

Utilization of colistin for treatment of multidrug-resistant *Pseudomonas aeruginosa*

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BACKGROUND: Colistin is uncommonly used in clinical practice; however, the emergence of multidrug-resistant organisms has rekindled interest in this potentially toxic therapeutic option. The present study describes the authors' experience with colistin in the management of patients who were infected with metallo-beta-lactamase (MBL)-producing *Pseudomonas aeruginosa* within the Calgary Health Region (Calgary, Alberta).

METHOD: Adult patients who received colistimethate sodium (colistin) between January 2000 and December 2005 were identified via pharmacy records, and their charts were reviewed retrospectively. Patients with cystic fibrosis were excluded. Patient demographics, clinical course and relevant laboratory data were extracted.

RESULTS: Twenty-eight courses of colistin were received by 22 patients. The majority of these treatments were directed at MBL-producing *Pseudomonas*. One-half of the patients received nebulized colistin. Intravenous (IV) colistin was administered to 12 patients for a mean \pm SD of 14.7 \pm 13.8 days (range 3.7 to 46 days). The highest IV dose used was 125 mg every 6 h or 6 mg/kg/day. Eight of 12 patients (67%) treated with IV colistin responded either fully or partially. Two patients received IV colistin as outpatients. Adverse effects considered to be due to colistin included drug fever, nephrotoxicity and neurotoxicity. Five of nine patients (56%) who had complete data available for evaluation had at least a doubling of creatinine levels from baseline.

CONCLUSION: Patients in the present study received both IV and nebulized colistin for multidrug-resistant *P. aeruginosa*. The use of IV colistin was associated with a favourable response, but mild nephrotoxicity occurred in two-third of patients. It was concluded that colistin may be a useful drug when choices are limited.

Key Words: Colistimethate; Colistin; Intravenous; Metallo-beta-lactamase; *Pseudomonas aeruginosa*

Despite its availability for decades, colistin is an antibiotic that has rarely been used in Canada. It is typically used as an agent of last resort because of its toxicity for the treatment of infections caused by multidrug-resistant organisms. In response to the emergence of multidrug resistance in *Pseudomonas*, *Acinetobacter* and *Stenotrophomonas* species observed in North America, Europe and Asia, colistin has

Utilisation de la colistine pour le traitement d'une souche multirésistante de *P. aeruginosa*

HISTORIQUE : La colistine est peu utilisée dans la pratique clinique; toutefois, l'émergence d'agents pathogènes multirésistants a suscité un regain d'intérêt pour cette option thérapeutique potentiellement toxique. La présente étude vise à décrire l'expérience des auteurs avec la colistine dans la prise en charge des patients qui ont contracté une infection à *P. aeruginosa* produisant des métallobétalactamases (MBL), dans la région sanitaire de Calgary (Calgary, Alberta).

MÉTHODE : Les auteurs ont recensé les patients adultes ayant reçu du colistiméthate sodique (colistine) entre janvier 2000 et décembre 2005 à partir des dossiers des pharmacies et ils ont analysé leurs dossiers rétrospectivement. Les patients atteints de mucoviscidose ont été exclus. Les auteurs ont extrait les données démographiques, l'évolution clinique et les résultats d'analyses de laboratoire pertinentes des patients.

RÉSULTATS : Vingt-huit traitements par colistine ont été administrés à 22 patients. La majorité de ces traitements ciblaient une infection à *Pseudomonas* produisant des MBL. La moitié des patients ont reçu la colistine en nébulisation et 12, par voie intraveineuse, pendant une moyenne \pm É.-T. de 14,7 \pm 13,8 jours (de 3,7 à 46 jours). La dose i.v. la plus forte administrée à été de 125 mg toutes les six heures ou de 6 mg/kg/jour. Huit patients sur 12 (67 %) traités avec la colistine par voie i.v. ont présenté une réponse partielle ou complète. Deux patients ont reçu leur colistine i.v. sans être hospitalisés. Les effets secondaires jugés attribuables à la colistine ont été la fièvre d'origine médicamenteuse, la néphrotoxicité et la neurotoxicité. Cinq patients sur neuf (56 %) pour lesquels on disposait de données évaluables complètes ont présenté un taux de créatinine au moins deux fois plus élevé qu'au départ.

CONCLUSION : Les patients de la présente étude ont reçu de la colistine en nébulisation et par voie i.v. pour une infection à *P. aeruginosa* multirésistante. L'emploi de la colistine par voie i.v. a été associé à une réponse favorable, mais une légère néphrotoxicité a affecté les deux tiers des patients. Les auteurs ont conclu que la colistine pouvait être utile comme agent thérapeutique lorsque les choix sont limités.

been increasingly used in recent years (1-9). Colistin, also known as polymyxin E, is a cyclic amphipathic antibiotic with a molecular mass of approximately 1000 Da (10). It interacts strongly with phospholipids and kills bacteria by disrupting their cell membranes (11). Colistimethate sodium (also known as colistin methanesulfonate [CMS]) is formulated for parenteral use because it is less toxic than colistin. The salt must

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be hydrolyzed to release the active free base, which occurs at body temperature and at physiological pH in aqueous systems (12). In the Calgary Health Region (Calgary, Alberta), vials of Colistimethate for Injection U.S.P (SteriMax Inc, Canada) are used, which provide the equivalent of 150 mg colistin base per vial (acquisition cost \$60 per vial).

Recent outbreaks of metallo-beta-lactamase (MBL)-producing *Pseudomonas aeruginosa* infections that occurred within the Calgary Health Region (13-15) resulted in a concomitant increase in the utilization of colistin. Given the limited Canadian experience with colistin use, the objective of the present study was to describe the authors' experiences with it – specifically, to determine the frequency of colistin use for the treatment of multidrug-resistant bacteria in the adult population, describe the route by which colistin was administered, determine whether adverse events occurred and assess response when colistin was used alone or in combination in the treatment regimen. The authors' experiences with this drug may be useful to others who have to consider the utility of colistin because of limited therapeutic options in the management of infections due to multidrug-resistant organisms.

METHODS

Identification of cases and data collection

The present retrospective, descriptive chart review included all adult patients hospitalized in the Calgary Health Region who were treated with colistin (Colistimethate for Injection U.S.P equivalent to 150 mg colistin base per vial) between January 2000 and December 2005. Patients younger than 18 years of age were excluded, as well as those who received nebulized colistin for suppression of colonizing organisms in patients with cystic fibrosis or bronchiectasis. A single regional pharmacy database (Centricity Pharmacy, version 8.0 [GE Healthcare, USA]) was used to identify all patients who received colistin during the study period. Medical records were screened for therapy of at least three days duration. Empirical use of colistin of less than three days duration was noted for completeness, but no data were abstracted from these records. One of the investigators (DS) retrospectively reviewed all of the charts and abstracted the following data for each course of treatment – demographic information, hospital service, colistin regimen, allergies, renal support, underlying diseases and length of stay. Relevant concurrent antibiotics and the use of concomitant potentially nephrotoxic drugs (aminoglycosides, acyclovir and cyclosporin) were also recorded (using a criterion of one-day overlap). With the recognition that the majority of the cases were hospital-acquired, infections for which colistin was prescribed were categorized using a modification of the 2004 Centers for Disease Control and Prevention definitions for nosocomial infections (16).

Microbiology

Microbiological data that were retrieved included causative organism(s) isolated from the site(s) of infection, the date of isolation and the *in vitro* susceptibilities to antibiotics, including colistin. Identification of all causative microorganisms was performed using routine microbiological methods at the Calgary Laboratory Services (Calgary, Alberta). All organisms, including imipenem-resistant strains of *P. aeruginosa* (minimum inhibitory concentration of 8 µg/mL or greater), were identified to the species level using the Vitek system (Vitek AMS, bioMérieux Vitek Systems Inc, USA). Since 2002, the production of MBL

was confirmed using a combination of an EDTA screen test and a MBL Etest (15). Antimicrobial susceptibilities were determined using microdilution panels (Microscan Gram-negative NMIC30, Dade Behring Canada Inc) and the disk diffusion technique using the Clinical and Laboratory Standards Institute criteria (17) for broth dilution and disk diffusion, respectively. In the case of colistin, isolates were considered susceptible if the inhibition zone was 11 mm or greater by disk diffusion (10 µg colistin sulphate disk).

Outcome definitions

For all patients receiving intravenous (IV) colistin, available serial serum creatinine values were recorded. Nephrotoxicity was defined as a peak serum creatinine level increase of 50% above the baseline level during treatment or as a decline in renal function requiring renal replacement therapy. Creatinine values were recorded at the time of colistin initiation (baseline); the highest creatinine value attained during colistin therapy and the creatinine value that was obtained within four days of the end of colistin therapy were recorded as well. Tolerance to colistin was assessed by reviewing the occurrence of potential adverse events documented in the patient chart. All reported symptoms were recorded as potential adverse events if the event followed a reasonable temporal sequence from administration of the drug, and a known or expected response pattern to the drug. Chart notations were reviewed for new dizziness, numbness, acral paresthesia, circumoral paresthesia, lack of coordination, unsteadiness, muscle weakness, pain at the injection site, chest wheezing and tightness.

Progress notes were followed up until the end of treatment for the determination of outcome based on clinical criteria and the evaluation by the attending physician. The clinical criteria used in the evaluation included resolution of clinical signs and symptoms, including fever, leukocytosis and improvement of diagnostic investigations where appropriate. With consensus agreement, based on clinical and microbiological data, patient outcomes were classified as favourable, unfavourable or indeterminate. A 'favourable response' was defined as complete or partial resolution of presenting symptoms and signs by the end of treatment, and an 'unfavourable response' was defined as persistence or worsening of presenting symptoms and signs or death occurring during treatment. An 'indeterminate response' was recorded when clinical assessment was not possible. The study was approved by the ethics review board of the University of Calgary (Calgary, Alberta) and the Calgary Health Region. Microbiological eradication or presumed microbiological eradication was considered present if repeat cultures were negative or if no follow-up cultures were clinically indicated.

RESULTS

A structured query of the pharmacy database revealed that 45 patients had orders recorded for colistin, for either inpatient or home use. The following patients were excluded – 13 patients who were younger than 18 years of age, four patients because a review of their medical records could not confirm that they had received the drug and three patients who received nebulized colistin for suppression of colonizing organisms or who received oral colistin for typhilitis. Three patients received IV colistin empirically for less than three days, and they were also excluded. Of the

TABLE 1
Summary of patients who received at least three days of intravenous colistin (COL) from 2000 to 2005

Patient	MBL*	Age, years	Site of care	Susceptibility profile of organism	Days on COL (n)	Infection	COL base equivalent			ME	Creatinine increase (%)	Other adverse effects
							Regimen	mg/kg/day†	Outcome			
1	Yes	33	ICU	Empirical	18.4	PNU2	100 mg q8h	4.6	Ind, died	Yes	30	Diarrhea
2	No	66	LTC	S: CAZ R: PIP, TZP, AG, CIP	5.8	SUTI	75 mg q8h 50 mg q8h	2.9	U, died	Yes	141	
3	Yes	49	HD	S: COL R: PIP, TZP, CAZ, FEP, AZT, AG, CIP	8.8	BONE	80–85 mg post-HD	N/A	F, home	No	N/A	
4	Yes	61	ONC	S: PIP, TZP, AZT, COL R: AG, CIP; I: FEP	8.5	LCBI	150 mg q36h	N/A	F, home	Yes	15	Neurotoxicity
5	No	21	AMB	S: PIP, CAZ, IPM; I: AZT	46.0	SUTI	50 mg q8h	2.9	Ind, home	No	N/A	–
6	Yes	51	ONC	S: PIP, TZP, AZT, COL R: CAZ, AG, CIP	7.9	LCBI	100 mg q6h 75 mg q8h	5.3	U, died	Yes	143	Neurotoxicity, GI
7	Yes	80	GEN	S: COL I: AZT R: PIP, TZP, FEP, CAZ, AG, CIP	4.7	SUTI	75 mg q8h	4.2	F, home	Yes	170	Drug fever, anorexia, nausea
8	Yes	47	GEN	I: COL R: PIP, TZP, CAZ, AG, CIP	9.6	SUTI	50 mg q8h 75 mg q8h	2.8	F, home	No	319	Neurotoxicity, drug interaction
9	No	49	AMB	Empirical	38.0	SUTI	50 mg q8h 50 mg q12h	2.1	F, home	Yes	N/A	Anorexia, myalgia
10	Yes	55	ONC	S: PIP, AZT, COL R: CAZ, AG, CIP	5.6	LCBI	75 mg q12h	2.7	F, home	Yes	1.5	Nausea
11	Yes	64	ICU	S: TZP, AZT, COL R: AG, CIP	3.7	PNU1	75 mg q8h	3.5	F, home	Yes	19	–
12	Yes	46	ICU	S: COL R: PIP, CAZ, AG, CIP	19.7	PNU2	125 mg q6h	6.0	F, home	Yes	100	Neurotoxicity

*Metallo-beta-lactamase (MBL)-producing *Pseudomonas aeruginosa* (resistant to imipenem [IPM] and meropenem). The most frequently encountered minimum inhibitory concentrations were as follows – piperacillin (PIP) 32 µg/mL (susceptible [S]), PIP/tazobactam (TZP) 16 µg/mL (S), ceftazidime (CAZ) 32 µg/mL (resistant [R]), cefepime (FEP) 16 µg/mL (intermediate [I]), aztreonam (AZT) 8 µg/mL (S), gentamicin greater than 128 µg/mL (R), tobramycin greater than 128 µg/mL (R), amikacin 64 µg/mL (R), ciprofloxacin (CIP) 64 µg/mL (R); †Using ideal/lean body weight. AG Aminoglycosides; AMB Ambulatory outpatient; BONE Osteomyelitis; F Favourable; GEN General ward; GI Gastrointestinal; HD Hemodialysis; Home Discharged home; ICU Intensive care unit; Ind Indeterminate; LCBI Laboratory-confirmed bloodstream infection; LTC Long-term care unit; ME Microbiological eradication; N/A Not available or not applicable; ONC Hematology/stem cell transplant unit; PNU1 Clinically defined pneumonia; PNU2 Pneumonia and specific laboratory findings; q Every; SUTI Symptomatic urinary tract infection; U Unfavourable

remaining 22 patients, 12 received IV colistin and are presented in Table 1. Two of these patients also received nebulized colistin, one as step-down therapy, and the other received both IV and nebulized routes separated in time. During the study period, a total of 12 patients received nebulized colistin and are presented in Table 2. Of the 22 patients, the mean ± SD age was 53±13 years; 23% were female. Four of the patients died in the hospital and 18 patients were discharged.

All of the MBL-producing *Pseudomonas* isolated were susceptible to colistin and were variably susceptible to aztreonam and piperacillin/tazobactam. All of the strains were resistant to aminoglycosides, quinolones and carbapenems. Other than resistance, reasons for initiating colistin included pending susceptibility reporting, empirical use, the presence of multiple drug allergies and clinical failure with other antibiotics.

The majority of patients treated with IV colistin received either 50 mg or 75 mg of colistin (base equivalent) every 8 h; the average dose used was 3.7 mg/kg/day. The highest dose used was 125 mg of IV colistin (base equivalent) every 6 h. The infections which were treated with colistin included urinary tract infection

(five cases), pneumonia (three cases), bacteremia (three cases) and one case of osteomyelitis. Excluding empirical therapy, the duration of IV therapy averaged 14.7±13.8 days. Eight (66.7%) of the 12 patients who received IV colistin had favourable outcomes and were eventually discharged home. Two patients had an indeterminate outcome. Nine patients (75%) receiving IV colistin were treated for MBL-producing *Pseudomonas* infections (either presumptively or confirmed), and seven (77.8%) of these patients had favourable outcomes and survived. When used for MBL-producing *Pseudomonas* infections, all of the patients received concurrent antibiotic therapy, usually with either piperacillin/tazobactam or aztreonam.

Unfavourable responses were observed in two of the 12 patients given IV colistin. One was a patient (patient 2) with advanced multiple sclerosis who had allergies to multiple antibiotics. Urine cultures revealed a multiply resistant OXA-type beta-lactamase-producing *P aeruginosa* and *Enterobacter* species. The other patient (patient 6) had an acute hematological malignancy and had received an allogeneic stem cell transplant from an unrelated donor. MBL-producing *P aeruginosa* was cultured from both blood and urine.

TABLE 2
Summary of patients who received at least three days of nebulized colistin (COL) for pneumonia

Patient	MBL*	Age, years	Site of care	Susceptibility profile of organism	Days on COL, n	COL base equivalent		Microbiological eradication	
						Regimen	mg/kg/day [†]	Outcome	eradication
1	Yes	49	ICU	Not available	10.0	150 mg bid	4.3	F, home	Yes
2	Yes	43	ICU	Not available	20.0	75 mg q8h	3.1	F, home	Yes
3	Yes	68	ICU	S: COL R: PIP, TZP, AG, CIP	16.5	150 mg bid	4.2	F, home	No
4	NC	48	ICU	S: PIP, CAZ, AG R: CIP	6.5	150 mg bid	5.1	F, home	Yes
5	Yes	37	ONC	S: PIP, TZP, AZT, COL R: AG, CIP; I: CAZ	6.7	50 mg tid	2.5	U, home	Yes
6	NC	51	ONC ICU	Not available	13.1	150 mg bid	4.2	F, home	Yes
7	Yes	54	ICU	S: COL R: PIP, CAZ, AZT, AG, CIP	22.5	150 mg bid	7.8	Ind, died	No
8	Yes	59	ICU	Not available	16.8	150 mg bid	3.3	F, home	Yes
9	No	60	GEN	Not available	59.1	150 mg bid	6.0	Ind, home	No
10	No	44	GEN	S: AG, CIP, COL; I: FEP R: TZP, CAZ, AZT	3.6	80 mg bid	3.7	U, home	Yes
11	Yes	64	ICU GEN	See Table 1	4.9	75 mg q8h	3.5	F, home	Yes
12	Yes	46	ICU	See Table 1	25.2	150 mg bid	3.6	F, home	Yes

*Metallo-beta-lactamase (MBL)-producing *Pseudomonas aeruginosa* (resistant to imipenem and meropenem). Isolates 4 and 6 were obtained before 2002, and were not confirmed with EDTA testing. The most frequently encountered minimum inhibitory concentrations were as follows – piperacillin (PIP) 32 µg/mL (susceptible [S]), PIP/tazobactam (TZP) 16 µg/mL (S), ceftazidime (CAZ) 32 µg/mL (resistant [R]), cefipime (FEP) 16 µg/mL (intermediate [I]), aztreonam (AZT) 8 µg/mL (S), gentamicin greater than 128 µg/mL (R), tobramycin greater than 128 µg/mL (R), amikacin 64 µg/mL (R), ciprofloxacin (CIP) 64 µg/mL (R); [†]Using ideal/lean body weight. AG Aminoglycosides; bid Twice a day; F Favourable; GEN General ward; Home Discharged home; ICU Intensive care unit; Ind Indeterminate; NC Not confirmed; ONC Hematology/stem cell transplant unit; q Every; tid Three times a day; U Unfavourable

The available data for pretreatment and post-treatment renal function were recorded for all IV colistin courses of at least three days duration. With the exception of one patient on hemodialysis (patient 3), all others had a normal baseline creatinine level (lower than 115 µmol/L) at the time of colistin initiation. Nephrotoxicity was observed at the end of colistin treatment compared with the baseline value in five of nine patients who could be evaluated. No correlations between dosage of colistin and nephrotoxicity could be made in the present case series. Death occurred in two of six patients with deterioration of renal function; both patients had normal baseline creatinine values. Potential neurotoxicity may have occurred in four instances of IV colistin use, although, in one of the cases (somnolence, patient 8), gabapentin, baclofen and tizanidine were used concurrently. Patient 4 had received fludarabine for a second allogeneic stem cell transplant (relapsed myelodysplastic syndrome) and cyclosporine concurrent with colistin before developing dizziness and vertigo, but magnetic resonance imaging revealed findings consistent with progressive multifocal leukoencephalopathy. The patient's health continued to deteriorate and he developed cortical blindness, progressive paraparesis and increasing weakness, but was eventually transferred from critical care to a medical ward. Finally, patient 12, who received the highest dose of colistin (equivalent of 500 mg colistin base/day or 13 million units [MU]/day in a 46-year-old man weighing 84 kg, with normal renal function) developed encephalopathy and respiratory muscle weakness, for which no organic cause could be identified.

Of the 12 patients who received inhaled colistin, 11 met the criteria for pneumonia, including seven cases due to MBL-producing *Pseudomonas* and one due to *Stenotrophomonas* species. Six of the patients who received colistin solely via nebulization had favourable responses. Two patients had unfavourable responses. One patient who had not met the criteria for definite pneumonia had an indeterminate response. One patient receiving nebulized colistin had care withdrawn. Patients receiving colistin only via the nebulized route did not have any increases in serum creatinine levels. Foaming with nebulization of colistin was noted. Finally, one patient with a history of asthma experienced wheezing and recurrent substernal chest tightness during colistin therapy, which was partially alleviated with an inhaled beta-agonist.

DISCUSSION

The present report focuses on our observational retrospective experience with the use of colistin involving a total of 28 courses of colistin in 22 adult patients. The mean IV dose observed in our case series was equal to 3.7 mg colistin base/kg/day (111,111 U/kg/day), which is concordant with manufacturer recommendations. There can be considerable confusion related to the labelling and dosing of colistin. Each vial of product contains approximately 400 mg of sodium CMS, which is equivalent to approximately 5 MU or 150 mg of base (18). The product monograph from the manufacturer and other references recommend colistin doses equivalent to 2.5 mg base/kg/day to 5 mg base/kg/day (based on lean body weight) for patients with normal renal function. Excluding

TABLE 3
Proposed adult dosing guidelines for colistin (as base equivalent)

Creatinine clearance	>90 mL/min	60–90 mL/min	30–60 mL/min	<30 mL/min
Divided doses	100 mg IV q8h (up to 100–125 mg IV q6h)	75–100 mg IV q12h	75–150 mg daily or q12h	100–150 mg IV q36h
Total daily	5 mg/kg/day	2.5–3.8 mg/kg/day	2.5 mg/kg/day	1.5 mg/kg/day

IV Intravenous; q Every

patients 3 and 4, the regimens in our case series averaged 7.6 MU/day or 605 mg/day CMS, or the equivalent of 227 mg colistin base/day. These doses are higher than those described by others, including the study by Levin et al (9), in which the mean dose of colistin base was 153 mg/day, as well as the study by Berlana et al (8), in which the mean dose was 2.7 MU/day. One study (6) of critically ill patients in Greece used higher doses, reporting an average daily dose of 9 MU or 270 mg of colistin base. Our cohort of intravenously treated patients had a mean \pm SD age of 53 ± 13 years; one-half were being treated in a critical care or bone marrow unit.

A favourable response (complete or partial resolution) was observed in 67% (eight of 12) of patients receiving IV colistin in our series. Similar outcomes ranging from 52% to 73% have been reported in patient populations similar to ours (6,9,19,20). We acknowledge the limitation in our series – attributing the response to colistin alone, although other antibiotics were used in these complicated patients. Consequently, no correlations may be made with respect to the dosages used and the outcomes achieved. All of the patients who were treated for MBL-producing *P aeruginosa* were administered at least one other active antibiotic, usually aztreonam or piperacillin/tazobactam. However, colistin has been used in combination with other agents in other studies. In addition, the effect of colistin in combination against multidrug-resistant Gram-negative organisms appears promising in vitro (21,22). One time-kill curve analysis (23) showed synergy and/or additivity with the combinations of colistin, and cefepime, colistin and piperacillin/tazobactam at 24 h in three of four carbapenem-resistant strains of *P aeruginosa*. One clinical trial (24) on the effectiveness of colistin in pulmonary exacerbations of infections due to *P aeruginosa* in patients with cystic fibrosis showed that the combination of colistin with an antipseudomonal agent was more effective than colistin alone.

Of those who received IV colistin, 56% (five of nine patients) experienced nephrotoxicity. However, all but one of the patients who developed nephrotoxicity received at least one other potentially nephrotoxic drug within three days of receiving colistin. This rate of toxicity is in keeping with what has been reported previously, with nephrotoxicity ranging from 14% to 58% (6,9,25). Potential neurotoxicity may have occurred in four instances of IV colistin use; although, in one of the cases, other potentially neurotoxic agents were used concurrently. The occurrence of neurotoxicity with colistin is difficult to evaluate, especially in patients with renal failure, those with variable serum levels and in patients receiving concurrent potentially neurotoxic drugs. All four of our patients had impaired renal function. Only mild transient neurological features (numbness, tingling and muscle weakness) were noted

when IV colistin sulphomethate (6 MU/day) was used as monotherapy in 33 adults with cystic fibrosis and normal renal function (24).

During the study period, colistin was administered off-label via nebulization in 12 patients who did not have cystic fibrosis. The most frequently used regimen was the equivalent of 150 mg colistin base (5 MU) every 12 h. Patients treated with nebulized colistin generally had clinically defined pneumonia, or were empirically treated when MBL-producing *P aeruginosa* was isolated from tracheobronchial secretions or sputum samples with a presentation of fever and leukocytosis. We observed a favourable response in 67% of patients. A preliminary study (26) recently showed that aerosolized colistin (1 MU every 8 h) reduced microbial counts and eliminated microbial growth of multidrug-resistant *P aeruginosa* by day 6 in five mechanically ventilated patients who did not have cystic fibrosis. No serious toxicities from nebulized administration were noted in our series. It is recommended that nebulized agents be administered after bronchodilator use to ensure maximum drug deposition and to protect against bronchoconstriction, which may occur.

MBL-producing *P aeruginosa* was the causative pathogen in 15 patients who received colistin. Consistent with reports in the literature, no strains were resistant to colistin, although colistin resistance with other organisms has been reported in Europe (27). We have previously shown that MBL-producing *P aeruginosa* strains are associated with a higher case-fatality rate and invasive disease (14). Hence, it is important to further examine the role of colistin for these serious infections.

It is acknowledged that a small case series has scientific limitations. However, to our knowledge, the present study is the first collated case series of colistin use in Canada, and our observations suggest that it is reasonable to continue to evaluate the use of this drug. Proposed dosing guidelines for colistin base are presented in Table 3. The use of IV or nebulized colistin for the treatment of infections due to MBL-producing *Pseudomonas* species or other multidrug-resistant pathogens, including carbapenem-resistant *Klebsiella pneumoniae*-producing KPC-3, appears to be relatively safe and may have an important therapeutic role when options are limited due to resistance or allergy (28–30). More prospective studies are needed to delineate the dosing, routes of administration toxicities and the precise therapeutic role of colistin for infections in these settings.

The current work was presented (abstract L3), in part, at the 2006 Annual General Meeting of the Association of Medical Microbiology and Infectious Diseases Canada and the Canadian Association of Clinical Microbiology and Infectious Diseases. Victoria, British Columbia, March 16 to 19, 2006.

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