Colistin, an Old Drug in a New Territory, Solid Organ Transplantation

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ABSTRACT

Background. The clinical experience with colistin therapy for multidrug-resistant Gram-negative pathogens in solid organ transplantation is limited.

Methods. Patients transplanted from January 2003 to July 2011 and treated with intravenous or nebulized colistin were included. Descriptive statistics were used to summarize patients' characteristics and Kaplan-Meier curves for survival analysis.

Results. Fifteen patients were included: 10 adults (median age, 54.6 y; range, 32.2–79.6 y) and 5 children (median age, 3.3 y; range, 1.1–10.4 y). Eight patients had intra-abdominal infections, 3 had pneumonia, and 4 had bacteremia. The infections were diagnosed at a median of 5.9 months (range, 0.8–49.8 mo) after transplantation. Eight patients had coinfections, mainly with enteric pathogens. *Pseudomonas aeruginosa* was isolated in 13 cases and ESBL *Klebsiella oxytoca* and ESBL *Escherichia coli* were isolated in 1 case each. Thirteen patients received concomitant antibiotics with colistin. The median dose of intravenous colistin (13 patients) was 2.7 mg/kg/d (range, 1–4.9 mg/kg/d) and nebulized colistin (2 patients) was 241.7 mg/d (range, 150–333.3 mg/d). Clinical cure was achieved in 9 patients (60%). Four-week survival rate after infection was 86.7% (95% confidence interval, 56.4%–96.5%). There was no difference in the median creatinine clearance in adults ($P = .38$) or children ($P = .88$) before and after colistin. One patient had both neurotoxicity and nephrotoxicity, and 1 patient had neurotoxicity only.

Conclusions. Colistin might be used as an alternate therapy for transplant patients with multidrug-resistant Gram-negative pathogens.

IN the past 2 decades, the SENTRY and MYSTIC surveillance programs have monitored antimicrobial resistance to identify resistance mechanisms, clonal spread, and relationship to local antibiotic use as well as to rank the susceptibility of the currently available agents for empiric treatment of serious Gram-negative bacterial infections [1,2]. The polymyxins, including colistin or polymyxin E, retained good in vitro activity against Gram-negative organisms, including those with reduced susceptibility to carbapenems, but resistance is trending upward, especially in regions where polymyxins are heavily prescribed owing to carbapenem resistance [1]. There are no systematic surveys to define the rate of infection with multidrug-resistant Gram-negative organisms in solid organ transplantation and its change over time. However, it would be expected that the rate of infection with these organisms would be higher in solid organ transplant recipients than in the general population, because these patients have frequent contact with the health care system, have multiple and prolonged hospital admissions, are exposed to multiple antibiotic agents, and require repeated surgical or invasive procedures. With the increasing incidence of multidrug-resistant Gram-negative pathogens and limited therapeutic options, there has been renewed interest in the use of colistin.

The recently published American Society of Transplantation guidelines [3] lists colistin as one of the

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treatment options for ESBL and carbapenemase-producing *Enterobacteriaceae*, *Acinetobacter*, multidrug-resistant *Stenotrophomonas*, and *Achromobacter*, based on susceptibility testing (II-2). For *Acinetobacter*, the same guidelines recommend consideration of colistin combinations with other antimicrobial agents when carbapenem resistance is suspected (III) [3].

Our goal with the present study was to describe our clinical experience with colistin, focusing on its clinical efficacy and safety, for the treatment of solid organ transplant recipients infected with multidrug-resistant Gram-negative bacteria.

METHODS

This was a retrospective study performed at the University of Nebraska Medical Center (Omaha, Nebraska), a tertiary referral center. The study was approved by the hospital Institutional Research Board. Patients who received ≥1 dose of colistin were identified from the pharmacy database. Patients were included in the study if they were solid organ transplant recipients from January 1, 2003, to July 31, 2011, had a documented Gram-negative bacterial infection, and received ≥24 hours of treatment with colistin (intravenous or nebulized). The year of 2003 was chosen as the starting date because a new immunosuppression protocol had been implemented. If a patient was treated with colistin for a 2nd episode of infection, only the 1st instance was included in the analysis. Data collected from patients' medical records included age, sex, type of transplant, date of transplantation, immunocompromised state (induction therapy, maintenance immunosuppression, and mean tacrolimus levels before start of colistin), culture results, including antibiogram, colistin regimen, earlier and concomitant antibiotics used during colistin treatment, creatinine clearance (before and after the treatment with colistin), need for renal replacement therapy (before and after treatment with colistin), severity of illness (serial Sequential Organ Failure Assessment [SOFA] score for adults and Pediatric Risk of Mortality [PRISM] score for children), and clinical and microbiologic outcomes, including renal and neurologic side effects. Creatinine clearance was calculated by means of the Schwartz formula for children and the Cockroft-Gault formula for adults. Identification and susceptibility testing of the bacteria were performed with the use of the Vitek 2 (Biomerieux) and Microscan (Siemens) microdiffusion systems. The minimal inhibitory concentration was determined by means of disk diffusion methods and E-test (Biomerieux). Antimicrobial susceptibility testing data were interpreted with the use of Clinical Laboratory Standards Institute standards.

Definitions

Airway colonization was defined by isolation of a microorganism from the respiratory tract or urine in the absence of attributable signs and symptoms or imaging. Infection was defined by the presence of clinical signs and symptoms or imaging that was attributable to the causative pathogen. Clinical response was defined as clinical cure and clinical improvement (complete and partial resolution of signs and symptoms of the infection by the end of therapy) [4]. Microbiologic response was defined as no growth of the causative pathogen at the end of therapy [4]. Emergence of resistance to colistin was defined as isolation of isolates resistant to colistin during and/or after treatment. Nephrotoxicity in patients with normal renal function was defined as an increased serum creatinine value (>2 mg/dL), a 50% reduction in the calculated creatinine clearance compared with baseline value, or need for renal replacement therapy [4–9]. Nephrotoxicity in patients with preexisting renal impairment was defined as 50% increase of the baseline creatinine level, 50% reduction in the calculated creatinine clearance compared with the baseline, or need for renal replacement therapy [4–9]. Neurotoxicity was defined by the presence of any of the following symptoms that developed during the treatment with colistin and were alleviated or disappeared after the discontinuation of colistin therapy: dizziness, muscle weakness, facial or peripheral paresthesia, partial deafness, visual disturbances, vertigo, confusion, hallucinations, seizures, ataxia, and neuromuscular blockade that could lead to respiratory failure or apnea [10]. Tacrolimus level was calculated as the average tacrolimus level during the 4 weeks before the initiation of therapy with colistin. Colistin was administered according to hospital protocol: intravenous administration at 5 mg/kg/d colistin base (divided into 3 doses and adjusted for creatinine clearance if necessary) ornebulized administration at 75 mg colistin base every 12 hours for pediatric patients and 150 mg colistin base every 12 hours for adults.

Statistical Analysis

All data were analyzed with the use of SAS procedures (version 9.2; SAS Institute). Summary statistics were presented for baseline characteristics and outcomes. Continuous variables were compared between adult and pediatric groups with the use of nonparametric exact Wilcoxon rank sum tests, and categoric variables were compared with the use of Fisher exact tests. Wilcoxon signed rank tests were used to compare continuous variables before and after colistin therapy. The Kaplan-Meier method was used to estimate overall survival distributions.

RESULTS

Demographics

Fifteen patients were included in the study (Fig 1; Table 1). There were 9 male and 6 female patients, and 10 adults (median age, 54.6 y; range, 32.2–79.6 y) and 5 children

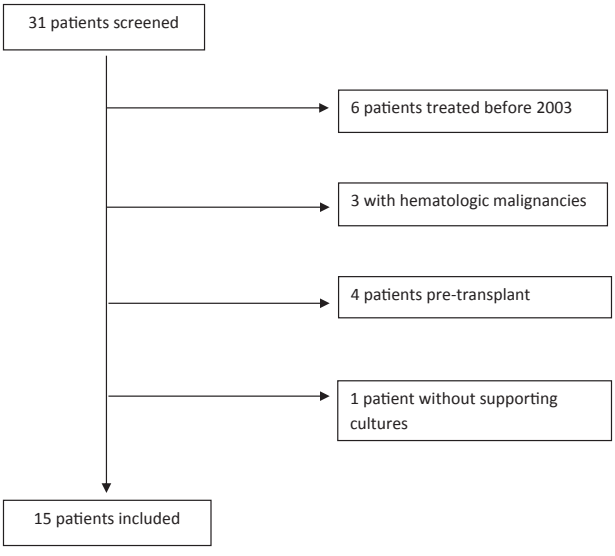

Fig 1. Flow chart.