Use of Colistin in a Pediatric Burn Unit in Argentina

Maria Rosanova, MD, Carolina Epelbaum, Alejandro Noman, MD, Mabel Villasboas, Veronica Alvarez, Griselda Berberian, Norma Sberna, Gabriela Mudryck, Roberto Lede

The use of sulmone methate sodium colistin for the treatment of infections caused by multiple drug resistant (MDR) Gram-negative microorganisms were studied in a burn unit to evaluate the safety of this drug. Prospective chart review of pediatric patients treated with intravenous colistin in a tertiary burn unit between January 2005 and December 2006. Forty-five courses of intravenous colistin treatment administered to 45 children were evaluated in the study period. Fourteen patients (31%) were infected by Pseudomonas aeruginosa spp and 20 patients (44.5%) by Acinetobacter spp and an association of both bacteria was found in six patients (13.5%). The mean age of the patients was 52 months (range, 2 to 360 months), and 28 patients (62%) were men. The percentage of burnt body surface was between 9 and 87% (mean, 38%). Forty patients (89%) were infected by MDR organisms. Colistin was empirically indicated in five patients (11%) with burn wound sepsis 7 days after admission to the unit despite negative cultures. Burn wound sepsis was the most frequent focus of infection in 19 patients (42%). In 14 patients (31%), burn wound infection occurred without sepsis. Intravascular catheter-related bacteremia occurred in three patients (7%) and bacteremia in one (2%). Three patients had pneumonia (7%), three osteomyelitis (7%), and two urinary tract infection (4%). The length of treatment with colistin was between 3 and 92 days (median, 21 days). Only one patient (2%) died for reasons other than infection. None of the children developed increases in serum creatinine concentrations or neurological complications during treatment with colistin. Colistin seems to be a safe drug in selected cases of infections with MDR Gram-negative microorganisms. Further studies are needed to confirm these results. (J Burn Care Res 2009;30:000–000)


METHODS

Type of Study: Observational and Prospective Study

Inclusion Criteria. We included all patients admitted to our burn unit treated with intravenous colistin between January 2005 and December 2006. Patients had documented infections by multiple-resistant microorganisms only susceptible to colistin or, in some cases were empirically treated for sepsis, pending culture results.

Dosage. The dosage of colistin was 5 mg/kg/day (maximum 160 mg/kg/every 6 hours).

Data Collection. Prospective chart review by the first author. We evaluated age, sex, type of burn, percentage of burnt body surface, presence of inhalation injury, depth of burns (presence of full thickness), invasive procedures, hydrotherapy, surgery, parenteral nutrition, microorganisms, site of isolation, days of treatment, neurological or renal complications, days of colistin administration, and adverse effects. Blood, wound, and urine cultures were obtained when appropriate, according to the patients’ clinical features.

Diagnosis of infection was based on clinical data and/or the isolation of microorganisms. Definitions of infectious complications were used according to Pruitt and Yurt as described in the article by Rodgers et al12 and the American Burn Association Consensus Conference1,13 with some modifications. Burn wound infection was diagnosed when local signs of infection were present and/or biopsy cultures were positive. Burn wound sepsis was defined as an evidence of burn wound infection concurrent with organ dysfunction in association or not with bacteremia. Catheter-associated infection was defined as a positive blood culture in a patient with catheter without any other source of infection. Bacteremia was defined as a positive blood culture in a patient without catheter and no evidence of organ dysfunction or extravascular infection. The other infections were defined according to the Centers for Disease Control and Prevention.11,12 Multiple organ dysfunction syndrome was defined according to the American Burn Association Consensus Conference.13

Susceptibility testing was performed according to the Clinical Laboratory Standard Institute, using automated methods. We considered that organisms were multidrug resistant, when they were resistant to three or more groups of antibiotics (β-lactam, aminoglycosides, quinolones, and carbapenems).6,8–10 Colistin sensitivity was tested in all cases. On isolation of strains of Pseudomonas spp and/or Acinetobacter spp that were resistant to all antibiotics but colistin, intravenous colistin sulfomethate sodium was initiated.

Nephrotoxicity was defined as an increase in creatinine levels above the normal value for age according to the Argentinean Society of Pediatrics (Committee of Nephrology).14 Serum creatinine levels (mg/%) were measured on initiation of therapy and every week until colistin treatment was completed. We clinically evaluated the appearance of neurological abnormalities such as seizures, vertigo, dizziness, muscle weakness, facial and peripheral paresthesia, confusion, ataxia, and neuromuscular blockage that were most frequently reported in the literature.5,7,9 Outcome was measured evaluating negative cultures and clinical features such as defervescence of fever.

Statistical Analysis

Data were summarized in frequency and percentage for categorical variables and as mean and range for continuous variables. Analysis of variance was used to compare means related with creatinine levels prior and post use of colistin.

RESULTS

Forty-five patients were included in the study. Of these, 28 (62%) were men. The mean age was 68 months (range 2–168 months). The burnt body surface area was between 9 and 87% (mean 38%). Full thickness was present in 17 patients (38%), inhalatory injury was present in 20 patients (44.5%), hydrotherapy was used in 41 patients (91%), and parenteral nutrition was received by five patients (11%). All patients had previously received antibiotics other than colistin because of other infections and concomitant with colistin, because of copathogens.

Forty-three patients (96%) had a central venous catheter as well as a bladder tract catheter and required surgical procedures (Table 1). MDR organisms were isolated in 40 patients (89%). In five children (11%), colistin was indicated empirically because of clinical burn wound sepsis and because of the epidemiology of our burn unit at that time, while waiting for culture results. The length of treatment was between 3 and 92 days (mean, 25 days; Figure 1).

The isolated microorganisms were Acinetobacter spp in 20 patients (44.5%); Pseudomonas spp in 14 patients (31%), and an association of both in six patients (13.5%). A total of 45 courses of colistin were given for the different infections (see Table 2). None of the patients showed increase in urea or creatinine levels or neurological impairment during treatment with colistin. Only two patients had increased levels of creatinine caused by the burns and sepsis on admission. To avoid mistakes with the interpretation of the results, these two patients with abnormal values of
creatinine prior treatment with colistin were excluded from the analysis of variance.

These patients had acute renal failure secondary to burns and septicemia, and after stabilization and during colistin treatment creatinine levels became and remained normal. In the analysis of variance, the results in 43 patients were as follows:

Creatinine levels prior colistin: mean 0.432 (variance 0.14), and post colistin: mean 0.375 (variance 0.021), $F$ statistic: 3.99 and $P = .0488$ (Figure 2).

The outcome was favorable in 44 patients (98%).

One patient (2%) died for reasons not related with infection or colistin administration.

**DISCUSSION**

Colistin is a polypeptide antibiotic of the polymixin group that is rapidly bactericidal to Gram-negative bacteria. This drug has a detergent-like mechanism interfering with the outer cytoplasmic membrane of the bacteria.\(^1\)-\(^5\) Colistin remains active against almost all strains of *Pseudomonas aeruginosa* and *Acinetobacter* spp. Acquired resistance is rare.\(^3\)

The emergence of multiresistant Gram-negative and β-lactamase positive microorganisms is a great concern in patients admitted to critical areas like intensive care and burn units.\(^1\),\(^4\),\(^10\) This problem has resurged the use of colistin as a therapeutic option in special situations. Only polymixin B and E (colistin) are used in clinical practice.

In the 1980s, colistin was abandoned because of renal and neurological toxicity.\(^5\)-\(^7\) Renal toxicity was associated with increased serum levels of urea and creatinine, crystalluria, tubular necrosis, and renal failure.\(^1\),\(^5\),\(^7\),\(^10\) Neurological problems reported were vertigo, seizures, ataxia, confusion, apneas, neuromuscular blockade, and dizziness among others.\(^5\),\(^7\),\(^9\) These adverse effects are reversible with drug discontinuation.

Studies on the clinical and microbiological success rate of colistin in the pediatric burn population are scarce.\(^3\) Clinical efficacy was reported to be 60 to 80%, but was poor when the foci were supplicative lung and bone infections. This is possibly due to poor concentration of colistin at these sites.\(^7\)-\(^10\) In a retrospective review of 15 years in 14 burned children,
Goverman et al\(^1\) reported 14.3% of renal disturbances and no neurological events. Clinical efficacy was 79%.

In adult patients, the reported nephrotoxicity rates are variable, between 0 and 37%; the reported neurotoxicity rates range between 0 and 14%.\(^2\)–\(^10\) Other less common adverse effects are rash, allergies, and bronchial obstruction if aerosolized colistin is used. Unlike other studies, none of our patients developed adverse events related to colistin. This may be due to the fact that our hospital is a tertiary referral center. The intensive care burn unit is specialized in the management of very complex patients. Adequate liquid management and correct intensive care support may have protected the kidneys from toxicity. We avoided (when possible) the use of other drugs with renal toxicity during the treatment with colistin. We carefully checked the dosage in each patient and we stopped the treatment as soon as it was possible.

Most of the studies are retrospective reports, in adult populations, and with few burn patients. Our study was prospective and only included pediatric burn patients. However, the lack of a control group and the use of concomitant drugs with colistin does not allow for a definitive conclusion regarding the clinical effectiveness of colistin.

**CONCLUSION**

Colistin is a safe drug in carefully selected patients in burn units with infections with MDR Gram-negative microorganisms when no other drug is available. Further studies with larger numbers of patients and control groups are necessary to confirm these results.

**ACKNOWLEDGMENTS**

We thank Janneke Deurloo and David Bes for the revision of the manuscript.

**REFERENCES**