Validation of a Model To Predict the Risk of Nephrotoxicity in Patients Receiving Colistin

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Despite concerns about its nephrotoxicity, colistin often remains the only effective agent for treating multidrug-resistant Gram-negative infections. Published studies have reported a wide range of nephrotoxicity risk factors. To assess the clinical utility of various models, we compared their performances for predicting the risk of nephrotoxicity. We identified a model demonstrating reasonable overall risk assessment, with an observed/expected ratio of 1.29 (95% confidence interval [CI], 0.68 to 1.90) and a positive predictive value of 87.5% for identifying patients at high risk of developing nephrotoxicity.

Multidrug-resistant (MDR) infections caused by Gram-negative bacteria are increasing worldwide and are associated with significant morbidity and mortality (1, 2). With a lack of new antibiotics in development, there has been a resurgence in the use of colistin, as it still demonstrates activity against many of these MDR organisms. However, colistin is associated with significant nephrotoxicity, which limits its widespread use.

Numerous studies have evaluated the prevalence of colistin-associated nephrotoxicity, but the rates vary widely in the literature, ranging anywhere from 10% to 48% (3–6). The reasons for such wide variability are multifactorial. One possible explanation is the different definitions used for nephrotoxicity. Earlier studies did not utilize a standardized definition and generally reported lower rates of nephrotoxicity (4, 7). In more recent years, studies have used the risk, injury, failure, loss, and end-stage renal disease (RIFLE) criteria as a standardized definition for acute kidney injury (8). The rates of colistin-associated nephrotoxicity in these studies are more consistent, with a range between 31% and 48% (5, 6, 9–12). However, the reported risk factors associated with nephrotoxicity vary considerably in these studies. Thus, it is unclear which risk factors are most predictive of colistin-associated nephrotoxicity.

With the high rate of nephrotoxicity associated with colistin use, identifying patients at high risk for developing nephrotoxicity is important for optimizing colistin therapy (i.e., weighing the risk versus benefits of initiating or continuing therapy). A direct comparison of the different mathematical models used to identify patients at high risk for colistin-associated nephrotoxicity has not been undertaken. To assess the clinical utility of various mathematical prediction models, the objectives of this study were to compare their performances in (i) predicting the overall risk of nephrotoxicity in a population of patients receiving colistin and (ii) identifying patients at high risk for developing colistin-associated nephrotoxicity.

A literature search was conducted using PubMed to identify prediction models from published studies that evaluated independent risk factors for colistin-associated nephrotoxicity. Studies were included if they were published in English in the last 10 years and they defined nephrotoxicity according to the RIFLE criteria. The full logistic equation for each prediction model was obtained by contacting the respective corresponding author.

Patients admitted from January 2012 through January 2014 to Baylor St. Luke’s Medical Center, an 850-bed tertiary care center in Houston, TX, were retrospectively screened as a validation cohort. Patients aged ≥18 years who received ≥72 h of intravenous colistin for suspected or documented infections were included. Patients were excluded if they had severe renal insufficiency (on any form of renal replacement therapy or baseline serum creatinine of >1.5 mg/dl) or fluctuating renal function (increase or decrease in serum creatinine of >50% in the 72 h immediately prior to the initiation of colistin). The patients were monitored for up to 30 days (or until hospital discharge, whichever occurred first), and nephrotoxicity was defined according to the RIFLE criteria. Institutional review board approval was obtained prior to the initiation of this study, and the need for informed consent was waived due to the retrospective nature of this study.

To predict the risk of nephrotoxicity for a patient, various prediction models were conditioned using specific risk factors from individual patients in the validation cohort (see Appendix). The performances of the models for predicting the overall risk of nephrotoxicity were assessed by comparing the percentage of ac-

### TABLE 1 Pertinent patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of males</td>
<td>17 (53.1)</td>
</tr>
<tr>
<td>No. (%) Caucasians</td>
<td>16 (50.0)</td>
</tr>
<tr>
<td>Age (mean ± SD) (yr)</td>
<td>54.7 ± 17.6</td>
</tr>
<tr>
<td>Daily dose (mean ± SD) (mg/kg of IBW/day)</td>
<td>4.2 ± 1.3</td>
</tr>
<tr>
<td>Duration of therapy (mean ± SD) (days)</td>
<td>9.2 ± 6.2</td>
</tr>
<tr>
<td>No. of concurrent nephrotoxins (mean ± SD)</td>
<td>1.8 ± 1.4</td>
</tr>
<tr>
<td>No. (%) with concurrent rifampin</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>No. (%) with cystic fibrosis</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>No. (%) with observed nephrotoxicity</td>
<td>17 (53.1)</td>
</tr>
</tbody>
</table>

* n = 32.
The study identified a model demonstrating a reasonable overall risk assessment and high PPV for identifying patients at high risk for developing colistin-associated nephrotoxicity. Mathematical prediction models could be used to identify patients at a high risk for nephrotoxicity. Strategies to minimize nephrotoxicity may be selectively implemented in these patients (e.g., closer monitoring of renal function using more sensitive biomarkers of renal injury, limiting the duration of therapy when possible, and ensuring the colistin dose is appropriate).

**APPENDIX**

Computation of the predicted risk of nephrotoxicity for an individual patient. The reasons for excluding models are shown in Table A1.

A 46-year-old (“46” in the Phe and Collins models below) patient without cystic fibrosis (“0” in the Phe model) was given colistin 4.1 mg/kg of IBW/day (“4.1” in the Phe model and the second “0” in the Pogue model) for 14 days (“14” in the Phe model). The patient was also on 2 concomitant nephrotoxins (first “0” in the Pogue model and “1” in the Collins model) but received no rifampin (last “0” in the Pogue model).

### TABLE 2 Reported risk factors for colistin-associated nephrotoxicity and overall risk assessment

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of subjects examined</th>
<th>No. (%) with nephrotoxicity</th>
<th>Risk factors identified</th>
<th>O/E ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>121</td>
<td>41 (34)</td>
<td>Age, duration of therapy, daily dose by IBW, cystic fibrosis (protective)</td>
<td>1.29</td>
<td>0.68 to 1.90</td>
</tr>
<tr>
<td>10</td>
<td>126</td>
<td>54 (43)</td>
<td>Colistin daily dose ≥5.0 mg/kg of IBW, receipt of concomitant rifampin, receipt of ≥3 concomitant nephrotoxins</td>
<td>6.11</td>
<td>3.20 to 9.01</td>
</tr>
<tr>
<td>12</td>
<td>174</td>
<td>84 (48)</td>
<td>Age, receipt of concomitant nephrotoxins</td>
<td>1.10</td>
<td>0.58 to 1.63</td>
</tr>
</tbody>
</table>

This is the first study to compare and validate the performances of various models for predicting the risk of colistin-associated nephrotoxicity. In our study, the independent risk factors for nephrotoxicity included age, duration of therapy, and daily dose by ideal body weight (IBW), which are consistent with other models (6, 9–12). Interestingly, we also found cystic fibrosis to be protective against the development of nephrotoxicity. Concomitant nephrotoxins were not found to be a risk factor in our model.
TABLE A1 Reasons for exclusion of study

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason(s) for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>No response from corresponding author</td>
</tr>
<tr>
<td>6</td>
<td>Evaluated overweight and obese patients only</td>
</tr>
<tr>
<td>11</td>
<td>No reported odds ratio</td>
</tr>
<tr>
<td>13</td>
<td>Risk factors not adjusted for confounders in multivariate analysis</td>
</tr>
<tr>
<td>14</td>
<td>Risk factors evaluated based on a time-to-event analysis</td>
</tr>
<tr>
<td>15</td>
<td>Plasma colistin concn monitoring not widely available</td>
</tr>
<tr>
<td>16</td>
<td>Did not report risk factors</td>
</tr>
</tbody>
</table>

Phe model:
\[
\logit P_{\text{nephrotoxicity}} = -4.419 + 0.036(46) + 0.337(4.1) + 0.076(14) - 3.554(0) \\
\hat{e}^{\logit} = 0.73 \\
P_{\text{nephrotoxicity}} = 42.2\%
\]

Pogue model:
\[
\logit P_{\text{nephrotoxicity}} = -4.2354 + 1.9164(0) + 3.1532(0) + 1.3362(0) \\
\hat{e}^{\logit} = 0.01 \\
P_{\text{nephrotoxicity}} = 1.4\%
\]

Collins model:
\[
\logit P_{\text{nephrotoxicity}} = -2.9016 + 0.03053(46) + 1.38827(1) \\
\hat{e}^{\logit} = 0.9 \\
P_{\text{nephrotoxicity}} = 47.3\%
\]

Note: \( P_{\text{nephrotoxicity}} = \frac{e^{\logit}}{1 + e^{\logit}} \)

\[ P_{\text{nephrotoxicity}} : \text{predicted risk of nephrotoxicity} \]

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REFERENCES