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Outcome analysis of colistin-treated burn center patients

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ABSTRACT

Objectives: Intravenous colistimethate sodium (CMS) use in burn center patients is increasing due to the emergence of multidrug-resistant gram-negative bacteria. However, optimal dosing strategies and factors that may contribute to treatment failure are limited. The purpose of this study was to determine factors that may contribute to treatment failure in colistin-treated burn center patients.

Methods: This retrospective, observational study included burn center patients that received ≥48 h of intravenous CMS between June 1, 2009 and June 30, 2014. Data was collected utilizing the institution's electronic medical record system. Statistical analysis included demographic, univariable, and multivariable analysis to determine factors that may predict clinical failure of burn center patients requiring intravenous CMS.

Results: Eighty-one patients were included in this study, with 55 patients (68%) achieving clinical success. A total daily dose (TDD) of >5 mg/kg ideal body weight (IBW) was associated with significantly less clinical failure (odds ratio=0.21; 95% CI, 0.05, 0.91). Additionally, clinical failure was significantly higher in patients with wounds as the primary source of infection, creatinine clearances of 91–120 mL/min, and those receiving renal replacement therapy. No difference was observed in nephrotoxicity when comparing TDD >5 mg/kg IBW and TDD ≤5 mg/kg IBW.

Conclusions: Clinical success was significantly higher with larger intravenous CMS doses in burn center patients. Higher CMS doses were not found to be associated with increased nephrotoxicity within this patient group.

1. Introduction

Colistimethate sodium (CMS) is a polymixin antibiotic that was first discovered in the late 1940s. It is an inactive prodrug that is rapidly hydrolyzed into the active form colistin. Until recently, CMS was rarely used largely due to the risk of nephrotoxicity [1,2]. However, the emergence of extensive multidrug-resistant gram-negative bacteria has necessitated the increased usage of this "last resort" antibiotic [1–3]. Multidrug-resistant gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumonia* are associated with an increase in morbidity and mortality in the intensive care unit [1].

Optimal dosing strategies for CMS are controversial. Initial studies evaluating CMS dosing have been largely criticized due to methodological issues [4]. Prescribing information found in the package insert recommends using a weight-based dose of

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2.5–5 mg/kg/day with a maximum daily dose of 300 mg [5]. More recent studies evaluating colistin dosing reveal various recommendations including the use of a loading dose followed by a uniform maintenance dose that may exceed package insert recommendations, extending infusion times, and the use of equations that account for patient weight and renal function [4,6,7]. Furthermore, many studies have suggested the use of combination therapy for the additional or synergistic coverage secondary to the impracticality of therapeutic drug monitoring and wide interpatient pharmacokinetic variabilities with CMS. Some antibiotics found in the literature to possibly be associated with improved outcomes when used in combination with colistin include rifampin, meropenem, imipenem, ampicillin/sulbactam, and tigecycline [8,9].

Progress is being made regarding the pharmacodynamic and pharmacokinetic profile of colistin and the prodrug CMS. However, data regarding optimal dosing strategies and factors that may contribute to treatment failure remain limited, especially in burn center patients. The purpose of this study is to determine factors that may contribute to treatment failure in colistin-treated burn center patients.

2. Materials and methods

2.1. Patient population

We retrospectively collected data from all patients admitted to the burn center between June 1, 2009 and June 30, 2014 that received ≥48 h of intravenous CMS. Patients were excluded if their only positive culture was a sputum culture or had an unknown source of infection. Only the first course of CMS administration for each patient was included for analysis in the study. The study received approval by two institutional review boards.

2.2. Data collection

The following information was collected utilizing the institution's electronic medical record system: age, sex, body weight, height, TBSA, length of stay, mechanical ventilation days, renal replacement therapy including intermittent hemodialysis (IHD) and continuous venovenous hemofiltration (CVVH), site of infection, infecting organism(s), CMS dose, duration of treatment, concurrent infections, antibiotics, nephrotoxic agents, and mortality. Laboratory data included: average blood glucose, white blood cells (WBC), serum creatinine (SCr), and follow-up cultures. WBC and SCr were assessed at baseline.

2.3. Definitions

Microbiological outcomes were assessed based on follow-up cultures. To meet criteria for persistent infection the following had to be true: follow-up culture collected between day 7 of therapy until the end of therapy resulting in growth of the same organism for which the patient was being treated. Infection relapse was defined as positive follow up cultures collected within 2 weeks after completion of therapy resulting in growth of the same organism at the same site for which the patient was previously being treated. Clinical success was defined as follow-up cultures exhibiting no growth or unknown microbiological outcome. Clinical failure was defined as persistent infection, infection relapse, or mortality likely due to infection. Nephrotoxicity was also evaluated and defined as a two-fold increase in SCr from baseline according to the RIFLE criteria. Estimated creatinine clearance (CrCl) was calculated using Cockroft-Gault.

2.4. Statistical analysis

Statistical tests were performed utilizing SAS 9.3 and SigmaPlot 11.0. Dichotomous variables were analyzed using Fisher's exact test to compute p-values. Continuous data were analyzed via Wilcoxon Rank-Sum test. Univariate analysis was conducted utilizing logistic regression models to identify potential predictor variables. To better ensure inclusion of all pertinent factors, factors with p-values ≤0.10 and potential clinical relevance, based on current available literature, were included in the multivariable logistic regression analysis. During multivariable logistic regression modeling, significance was defined by a p-value of ≤0.05. P-values were not adjusted for multiplicity.

3. Results

A total of 105 patients were reviewed for inclusion in the study. Twenty-four patients were excluded with the majority (46%) due to unknown source of infection, leaving 81 patients for our study population. Most patients were male (73%) with an average age of 48±17 years, and median TBSA of 31% (range: 17.3, 42%). Baseline demographics (Table 1) did not differ significantly among patient groups. Based on cultures, the most common site of infection was the blood (31%), followed by lungs (26%) and wound (26%). Pathogens responsible for infection in each patient were *A. baumannii* or *P. aeruginosa*, with 9 patients (11%) being infected with both pathogens. Of the 81 patients included in the analysis, 55 patients (68%) achieved clinical success and 26 patients experienced clinical failure. Of the 26 patients that experienced clinical failure, 1 was due to recurrent infection, 10 due to persistent infection, and mortality related to infection was discovered in 15 patients.

Univariate analysis was conducted on all data collected for potential predictors of clinical failure. Factors with p-values ≤0.10 and clinically relevant can be found in Table 2. Patients with longer mechanical ventilation days, creatinine clearances 91–120 mL/min, receiving renal replacement therapy, having wounds as the primary site of infection, and receiving inappropriate empiric antibiotic therapy were more likely to result in clinical failure. Clinical success was more common in patients with urinary tract infections and those receiving a larger total daily dose (TDD). TDD, TDD>300 mg, TDD per ideal body weight (IBW), and TDD >5 mg/kg IBW were all found to be associated with clinical success.

After logistic regression (Table 3), TDD >5 mg/kg IBW showed a statistically significant reduction in clinical failure (odds ratio=0.21; 95% CI, 0.05, 0.91). Many regressions were performed with only one variable relating to TDD utilized at a