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FEATURED ARTICLE

Nebulized Colistin for the Treatment of Multidrug-Resistant Gram-Negative Pneumonia

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Abstract

Purpose: To describe the use of nebulized colistin (colistimethate sodium) for the treatment of multidrug-resistant gram-negative infections. Specific aims were to identify dose and frequency of nebulized colistin therapy currently used, to assess clinical and microbiological efficacy, and to assess the prevalence of adverse events resulting from colistin therapy.

Methods: A retrospective chart review was performed at a tertiary care, level I trauma center and teaching hospital. The review included examination of 29 courses of colistin therapy administered to 24 adults receiving at least 24 hours of nebulized colistin for the treatment of gram-negative pneumonia.

Results: Demographic, medication, adverse event, and outcome data were collected for the duration of colistin therapy. Colistin was administered to patients with multidrug-resistant infections caused by gram-negative organisms. Many patients had a history of exposure to multiple antibiotics or drug allergies. Resistance to colistin was observed in 3 of 18 isolates with available susceptibility data. Determining the prevalence of adverse events was difficult because of the use of multiple medications. Many patients had missed antibiotic doses. A 25% mortality rate was observed.

Conclusion: The findings of this study serve to demonstrate the use of nebulized colistin for treatment of multidrug-resistant gram-negative pneumonia in patients without cystic fibrosis; to raise concern with regard to the large number of missed antibiotic doses; and to emphasize the need for further investigation by a larger, prospective, randomized trial.

Key Words—colistimethate sodium, gram-negative pneumonia, inhaled colistin, multidrug resistant, nebulized colistin

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INTRODUCTION

Pneumonia caused by multidrug-resistant gram-negative organisms is characterized by a high mortality rate, increased length of hospital stay, and increased costs for the patient and the health care institution.[1,2] It is also the most common reason for the use of intravenous (IV) antibiotics in the intensive care unit (ICU).[3] Organisms that frequently show resistance to current antimicrobial agents include *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[2,4-6] Increasing resistance generates a need for new treatment options; however, there are few novel antibiotics targeted at gram-negative organisms being developed.[7]

To account for gaps in the span of available therapies for resistant organisms, attention has turned recently to the reintroduction of older antibiotics with activity against gram-negative organisms.[3,8,9] Polymyxin E and B have been utilized since the 1950s. Polymyxin E (colistin) is a cationic polypeptide antibiotic that acts by interacting with phospholipids and displacing calcium and magnesium from the outer cell membrane of gram-negative organisms. This results in the cell contents leaking through damaged cell walls and, eventually, cell death. The drug exerts its action in a bactericidal and concentration-dependent manner.[10] This mechanism of action differs from other antipseudomonal agents, making it less likely that the agent will develop cross-resistance through traditional mechanisms, such as those involving antibiotic-inactivating

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enzymes (penicillinases and cephalosporinases).[8]

Colistin is active against many gram-negative aerobic bacilli. This includes species of *Acinetobacter, Enterobacter, Escherichia coli, Klebsiella, Pseudomonas, Salmonella,* and *Shigella*. *Stenotrophomonas maltophilia* strains are also susceptible to colistin. It is inactive against species of *Burkholderia, Edwardsiella, Proteus, Providencia,* and *Serratia*.[9,10] The spectrum of colistin activity is promising because many of these gram-negative organisms have developed resistance to other antibiotics.

Adverse effects of IV colistin include nephrotoxicity (acute renal failure) and neurotoxicity (facial paresthesias, dizziness, muscle weakness, vertigo, confusion, neuromuscular blockade, and apnea).[9,10-12] Nebulized forms may show less systemic absorption, resulting in a much lower incidence of nephrotoxicity and neurotoxicity. However, there may be a greater incidence of bronchoconstriction, and there is also potential for hydrolysis of colistimethate into chemicals that may damage lung tissue if not administered promptly after preparation.[3,13] The sodium salt of colistin, which is used for nebulized colistin, is commonly referred to as colistimethate sodium, colistin methanesulfate, or colistin sulfamethate.[9,14,15] It has been associated with less cough, chest tightness, and bronchoconstriction than the sulfate salt or other polymyxins, such as polymyxin B.[9,14,15]

The use of an aerosolized form of colistin offers promise for effective bacterial killing because of its potential for achieving high bactericidal concentrations directly in the lungs, though its penetration and bactericidal lung activity have not yet been proven in patients without cystic fibrosis.[16]

There is some clinical evidence regarding the use of aerosolized polymyxins for the treatment of patients with cystic fibrosis but a lack of data for treatment of patients without cystic fibrosis.[17-19] Recent case reports and small studies have shown the benefit of nebulized colistin in the population without cystic fibrosis for the treatment of multidrug-resistant gram-negative infections caused by organisms such as *P. aeruginosa* and *Acinetobacter,* but there is no current consensus about ideal dosing regimens and intervals.[12,20-23]

The objective of this study was to describe the use of nebulized colistin (colistimethate sodium) for the treatment of multidrug-resistant gram-negative infections in patients hospitalized at a tertiary care, community teaching hospital. Specific aims of the study were to identify the dose and frequency of nebulized colistin therapy used at the institution; to assess clinical and microbiological efficacy; and to assess the prevalence of nephrotoxicity, neurotoxicity, and bronchoconstriction from colistin therapy.

MATERIALS AND METHODS

Study Design and Patient Population

A retrospective chart review of all patients treated with nebulized colistin at Orlando Regional Medical Center from August 2006 through December 2007 was performed. Patients were identified using the hospital computer systems. The Institutional Review Board (IRB) approved the study protocol.

Adults 18 years of age and older receiving at least 24 hours of nebulized colistin for the treatment of gram-negative pneumonia were eligible for inclusion in the study. Pneumonia was defined as a new or progressive infiltrate on chest x-ray plus at least 2 of 3 clinical criteria indicating an infectious origin: purulent sputum, fever higher than 38°C, and leukocytosis (more than 10,000 cells/mm^3) or leukopenia (less than 4,000 cells/mm^3).[6] Pneumonia was considered gram negative if the patient had positive isolation of a gram-negative organism from a sputum sample, endotracheal tube aspirate, bronchoalveolar lavage, or bronchoscopy.

Exclusion criteria were as follows: younger than 18 years of age, pregnancy, imprisonment (per IRB standard), therapy started at outside health care facility, and cystic fibrosis.

Data Collection

Patient Data

Data collection included demographic data such as age, sex, height, weight, admission date, discharge date, allergies, location of patient at therapy initiation, and comorbid conditions. To assess severity of patient illness, Acute Physiology and Chronic Health Evaluation (APACHE) III scores were calculated on admission to the ICU.[24] APACHE IV scores were recorded as a predictor of hospital mortality risk. Therapy efficacy was assessed by obtaining markers of infection and clinical improvement, such as white blood cell count, percentage of bands, maximum temperature, respiratory rate, sputum production, chest x-ray findings, culture results and susceptibilities, and ventilator settings (oxygen saturation, fraction inspired oxygen, positive end-expiratory pressure, pressure support). Patient discharge disposition was also recorded. If a particular organism grew in more than 1 culture from a patient, only 1 of each species per patient was included in the data. Previous and concurrent antibiotics administered to the patient during the hospital stay were recorded. Neph-

Table 1. Demographic Data of 24 Patients Receiving Nebulized Colistin Therapy

Characteristic	*Number (%) of Patients (N = 24)*
Male	18 (75)
PMH	
Renal dysfunction	5 (20.8)
Pulmonary disorders	3 (12.5)
Allergies	
Penicillin	8 (33.3)
Cephalosporins	3 (12.5)
Other	2 (8.3)
	Mean ± SD
Age (y)	48 ± 17
APACHE III (0 to 299)	62.5 ± 17.6
APACHE IV (1% to 100%)	26.2 ± 18.3
	Median (Range)
ICU LOS (days)	20 (13 to 33)
Hospital LOS (days)	58.5 (41 to 100)
	Number (%) of Courses (N = 29)
Diagnosis	
HAP	10 (34.4)
VAP	19 (65.5)

APACHE = Acute Physiology and Chronic Health Evaluation; HAP = hospital-acquired pneumonia; ICU = intensive care unit; LOS = length of stay; PMH = past medical history; SD = standard deviation; VAP = ventilator-associated pneumonia.

rotoxicity, neurotoxicity, and colistin-related bronchoconstriction were examined. Markers of renal function were obtained, such as serum creatinine, serum urea nitrogen, urine output, doses of concurrent nephrotoxic drugs, and exposure to IV contrast. A patient was considered as having acute renal failure if there was a greater than 50% increase in serum creatinine from the beginning of therapy or a need for dialysis. Nursing and progress notes were examined for signs and symptoms of neurotoxicity, such as facial paresthesias, dizziness, muscle weakness, vertigo, confusion, neuromuscular blockade, and apnea. Bronchoconstriction was assessed by recording the number of as-needed short-acting beta 2 agonist uses within 2 hours of colistin administration.

Treatment Data

Data collection for colistin therapy included initial dose, total daily dose, and frequency and duration of treatment. Data were recorded for the 24 hours before initiation of colistin therapy through 24 hours after treatment conclusion. If there was a gap in a patient's colistin therapy greater than 72 hours, treatment before and after the lapse in therapy was considered 2 separate courses of treatment. Colistin minimum inhibitory concentrations (MICs) were determined by the *Etest* (AB Biodisk; Solna, Sweden), and susceptibility results were recorded based on hospital laboratory breakpoints for *Pseudomonas* (sensitive, 2 mcg/mL or less; intermediate, 4 mcg/mL or less; resistant, greater than 4 mcg/mL) and *Acinetobacter* (sensitive, 2 mcg/mL or less; resistant, greater than 2 mcg/mL).

Data Analysis

Descriptive statistics for all data were collected, analyzed, and stored using *Microsoft Excel* software. Ordinal data were reported as a median, nominal data was recorded in proportions, and means were calculated for interval data.

RESULTS

Patients

During the study period, 30 patients received inhaled colistin. With a total of 29 courses of colistin therapy, 24 patients were eligible for study entry; 3 patients were excluded for receiving less than 24 hours of colistin therapy and 3 were excluded for beginning therapy at an outside facility. Table 1 summarizes patient demographic information, as well as medical history.

All patients had a prolonged hospital course and a history of prior antibiotic exposure and were receiving other antibiotics at the time of colistin therapy. Past and concurrent antibiotic exposure is depicted in Figure 1.

Colistin-Usage Patterns

As summarized in Table 2, colistin therapy was targeted at an identified organism in 100% (24/24) of patients and was prescribed most commonly for patients who underwent surgery (21/24). The most common dosing regimen used was colistin 150 mg nebulized every 12 hours (28

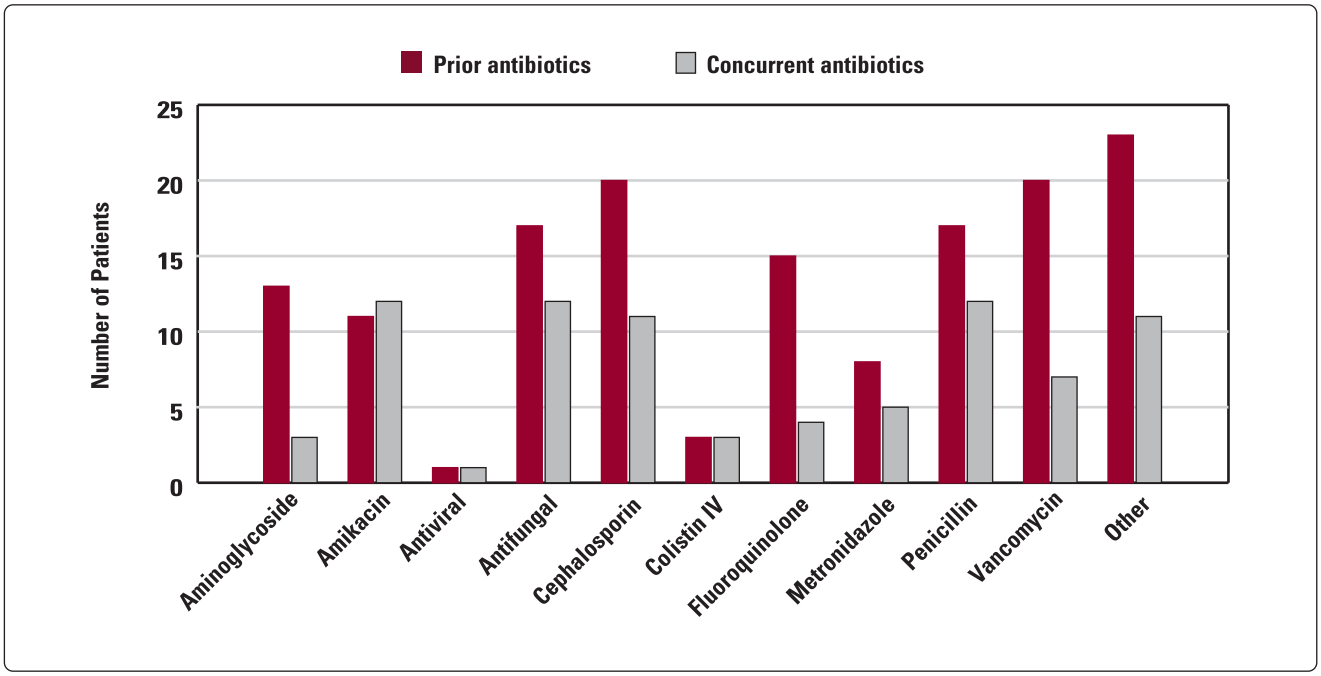

Figure 1. Antibiotics that patients received before and during nebulized colistin therapy. Aminoglycoside = gentamicin/tobramycin; IV = intravenous; Other = aztreonam, linezolid, clindamycin, carbapenems, sulfamethoxazole/trimethoprim, macrolides.

Table 2. Characteristics of Nebulized Colistin Therapy

Characteristic	*Number (%) of Patients (N = 24)*
Indication	
Targeted	24 (100)
	Number (%) of Courses (N = 29)
Prescriber	
Surgical	21 (72.4)
Medical	1 (3.4)
Infectious diseases	7 (24.1)
Dose	
150 mg every 12 hours	28 (96.6)
150 mg every 8 hours	1 (3.4)
	Mean ± SD (N = 29)
Doses (number)	18 ± 9
Total course (mg)	2,815 ± 1,513

SD = standard deviation.

courses), with 1 patient receiving 150 mg every 8 hours. Patients received a mean of 18 doses per therapy course.

P. aeruginosa was the most common organism isolated in cultures, as shown in Table 3. Not all isolates were tested for susceptibility to colistin. Organisms that showed resistance to colistin included 2 *P. aeruginosa* isolates (MIC = 8 mcg/mL), 1 culture reported as resistant with no MIC data, and 1 *S. maltophilia* isolate (MIC = 32 mcg/mL). One *P. aeruginosa* isolate was considered intermediate to colistin (MIC = 4 mcg/mL).

Adverse events are summarized in Table 4. In the cases studied, 10 patients experienced an adverse event and 3 patients experienced more than 1 adverse event. One patient experienced worsening renal function that progressed to dialysis.

Outcomes

Patient clinical and microbiological outcomes are summarized in Table 5. Discharge from this facility was possible for 75% of patients.

Table 3. Colistin Activity Against Gram-Negative Isolates in 24 Patients

Organism	*Number Isolated*	*Number of Sensitivities Obtained*	*Percentage Susceptible*	*Mean MIC (mcg/mL) ± SD*[a]
Pseudomonas aeruginosa	26	14	71	1.4 ± 0.4
Mucoid *P. aeruginosa*	1	1	100	1 ± 0
Stenotrophomonas maltophilia	3	1	0	
Acinetobacter baumannii	3	2	100	1 ± 0.7

[a]Mean minimum inhibitory concentration (MIC) (mcg/mL) ± standard deviation (SD) of organisms sensitive to colistin.

Table 4. Adverse Events Seen in 29 Courses of Nebulized Colistin

Adverse Event	*Number (%) of Courses (N = 29)*
Neurotoxicity	5 (17.2)
Bronchoconstriction	3 (10.3)
Change in Renal Function	
Greater than 0.5 mg/dL	5 (17.2)
SCr greater than 2 mg/dL	2 (6.9)
Newly requiring dialysis	1 (3.4)

SCr = serum creatinine.

Table 5. Patient Outcomes for 24 Patients Receiving Nebulized Colistin Therapy

Outcome	*Number (%) of Courses (N = 29)*
Cultures	
Microbiological cure	8 (27.6)
Continued positive cultures	11 (37.9)
Unknown	10 (34.5)
	Number (%) of Patients (N = 24)
Discharge Disposition	
Home	2 (8.3)
Other hospital	2 (8.3)
Rehabilitation center	5 (20.8)
Skilled nursing facility	9 (37.5)
Death	6 (25)

DISCUSSION

With the emergence of multidrug-resistant organisms in recent years, seeking alternative antibiotic therapies with activity against these species has become increasingly important. Gram-negative organisms are often the cause of such infections, and they are associated with a high mortality rate. Nebulized colistin has been used in the past for patients with cystic fibrosis. Recently, it has begun receiving attention as treatment for multidrug-resistant gram-negative pneumonia in patients without cystic fibrosis.

Literature on the use of nebulized colistin in patients without cystic fibrosis includes several retrospective studies and case reports. Kwa et al examined 21 patients who received nebulized colistin for the treatment of multidrug-resistant pneumonia caused by *A. baumannii* and *P. aeruginosa*. The study found a microbiological response rate of 85.7% and a clinical response rate of 57.1%. Significant occurrence of renal dysfunction was not observed in relation to nebulized colistin.[20] Michalopoulos et al described experiences with 8 patients who received aerosolized colistin concurrently with other antibiotics for multidrug-resistant pneumonia. Colistin was well tolerated, and 7 of 8 patients showed clinical improvement.[22] Hamer reported the successful use of nebulized colistin as adjunctive therapy for nosocomial pneumonia or tracheobronchitis in 3 patients.[23]

Based on patient demographics of the population studied, nebulized colistin is used at this institution as targeted therapy for multidrug-resistant gram-negative pneumonia in patients who have failed previous courses of multiple antibiotics, as concurrent double-coverage for resistant organisms, or as a treatment method for patients with multiple allergies and limited treatment options. Prolonged length of ICU and hospital stays in the study population placed these patients at high risk for multidrug-resistant infections.

Previous literature has shown a wide variation in dosing regimens for nebulized colistin, including 40 mg every 8 hours; 80 mg every 6, 8, or 12 hours; 100 mg every 12 hours; and 150 mg every 12 hours. Doses were selected based on body weight and infection severity, with higher doses used for patients with pneumonia.[20-24] Colistin dosing also may be expressed in units (1 mg = 12,500 units), translating to a common dose of 1 to 2 million units.[22] The most common dosing regimen used in this study was 150 mg every 12 hours, which is on the higher end of total daily dosing regimens previously studied, likely because of the severity of illness in the population studied.

Concern about bronchoconstriction with nebulized colistin has been raised in previously published literature.[25,26] Only 1 patient in this study had a dose withheld and a rescue medication administered as a result of bronchoconstriction during drug administration. However, 10 patients had scheduled bronchodilators that could have negated the need for additional rescue medication. Near the time of drug administration, 2 patients had other respiratory symptoms such as wheezing and a decrease in oxygen saturation. There were no cases in which bronchoconstriction resulted in drug discontinuation. Baseline and posttreatment serum creatinine levels were similar (1.3 and 1.4 mg/dL, respectively). Directly attributing any nephrotoxicity to colistin is difficult because many patients were receiving other medications that may affect renal function, such as aminoglycosides and IV colistin. Possible signs of neurotoxicity were observed in 5 patients; 3 were disoriented or confused and 2 had tremors/choreiform movements. Tremors in one of these patients worsened with medication administration (medication not specified in nursing documentation). Also, many patients were heavily sedated on a ventilator and were receiving multiple medications that can cause disorientation, which makes assessing signs of neurotoxicity difficult. Symptoms were nonspecific to colistin and never directly associated with the administration of colistin. Because the study was retrospective, determination of the causality of adverse events is not possible.

Of concern in this study was a relatively high incidence of missed doses (22/508 total doses). The most common reasons for missed doses cited in respiratory therapy documentation were that the drug was not available or that the patient was not on the floor. Recently, colistin has not been delivered with IV batches because of concerns regarding the stability of the nebulized form.[13] The need for daily preparation might have led to problems with the pharmacy providing the medication on time. Missed doses are significant considering the 12-hour dosing interval of colistin, and they can lead to prolonged antibiotic-free periods for the patient, which could have affected patient outcomes. Missed doses can be minimized by specifying an administration time on the orders and standardizing daily times that colistin is delivered. It is also important that patient caregivers be advised that if a patient or drug is not available at the scheduled time of medication administration, the antibiotic dose should be administered as soon as the patient returns or the drug becomes available. The prevalence of missed doses in this study raises concern that missed antibiotic doses may be an underrecognized problem in other hospitals, as well as in this study.

Of the patients receiving nebulized colistin, 9 did not have susceptibilities to colistin available. The resistance/intermediate rate of 4 of 18 (22%) isolates with susceptibility data identified in this patient population raised concern that patients may not have been receiving an antibiotic targeting the identified organism if it was resistant to colistin and susceptibilities were not tested. Case reports have described emergence of resistance to colistin in isolates of *P. aeruginosa* and *Enterobacter aerogenes*.[27,28] The presence of resistance noted in the literature and in this study emphasizes the importance of obtaining susceptibility results during colistin therapy to ensure adequate treatment.

The overall all-cause mortality rate (25%) correlated closely with the average APACHE IV predicted mortality rate of 26.2% ± 18.3%. Deaths were attributed to causes other than pneumonia in 3 patients (renal cell carcinoma, closed head injury, and gastrointestinal bleed). All mortalities were associated with multiple comorbid conditions, including posttraumatic injuries, and death could not be attributed to pneumonia alone. A low proportion of patients (27.5%) achieved confirmed microbiological cure, but 34.5% of patients did not have repeat cultures preformed to assess response to therapy; thus, the true eradication rate cannot be determined accurately. Despite the lack of repeat cultures, clinical outcomes were favorable in many patients for whom therapy was discontinued based on clinical indicators of improvement or when it was thought that repeat positive cultures represented colonization.

During colistin therapy, 6 patients received at least 24 hours of concurrent IV antibiotic therapy with an agent active against the identified organism. Ten patients received antibiotics that were classified as intermediate or had higher MICs (amikacin MIC = 16 or 32), and 8 patients received concurrent antibiotics that eventually were determined as having no activity. Discharge disposition was similar among each patient group. Of the patients who died, 2 concurrently received an active agent, 1 received an intermediate agent, and 2 were administered a nonactive agent. This may indicate that colistin could have a role as monotherapy for resistant organisms.

The limitations of this study include that determination of the efficacy of nebulized colistin was not possible because of the lack of a control group. Furthermore, all patients in this study were receiving other antibiotics concurrently with colistin therapy, some of which were reported as having activity against the organism targeted by colistin. Attributing adverse events to colistin is also difficult because of the concurrent use of other nephrotoxic drugs, including aminoglycosides. This can result in confounding of the results. Because this was a retrospective study, collection of laboratory findings and clinical indicators was reliant on those that had been previously obtained and values were not always available for all days of therapy.

CONCLUSION

The findings of this study demonstrate promise for the use of nebulized colistin for the treatment of multidrug-resistant gram-negative pneumonia, raise concern over the large number of missed antibiotic doses, and emphasize the need for further investigation by a larger, prospective, randomized trial.

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REFERENCES

1. Waterer GW, Wunderink RG. Increasing threat of Gram-negative bacteria. *Crit Care Med*. 2001;29(4)(suppl):N75-N81.

2. Jones RN. Resistance patterns among nosocomial pathogens: trends over the past few years. *Chest*. 2001;119(2)(suppl):397S-404S.

3. Linden PK, Paterson DL. Parenteral and inhaled colistin for treatment of ventilator-associated pneumonia. *Clin Infect Dis*. 2006;43(suppl 2):S89-S94.

4. Van Eldere J. Multicentre surveillance of *Pseudomonas aeruginosa* susceptibility patterns in nosocomial infections. *J Antimicrob Chemother*. 2003;51(2):347-352.

5. Gales AC, Jones RN, Forward KR, Linares J, Sader HS, Verhoef J. Emerging importance of multidrug-resistant *Acinetobacter* species and *Stenotrophomonas maltophilia* as pathogens in seriously ill patients: geographic patterns, epidemiological features, and trends in the SENTRY Antimicrobial Surveillance Program (1997-1999). *Clin Infect Dis*. 2001;32(suppl 2):104-113.

6. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator associated, and healthcare associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(4):388-416.

7. Talbot GH, Bradley J, Edwards JE Jr, Gilbert D, Scheld M, Bartlett JG; Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;42(5):657-668.

8. Mesaros N, Nordmann P, Plésiat P, et al. *Pseudomonas aeruginosa:* resistance and therapeutic options at the turn of the new millennium. *Clin Microbiol Infect*. 2007;13(6):560-578.

9. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. *Clin Infect Dis*. 2005;40(9):1333-1341.

10. *Coly-Mycin M Parenteral* [package insert]. Bristol, TN: Monarch Pharmaceuticals; 2002.

11. Falagas ME, Kasiakou SK, Tsiodras S, Michalopoulos A. The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. *Clin Med Res*. 2006;4(2):138-146.

12. Brown JM, Dorman DC, Roy LP. Acute renal failure due to overdosage of colistin. *Med J Aust*. 1970;2(20):923-924.

13. US Food and Drug Administration. Information for healthcare professionals colistimethate (marketed as *Coly-Mycin M* and generic products). www.fda.gov/cder/drug/InfoSheets/HCP/colistimethateHCP.htm. Published June 28, 2007. Accessed September 19, 2007.

14. Michalopoulos A, Kasiakou SK, Falagas ME. The significance of different formulations of aerosolized colistin. *Crit Care*. 2005;9(4):417-418.

15. Westerman EM, Le Brun PPH, Touw DJ, Frijlink HW, Heijerman HGM. Effect of nebulized colistin sulphate and colistin sulphomethate on lung function in patients with cystic fibrosis: a pilot study. *J Cyst Fibros*. 2004;3(1):23-28.

16. Mubareka S, Rubinstein E. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. *Crit Care*. 2005;9(1):29-30.

17. Jensen T, Pedersen SS, Garne S, Heilmann C, Høiby N, Koch C. Colistin inhalation therapy in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection. *J Antimicrob Chemother*. 1987;19(6):831-838.

18. Bauldoff GS, Nunley DR, Manzetti JD, Dauber JH, Keenan RJ. Use of

aerosolized colistin sodium in cystic fibrosis patients awaiting lung transplantation. *Transplantation.* 1997;64(5):748-752.

19. Conway SP. Nebulized antibiotic therapy: the evidence. *Chron Respir Dis.* 2005;2(1):35-41.

20. Kwa AL, Loh C, Low JG, Kurup A, Tam VH. Nebulized colistin in the treatment of pneumonia due to multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *Clin Infect Dis.* 2005;41(5):754-757.

21. Berlana D, Llop JM, Fort E, Badia MB, Jódar R. Use of colistin in the treatment of multiple-drug-resistant Gram-negative infections. *Am J Health Syst Pharm.* 2005;62(1):39-47.

22. Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagas ME. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. *Crit Care.* 2005;9(1):R53-R59.

23. Hamer DH. Treatment of nosocomial pneumonia and tracheobronchitis caused by multidrug-resistant *Pseudomonas aeruginosa* with aerosolized colistin. *Am J Respir Crit Care Med.* 2000;162(1):328-330.

24. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest.* 1991;100(6):1619-1636.

25. Maddison J, Dodd M, Webb AK. Nebulized colistin causes chest tightness in adults with cystic fibrosis. *Respir Med.* 1994;88(2):145-147.

26. Cunningham S, Prased A, Collyer L, Carr S, Lynn IB, Wallis C. Bronchoconstriction following nebulised colistin in cystic fibrosis. *Arch Dis Child.* 2001;84(5):432-433.

27. Denton M, Kerr K, Mooney L, et al. Transmission of colistin-resistant *Pseudomonas aeruginosa* between patients attending a pediatric cystic fibrosis center. *Pediatr Pulmonol.* 2002;34(4): 257-261.

28. Thiolas A, Bollet C, La Scola B, Raoult D, Pagès JM. Successive emergence of *Enterobacter aerogenes* strains resistant to imipenem and colistin in a patient. *Antimicrob Agents and Chemother.* 2005:49(4):1354-1358.