Nebulized Colistin in the Treatment of Pneumonia Due to Multidrug-Resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*

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Twenty-one patients with multidrug-resistant (MDR) *Acinetobacter baumannii* and *Pseudomonas aeruginosa* pneumonia were treated with nebulized polymyxin E (colistin). Overall clinical and microbiological response rates were 57.1% and 85.7%, respectively. Nebulized colistin may be reasonably efficacious and safe for treatment of MDR pneumonia. Its role in therapy warrants further investigation in comparative studies.

In the past decade, multidrug-resistant (MDR) gram-negative bacteria have become the focus of increased attention, especially with respect to patients in intensive care units [1, 2]. The virulence of these MDR pathogens severely restricts viable therapeutic options. Polymyxin E (colistin) was first used in the 1960s to the early 1980s. However, its use fell out of favor because of perceived drug-related nephrotoxicity and neurotoxicity. It has demonstrated excellent in vitro activity against many species of aerobic gram-negative bacilli, including MDR pathogens. The mechanism of action of the polymyxins is not very clear. They are cationic detergents and are believed to interact with the phospholipids of bacterial cell membranes, thereby leading to increased cell-wall permeability and cell death [3]. The use of nebulized colistin has been limited primarily to patients with cystic fibrosis [4]. Currently, little is known of the clinical utility of nebulized colistin in the general patient population. We report our experience with 21 patients who received nebulized colistin for the treatment of nosocomial pneumonia due to MDR pathogens.

Methods. We preformed a retrospective review of the case records of patients at our hospital (Singapore General Hospital, Singapore) who had nosocomial pneumonia and were treated with nebulized colistin. The patients were identified by cross-referencing the databases of the pharmacy and the microbiology laboratory. Pneumonia was diagnosed on the basis of a radiographic finding of a new and progressive pulmonary infiltrate and at least 2 of the following clinical criteria: a temperature of >38°C, leukocytosis (defined as a leukocyte count of >10,000 cells/μL) or leukopenia (defined as a leukocyte count of <4000 cells/μL), and clinical evidence suggestive of pneumonia (e.g., purulent bronchial secretions and decrease in oxygenation) [5]. Pneumonia was considered to be ventilator associated if onset occurred after receipt of mechanical ventilation for at least 48 h and the infection was judged not to have been incubating before the initiation of mechanical ventilation. Findings of Gram staining of tracheal aspirates were considered significant if there were ≥25 neutrophils and ≤10 epithelial cells per high-power field. In addition, diagnosis required that culture of a sputum or endotracheal tube aspirate specimen yielded *Acinetobacter baumannii* and/or *Pseudomonas aeruginosa* strains resistant to all available systemic antibiotics (β-lactams, quinolones, and aminoglycosides) tested, except the polymyxins. The severity of illness was assessed by APACHE II score determined at the onset of infection.

Patients were required to have received nebulized colistin therapy for ≥2 days to be evaluated. The primary outcome was clinical and/or microbiological cure. Clinical outcomes were classified as cure, improvement, failure, or indeterminate [6]. They were assessed at the time of discontinuation of therapy or at the time of discharge from the hospital, whichever was earlier. Microbiologic outcomes were classified as eradication, presumed eradication, presumed persistence, or indeterminate [6]. They were assessed on the basis of the results of culture(s) (if any) of specimens obtained from the original site of infection at any time during therapy. The following secondary outcomes were also assessed: crude mortality rate (all-cause mortality), attributable mortality rate (death related to pneumonia), number of days to defervescence, number of days to normalization of WBC count, length of stay in the hospital and/or intensive care unit, and occurrence of drug-related adverse effects. Renal function was monitored daily by measurement of the serum creatinine level. Acute renal failure was defined as a decrease in the estimated creatinine clearance rate of 50%, compared

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with the rate at the start of therapy, or a decline in renal function that necessitated renal replacement therapy.

Results. Between 1 June 2002 and 1 September 2004, there were 21 patients identified who received nebulized colistin sulphomethate (Colomycin; Pharmax) for the treatment of pneumonia due to MDR gram-negative bacteria. The patients were of various ethnicities: 17 were Chinese, 3 were Malays, and 1 was Indian. Three of the 21 patients had ventilator-associated pneumonia. Patients' demographic and clinical characteristics were as summarized in table 1. Pneumonia was due to MDR *A. baumannii* in 17 patients and was due to MDR *P. aeruginosa* in 4 patients. The dosage of nebulized colistin used for the majority of patients (19 of 21) was 1 million U (~80 mg) twice daily; 1 morbidly obese patient received 1 million U 3 times daily, and 1 burn patient received 1 million U 4 times daily. Each dose of colistin was reconstituted in 4 mL of normal saline and water for injection, according to the manufacturer's instructions, to obtain an isotonic solution, and each dose was nebulized immediately on reconstitution. The median duration of nebulized colistin therapy was 14 days (range, 2–36 days). Most patients were also receiving systemic antimicrobial therapy (e.g., carbapenems, piperacillin-tazobactam, aztreonam, sulfamethoxazole-trimethoprim, vancomycin, and/or ciprofloxacin) for concomitant infections at other sites, but none of these agents was active against the MDR pathogen isolated. None of the patients received concurrent parenteral colistin therapy.

Eighteen (85.7%) of 21 patients responded favorably to nebulized colistin therapy; the median duration of therapy for this group was 14 days (range, 5–36 days). Both favorable clinical outcomes (clinical cure or improvement) and favorable microbiological outcomes were observed in 12 patients (57.1%), and favorable microbiological outcome only was observed in another 6 patients. Of 18 patients with a favorable microbiological outcome 11 (61.1%) had documented eradication of the MDR pathogen, and eradication was presumed in the remaining 7 patients. Other pertinent outcomes are summarized in table 1.

Death due to any cause occurred in 10 of 21 patients, for a crude mortality rate of 46.7%. However, 7 patients cured of MDR bacterial pneumonia subsequently died of underlying and unrelated conditions (myocardial infarction in 2 patients; necrotizing fasciitis in 1 patient; advanced colon cancer in 1 patient; and multiorgan failure secondary to sepsis but unrelated to the

Table 1. Demographic and clinical characteristics and outcomes for a series patients who received nebulized colistin therapy for multidrug-resistant pneumonia.

Variable	Value
Patient characteristic	
Age in years	60.6 ± 15.0
Sex	
Male	12
Female	9
APACHE II score at baseline, mean ± SD (range)	23.1 ± 9.1 (6–40)
Length of stay	
In the hospital, mean days ± SD (range) (n = 21)	67.2 ± 49.5 (8–227)
In the intensive care unit, mean days ± SD (range) (n = 17)	69.3 ± 50.4 (8–157)
Etiologic agent	
Acinetobacter baumannii	17
Pseudomonas aeruginosa	4
Outcome	
Clinical success (cure or improvement), proportion of patients	12/21
Microbiological eradication	
Documented or presumed, proportion of patients	18/21
Documented, proportion of patients	11/21
Time to eradication, mean days ± SD (range) (n = 11)	11.6 ± 5.7 (3–21)
Defervescence	
Proportion of patients	11/16
Time to defervescence, mean days ± SD (range) (n = 11)	8.8 ± 4.9 (3–57)
Leukocytosis normalization	
Proportion of patients	11/16
Time to normalization, mean days ± SD (range) (n = 11)	13.1 ± 15.9 (3–57)
Discharge from hospital	11
Death	10

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episode of MDR bacterial pneumonia being reviewed in 3 patients). For 3 patients, death was deemed to be related to MDR bacterial pneumonia, for an attributable mortality rate of 14.3%. Most of the patients tolerated nebulized colistin therapy well. Two patients had underlying renal disease, but, in all patients, renal function before the start and after the end of nebulized colistin therapy did not differ significantly (i.e., the decrease in the estimated creatinine clearance, compared with the rate at the start of therapy, was <50%). No symptoms of neurotoxicity (e.g., facial paresthesia, vertigo, slurred speech, or confusion) were observed clinically during daily physical examinations. One patient suffered from bronchospasm likely associated with nebulized colistin therapy, which resolved on discontinuation of colistin therapy and initiation of symptomatic treatment with nebulized albuterol.

Discussion. The prevalence of multidrug resistance among gram-negative bacteria is rising at an alarming rate, rendering many antimicrobial agents ineffective. Recently, there has been much rekindled interest in using the polymyxin E and polymyxin B for the treatment of MDR gram-negative infections [7–10]. Despite a lack of data on efficacy and safety from randomized, controlled clinical trials, these agents have been recommended as viable therapeutic options for MDR nosocomial pneumonia and MDR ventilator-associated pneumonia in adults [5].

Most of the published experience on the use of colistin for the treatment of pneumonia has involved parenteral administration. Levin et al. [7] reported their experience with 60 patients who had nosocomial infections caused by MDR *P. aeruginosa* and MDR *A. baumannii*. Overall, a favorable outcome was observed in 58% of the patients. However, they noted a much lower rate of favorable outcome (25%) among patients with pneumonia. The reason for the less favorable outcome in this cohort was not specifically investigated, but it might have occurred because colistin given parenterally achieved inadequate concentrations in the epithelial lining fluid of the pulmonary parenchyma. Furthermore, renal dysfunction was repeatedly reported to be a major adverse effect associated with intravenous colistin therapy [7, 9, 10]. In view of these findings, nebulized colistin was thought to be a reasonable choice for therapy, to minimize systemic exposure, and to optimize the benefit-risk ratio of colistin therapy.

There are anecdotal reports regarding therapy with nebulized colistin in 3 patients [11] and 8 patients [12]. To the best of our knowledge, our study is the largest case series to date that attests to the efficacy and safety of nebulized colistin therapy in the general patient population. Consistent with previous findings, we noted a reasonably satisfactory clinical and/or microbiological response in majority of the patients who were otherwise untreatable with available antimicrobial agents. Moreover, we did not observe a significant incidence of renal dysfunction associated with nebulized colistin therapy. Although a favorable microbiological response was observed in 18 patients, a favorable clinical response was observed in only 12 patients. In the remaining 6 patients, the fever, leukocytosis, or chest x-ray findings did not resolve or improve; the reasons could be underlying illnesses and/or concomitant infections with other confounding pathogens not susceptible to colistin (e.g., methicillin-resistant *Staphylococcus aureus*).

We recognized that the true efficacy of nebulized colistin therapy could not be accurately assessed because of the lack of a control group. As with any retrospective study, the observed number of days to documented microbiological eradication, leukocytosis normalization, and defervescence were dependent on the frequency of sampling. Furthermore, the observed clinical outcomes (e.g., leukocytosis normalization and defervescence) were dependent on other coexisting infectious processes. In spite of that, our experience corroborates previous case reports that nebulized colistin might be a viable therapeutic option for pneumonia caused by MDR gram-negative bacteria. It also provides support for the recommendations in the guidelines on the management of nosocomial pneumonia [5]. Larger prospective clinical studies are warranted to further validate the efficacy and safety of nebulized colistin therapy.

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