p=0.01$) due to weakness, technical problem with aerosol delivery, and cough; increase in serum creatinine concentration was not observed in treatment group; no drug-related serious adverse events were reported
Using on-treatment analysis, 13 of 97 patients in placebo group vs 2 of 91 in treatment group developed aspergillosis (OR 0.14; 95% CI 0.02–0.66, $p=0.007$)	
Treatment ($n=44$) decreased risk of infection (OR 0.13; 95% CI 0.02–0.69, $p<0.05$)	A few patients experienced mild side effects; one withdrew due to bronchospasm

Appendix 1. Summary of Clinical Studies on Aerosolized Antimicrobial Agents (continued)

Condition	Antimicrobial Dosing Regimen	Study Design	Sample Size and Population
Invasive aspergillosis, prophylaxis in patients with lung transplants (continued)	Amphotericin B deoxycholate 25 mg/day nebulized or amphotericin B lipid complex 50 mg/day for 4 days, then weekly for 7 wks (double dose for those mechanically ventilated) ³	Randomized, double-blind	100 lung and heart-lung recipients
	Amphotericin B lipid complex 50 mg nebulized once every 2 days for 2 wks with oral fluconazole 200 mg every 12 hrs ⁹⁷	Retrospective	60 lung transplant recipients
Nontuberculosis mycobacterial infection	Amikacin 15 mg/kg aerosolized once/day with macrolide-based oral antibiotic regimen for prolonged therapy (range 4–52 mo) ⁹⁸	Observational case series	6 patients with pulmonary MAC infections who were refractory or intolerant to the macrolide-based oral regimens
<i>Pneumocystis jiroveci</i> pneumonia, primary prophylaxis	Pentamidine 300 mg nebulized once every 4 wks for a median follow-up of 39 mo ⁹⁹	Randomized, open-label, multicenter	843 patients with HIV infection taking zidovudine whose CD4 ⁺ cell count was < 200 cells/mm ³
	Pentamidine 300 mg nebulized once every 4 wks for a median follow-up of 264 days ¹⁰⁰	Randomized, open-label, multicenter	215 patients with HIV infection whose CD4 ⁺ cell count was < 200 cells/mm ³
	Pentamidine 300 mg nebulized once/mo for median follow-up of 539 days ¹⁰¹	Randomized, open-label, multicenter	349 patients with HIV infection whose CD4 ⁺ cell count was < 200 cells/mm ³
<i>Pneumocystis jiroveci</i> pneumonia, secondary prophylaxis	Pentamidine 300 mg nebulized once every 4 wks for a median follow-up of 483 days ¹⁰²	Randomized, open-label, multicenter	533 patients with symptomatic HIV infection and/or having a CD4 ⁺ cell count < 200 cells/mm ³
	Pentamidine 300 mg nebulized once every 4 wks for a median follow-up of 17 mo ¹⁰³	Randomized, open-label, multicenter	310 patients meeting the definition for acquired immunodeficiency syndrome with a recent episode of PJP
<i>Pneumocystis jiroveci</i> pneumonia, mixed primary/secondary prophylaxis	Pentamidine 400 mg nebulized once every 4 wks for a median follow-up of 18 mo ¹⁰⁴	Randomized, open-label, single-center	96 patients with a previous AIDS-defining illness and/or a CD4 ⁺ cell count < 200 cells/mm ³
	Pentamidine 300 mg nebulized once/mo for median follow-up of 11.3 mo ¹⁰⁵	Randomized, open-label, multicenter	549 patients with symptomatic HIV infection and/or a CD4 ⁺ cell count < 200 cells/mm ³

ICU = intensive care unit; ET = endotracheal instillation; NS = not statistically significant ($p > 0.05$); HAP = hospital-acquired pneumonia; PJP = *Pneumocystis jiroveci* pneumonia; TMP-SMX = trimethoprim-sulfamethoxazole; CI = confidence interval; OR = odds ratio; NR = not reported; MIC = minimum inhibitory concentration; FEV₁ = forced expiratory volume in 1 sec; FVC = forced vital capacity; BAL = bronchoalveolar lavage; cfu = colony-forming units; PFTs = pulmonary function tests; PEFR = peak expiratory flow rate; MAC = *Mycobacterium avium* complex; MDI = metered-dose inhaler; CT = computed tomography; HIV = human immunodeficiency virus; PaO₂ = partial pressure of oxygen; PaCO₂ = partial pressure of carbon dioxide.

^aObservational studies with small sample sizes were excluded from the table.^{85, 106–113}

Appendix 1. (continued)

	Outcomes	Comments
Invasive fungal infections within 2 mo of treatment initiation occurred in 14% of 49 patients who received amphotericin B deoxycholate and in 12% of 51 who received amphotericin B lipid complex	Experience of adverse event more likely to occur with amphotericin B deoxycholate (OR 2.16; 95% CI 1.10–4.24, $p=0.02$)	
Invasive fungal infections within 6 mo of treatment initiation occurred in 2% of patients	Adverse effects included nausea and vomiting reported in 4 patients	
5/6 patients experienced symptomatic improvement; 4/6 had negative sputum culture after 6 mo of therapy (although 2 became reinfected later)	Albuterol via MDI was administered before amikacin in patients with cough or shortness of breath	
Estimated 36-mo cumulative risk of developing PJP was 18%, 17%, and 21% in the TMP-SMX, dapsone, and pentamidine groups, respectively ($p=0.22$); pentamidine offered a significantly lower level of protection in patients with baseline CD4 ⁺ cell counts of < 100 cells/mm ³	Toxoplasmosis rates were low in the study (3%); 29% of patients receiving systemic therapy were still receiving their assigned drug and dose on completion, compared with 88% in the pentamidine group	
TMP-SMX (combining two groups of different doses) demonstrated fewer occurrences of PJP (0 of 142 patients vs 6 of 71) than nebulized pentamidine ($p=0.002$)	More patients randomized to pentamidine at baseline were receiving zidovudine than either TMP-SMX group (65% vs 49%; $p=0.04$); more patients taking TMP-SMX required discontinuation due to toxicity (25% vs 3%)	
Pentamidine and dapsone-pyrimethamine groups had a PJP incidence of 5.7% and 5.8%, respectively	Toxoplasmosis developed in 18% of pentamidine-treated patients vs 11% of dapsone-pyrimethamine-treated patients, leading to an adjusted relative risk of ?? ($p=0.006$); toxicity-related interruptions in prophylaxis occurred more frequently in the dapsone-pyrimethamine group than the pentamidine group (24.3% vs 1.7%, $p<0.001$)	
Pentamidine demonstrated comparable efficacy to weekly dapsone-pyrimethamine in preventing PJP (12 vs 13 cases); there was trend in favor of dapsone-pyrimethamine for preventing toxoplasma encephalitis	Dapsone-pyrimethamine had a much higher discontinuation rate (30%) due to toxicity	
TMP-SMX demonstrated fewer recurrences of PJP (14/154 vs 36/156 patients) than nebulized pentamidine ($p<0.001$)	Study was terminated early due to the detected significant difference; a third group, pyridoxine-sulfadoxine, was stopped after only 22 patients and was not discussed in the results; one fourth of the patients randomized to TMP-SMX were converted to pentamidine (vs 4% conversely) due to toxicity	
Pentamidine-treated patients demonstrated a similar rate of PJP development (17% vs 18%) compared with dapsone	This was a small, single-center study using a nonstandard dose of pentamidine; 72% of patients were receiving primary prophylaxis; hematologic toxicity markers were comparable between the two groups	
Pentamidine-treated patients demonstrated a trend of fewer episodes of PJP compared with two different dose strategies of oral atovaquone (17%, 22%, and 25%)	Atovaquone 1500 mg/day resulted in the secondary composite outcome of fewer episodes of PJP and death than atovaquone 750 mg/day; more patients required discontinuation of therapy on atovaquone than pentamidine (21% vs 7%, $p<0.03$)	