Colistin dosing and nephrotoxicity in a large community teaching hospital

Authors:

1) C. Andrew DeRyke*, Pharm.D., Clinical Specialist, Infectious Diseases, Department of Pharmacy, Orlando Health

2) Amanda J. Crawford, MPH, Department of Public Health & Health Professions, University of Florida; current affiliation, Research Health Science Specialist, Rehabilitation Outcomes Research Center Research Enhancement Award Program (RORC REAP), North Florida/South Georgia Veterans Health System, Gainesville, FL

3) Nizam Uddin, Ph.D., Department of Statistics, University of Central Florida

4) Mark R. Wallace, MD, Division of Infectious Diseases, Orlando Health

Keywords: colistin, colistimethate sodium, polymyxins, nephrotoxicity, antibiotic dosing

Running title: Colistin dosing and nephrotoxicity

*Corresponding Author:

C. Andrew DeRyke, Pharm.D.
Clinical Specialist, Infectious Diseases
Orlando Regional Medical Center
Department of Pharmacy, MP 180
1414 Kuhl Ave.
Orlando, FL 32806
phone: 321-841-1951
fax: 407-649-6839

email: andrew.deryke@orlandohealth.com
ABSTRACT

Thirty adult patients who received intravenous colistin (5.1 ± 2.4 mg/kg/day) were reviewed to evaluate dosing with respect to nephrotoxicity, which occurred in 10 (33%) patients within the first 5 days of treatment. Excessive colistin dosing was frequent (47%), often (71%) resulted from the use of actual body weight in obese patients, and was associated with higher rates of nephrotoxicity (80% vs. 30%, \( p = 0.019 \)).
Despite over 50 years of clinical use, definitive recommendations regarding the most efficacious and least toxic way to dose colistin do not exist (13). Package insert dosing recommendations are often used, but these are inconsistent among the different available products and were derived using inaccurate pharmacokinetic data (12, 14, 16-18). Colistin use was abandoned in the 1970s due to nephrotoxicity concerns and the introduction of safer alternatives; recent studies have demonstrated less than expected rates of renal impairment (4-7). The purpose of this study was to critically evaluate colistin dosing with respect to the development of nephrotoxicity at a large community teaching hospital.

A retrospective cohort of adult patients treated with intravenous (IV) colistimethate sodium for injection (Paddock Laboratories, Minneapolis, MN) for 48 hours or greater from 2006 to 2008 at Orlando Health was conducted. Each vial contained 150 mg of colistin base activity (CBA). Throughout this manuscript, the term colistin refers to colistimethate sodium for injection and dosing is expressed as CBA. Patients were excluded if on dialysis at the start of colistin treatment. The study was approved by both the Orlando Health and University of Florida Institutional Review Boards.

The following clinical data were collected for each patient: age, gender, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II score (10), weight and hospital ward at the time of colistin initiation, dose and duration of all colistin administered, concomitant nephrotoxic agents, and serum creatinine (S\textsubscript{CR}) levels.

Colistin dosing was evaluated based on two weight-based daily milligram of colistin per kilogram of body weight regimens: actual body weight (ABW) and ideal body weight (IBW). Ideal body weight was calculated as follows: 50 + 2.3 x (height in inches exceeding 5 feet) for men; 45.5 + 2.3 x (height in inches exceeding 5 feet) for women (2). Patients were considered
obese if ABW was greater than 140% of the IBW. Classification of each dosing regimen was
based on a modification of the package insert as described by Evans et al. (3) in which dosing
recommendations are based on creatinine clearance (CrCl) estimates (1). A daily dose was
considered excessive, normal, or low-normal if it was greater than, within, or below ± 0.4
mg/kg/day of the recommended dosing range using IBW.

Nephrotoxicity was defined as at least two consecutive Scr measurements with an
increase of 0.5 mg/dL from baseline at least 24 hours apart after two or more days of colistin
therapy. The RIFLE criteria were used to evaluate the severity of acute kidney injury (9).

All statistical analyses were performed using SPSS version 14.0 for Windows (Chicago,
IL). Continuous variables were analyzed using either the t test or Mann Whitney U; categorical
data were compared using either the $X^2$ or Fisher’s exact test when appropriate.

Thirty patients were prescribed colistin for treatment of multi-drug resistant
Pseudomonas aeruginosa and Klebsiella pneumoniae isolated from respiratory (63%) or urine
(20%) sources. The mean cumulative dose of thirty patients receiving intravenous colistin was
2559 ± 2088 mg and was administered for a median of 8 (3-24) days. Dosing of colistin based on
ABW and IBW was 3.9 ± 1.2 and 5.1 ± 2.4 mg/kg/day, respectively. Subsequent analysis of
dosing is listed in Table 1. Fourteen patients (47%) received an excessive colistin dose. In ten of
these cases (71%), the dose was calculated based on ABW, instead of IBW, in obese patients.
Eleven patients (37%) received low-normal doses (Table 1).

Ten patients (33%) developed nephrotoxicity during colistin treatment; all had baseline
Scr values ≤ 1.4 mg/dL, received greater than 4 mg/kg/day, and developed renal impairment
within the first 5 days of treatment. The median Scr at the beginning and end of therapy was 1.0
and 2.5 mg/dL, respectively. Based on RIFLE criteria, 3, 5, and 2 patients met the criteria for
injury, failure, and end stage kidney disease, respectively. Table 2 lists a comparison of patient characteristics based on development of nephrotoxicity. Patients who developed nephrotoxicity were older, had a higher baseline APACHE II score, and were more likely being treated in an ICU; however, only age was statistically significant. No differences in treatment duration or cumulative dose of colistin were observed, however, patients administered excessive daily colistin doses were significantly more likely to develop nephrotoxicity compared to those who received normal or low-normal doses ($p = 0.019$). Patients who received excessive doses because ABW was used for dose calculation in the obese were 13.2 times more likely to develop nephrotoxicity (95% confidence interval [2.1, 82.1]) compared to patients who received normal or low-normal doses ($p = 0.005$). Alternative explanations for developing nephrotoxicity that were statistically significant included receipt of concomitant diuretics and/or vasopressors. All 4 patients receiving vasopressors in this study developed nephrotoxicity; the remaining 6 patients who developed nephrotoxicity all received excessive daily colistin doses.

The major findings of this study were the 33% nephrotoxicity rate among hospitalized patients who received colistin, the statistically significant association between development of nephrotoxicity and excessive colistin dosing, and the observation that excessive colistin doses were usually administered because ABW rather than IBW was used to calculate the daily mg/kg dose. For example, in one 166 kg patient with a CrCl > 120 mL/min at baseline, a 5.1 mg/kg/day dose based on ABW was given. Based on IBW, however, the dose given was 14.3 mg/kg/day. The patient developed nephrotoxicity on day 2 of therapy. Although the IBW is recommended in the package insert, data validating this recommendation do not exist and it is unclear which weight measure is most appropriate. Alternative reasons other than colistin dosing that could have explained development of nephrotoxicity were older age, receipt of diuretics, and receipt of
vasopressors. After excluding patients who received vasopressors from the analysis, nephrotoxicity was observed only in patients who received excessive daily dosing. Due to the small number of patients remaining (n = 26), a multivariate logistic regression model could not be performed.

The 33% rate of nephrotoxicity observed is similar to a report by Levin et al. (11) but higher than other contemporary studies (4-7, 15). The majority of these studies used less than 3 mg/kg/day of CBA (4-7). The higher dosing of 5.5 mg/kg/day in patients who developed nephrotoxicity in this cohort may account for the differences among studies. Wallace et al. found a higher incidence of renal lesions in rats receiving once daily administration of a clinically relevant colistin dose compared to a twice daily regimen (19). Since all patients were dosed multiple times daily in this cohort, this relationship could not be evaluated. Additionally, a study by Hartzell et al. (8) found that patients treated with colistin for greater than 14 days were 3.7 times more likely to develop nephrotoxicity. Since all patients developed nephrotoxicity by day 5 of therapy, this relationship could not be evaluated.

Contemporary, reliable colistin pharmacokinetic (PK) data show a much lower concentration-time profile than previously described (12, 14, 16, 18). For example, Plachouras et al. (18) shows sub-MIC colistin concentrations during the first few days of therapy in critically-ill patients. These PK data suggest increased daily doses are warranted, however, the data from this analysis suggest any recommendation to increase the daily colistin dose greater than that currently recommended (i.e. 2.5 to 5 mg/kg/day) be done cautiously as this may increase nephrotoxicity risk.

In conclusion, excessive daily colistin dosing led to the more frequent development of nephrotoxicity and was often due to the use of the ABW for dose calculation in obese patients.
These data suggest that using a measure of lean body mass, such as IBW, to dose colistin may be less nephrotoxic. Close monitoring of renal function, specifically during the first 5 days of therapy, may identify patients in whom renal toxicity of colistin is likely to occur. Further investigation must continue to identify the optimal colistin dose from both efficacy and toxicity perspective.

This work was not funded. All authors: no conflict of interest.
References


TABLE 1. Intravenous colistin dosing based on renal function (N = 30).

<table>
<thead>
<tr>
<th>Baseline creatinine clearance</th>
<th>&gt; 80 mL/min (n = 20)</th>
<th>Between 30-80 mL/min (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended dose*</td>
<td>5 mg/kg/day</td>
<td>2.5 - 3.8 mg/kg/day</td>
</tr>
<tr>
<td>Dosing based on:*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual Body Weight</td>
<td>4.2 ± 1.2</td>
<td>3.3 ± 1.1</td>
</tr>
<tr>
<td>Ideal Body Weight</td>
<td>5.3 ± 2.9</td>
<td>4.7 ± 1.2</td>
</tr>
<tr>
<td>Analysis of patient dose:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive*</td>
<td>(n = 5) 9.0 ± 3.8</td>
<td>(n = 9) 5.0 ± 0.6</td>
</tr>
<tr>
<td>Normal</td>
<td>(n = 5) 5.0 ± 0.3</td>
<td>None</td>
</tr>
<tr>
<td>Low-normal*</td>
<td>(n = 10) 3.6 ± 0.7</td>
<td>(n = 1) 1.8</td>
</tr>
</tbody>
</table>

*Dosing recommendations based on Evans et al. (3)

*bAll dosing expressed as mean ± standard deviation in mg/kg/day

*cExcessive, normal, and low-normal dosing was denoted if the daily dose administered was greater than, within, or lower than 0.4 mg/kg/day of the recommended dose using ideal body weight

Creatinine clearance as calculated by Cockcroft & Gault (1)
TABLE 2. Patient characteristics based on the development of nephrotoxicity during intravenous colistin therapy (N = 30).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nephrotoxicity</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES (n = 10)</td>
<td>NO (n = 20)</td>
</tr>
<tr>
<td><strong>DEMOGRAPHICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, mean ± SD</td>
<td>57.5 ± 15.5</td>
<td>43.3 ± 16.5</td>
</tr>
<tr>
<td>APACHE II</td>
<td>13 (7 – 18)</td>
<td>7 (3 -15)</td>
</tr>
<tr>
<td>Male</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>ICU stay during COL administration (%)</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td><strong>COLISTIN DOSING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S&lt;sub&gt;Cr&lt;/sub&gt; at beginning, mg/dL</td>
<td>1.0 (0.6 – 1.2)</td>
<td>0.8 (0.5 – 0.9)</td>
</tr>
<tr>
<td>S&lt;sub&gt;Cr&lt;/sub&gt; at end, mg/dL</td>
<td>2.5 (2.1 – 4.0)</td>
<td>0.7 (0.5 – 0.9)</td>
</tr>
<tr>
<td>CrCl at beginning, mL/min</td>
<td>86 (60 -144)</td>
<td>122 (77 – 144)</td>
</tr>
<tr>
<td>Treatment duration, days</td>
<td>7 (5 – 16)</td>
<td>9 (5 – 12)</td>
</tr>
<tr>
<td>Every 12 hour dosing frequency</td>
<td>90</td>
<td>65</td>
</tr>
<tr>
<td>Dose per ABW, mg/kg/day</td>
<td>4.2 (3.4 – 5.0)</td>
<td>4.0 (2.7 – 4.6)</td>
</tr>
<tr>
<td>Dose per IBW, mg/kg/day</td>
<td>5.5 (4.6 -7.7)</td>
<td>4.4 (3.1 – 5.3)</td>
</tr>
<tr>
<td>Cumulative IV dose, mg</td>
<td>1838 (1519 – 4613)</td>
<td>1823 (975 – 3184)</td>
</tr>
<tr>
<td>Cumulative IV + aerosolized dose, mg</td>
<td>1838 (1519 – 6263)</td>
<td>1823 (975 – 3430)</td>
</tr>
<tr>
<td>Excessive daily dosing (all) (%)</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>Excessive daily dosing (because ABW used in obese patient) (%)</td>
<td>70</td>
<td>15</td>
</tr>
</tbody>
</table>
### ALTERNATIVE EXPLANATIONS FOR NEPHROTOXICITY\(^c\)

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IV contrast use (%)</td>
<td>20</td>
<td>35</td>
<td>0.675</td>
</tr>
<tr>
<td>Concomitant vancomycin (%)</td>
<td>50</td>
<td>30</td>
<td>0.425</td>
</tr>
<tr>
<td>Concomitant aminoglycosides (%)</td>
<td>30</td>
<td>40</td>
<td>0.702</td>
</tr>
<tr>
<td>Concomitant ACE/ARBs (%)</td>
<td>40</td>
<td>15</td>
<td>0.181</td>
</tr>
<tr>
<td>Concomitant diuretic use (%)</td>
<td>80</td>
<td>20</td>
<td>0.004</td>
</tr>
<tr>
<td>Concomitant vasopressors (%)</td>
<td>40</td>
<td>0</td>
<td>0.008</td>
</tr>
</tbody>
</table>

\(^a\) All data represent median (25\(^{\text{th}}\) – 75\(^{\text{th}}\) percentile) unless otherwise stated

\(^b\) An every 8 and every 6 hour dosing frequency was administered in 6 and 1 patient respectively.

\(^c\) No patients received an every 24 hour dosing regimen

No patients received an every 24 hour dosing regimen

\(^c\) Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and amphotericin B were not given in this cohort

SD = standard deviation

APACHE = Acute physiology and chronic health evaluation

ICU = intensive care unit

SCR = serum creatinine

CrCl = creatinine clearance as calculated by Cockcroft & Gault (1)

ABW = actual body weight

IBW = ideal body weight

ACE = angiotensin converting enzyme inhibitors

ARB = angiotensin receptor blockers