Brief communication

Effect of polymyxin B-containing regimens on renal function for the treatment of carbapenem-resistant Enterobacteriacea mediastinitis

Cely Saad Abboud a,*, Gauri G. Rao b, Ercilia E. Souza c, Alexandre P. Zavascki c, Carlos Kiffer d

a Instituto Dante Fazzanese de Cardiologia, São Paulo, SP, Brazil
b The University of North Carolina at Chapel Hill, UNC Eshelman School of Pharmacy, Division of Pharmacotherapy and Experimental Therapeutics, Chapel Hill, United States
c Hospital de Clínicas de Porto Alegre, Serviço de Doenças Infecciosas, Porto Alegre, RS, Brazil
d Universidade Federal de São Paulo (UNIFESP), Escola Paulista de Medicina, São Paulo, SP, Brazil

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ABSTRACT

A retrospective cohort study, were evaluated: polymyxin B plus aminoglycosides or polymyxin B plus other antibiotics. Any degree of acute kidney injury occurred in 26 (86.6%) patients. The median time to acute kidney injury was 6.0 (95% CI 3–14) days in the polymyxin-aminoglycoside containing regimen group, against 27.0 (95% CI 6–42) days in the polymyxin with other antimicrobial combinations group (p = 0.03). Polymyxin B with aminoglycosides group progressed faster to any degree of renal dysfunction.

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Introduction

Nephrotoxicity is an important adverse effect associated with polymyxin (polymyxin B or colistin)-based treatments, with rates of acute kidney injury (AKI) ranging from 20% to 60%. Recently, some studies have shown a better nephrotoxicity profile for polymyxin B compared to colistin.1–4

However, all studies that have evaluated the use of polymyxins for the treatment of infections had relatively short treatment periods, i.e., 7–14 days. No study thus far has addressed the incidence and evolution of AKI in patients treated for longer periods with polymyxins, specifically in conjunction with aminoglycosides or other antimicrobials.

Recently, we evaluated the clinical and epidemiological features of post-cardiac surgery patients with mediastinitis...

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* Corresponding author.
E-mail address: cely.saad@gmail.com (C.S. Abboud).

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infected with carbapenem-resistant Enterobacteriacea (CRE).5
Due to the peculiarity of the infection, polymyxin B was the
treatment of choice, and a prolonged period of four to six
weeks was recommended.6

This study aimed to evaluate the real-world evidence
for the development of AKI during prolonged periods of
polymyxin B-based antimicrobial combinations assessed by
specific criteria.7

Material and methods

This was a retrospective cohort study conducted at a 350-bed
hospital specialized in cardiology and cardiovascular surgery
in São Paulo, Brazil between December 2010 and June 2014.

Thirty patients diagnosed with mediastinitis based on the
CDC criteria,8 who were infected with CRE were included in
the analysis of time to evolution to AKI.

Patient charts were reviewed to capture demographic and
clinically relevant data, including comorbidities, baseline
creatinine, weight, body mass index (BMI), and APACHE II score while at the intensive care unit (ICU). The outcomes
measured were development of AKI during treatment, which
was assessed according to the “RIFLE” criteria.7

All Gram-negative strains recovered from patients diag-
nosed with mediastinitis were submitted to the local
microbiology laboratory for identification and determination
of antimicrobial susceptibility profiles by VITEK®.2
(bioMérieux, Marcy-l’Etoile, France). Resistance was defined as
a minimum inhibitory concentration (MIC) of ≥4 g/mL
for carbapenems (imipenem and meropenem), according
to the Clinical and Laboratory Standards Institute (CLSI),9
and resistance to polymyxins was defined by a colistin
MIC ≥4 g/mL.10,11 The screening test of carbapenemase was
performed using a modified Hodge test as recommended by
the CLSI,9 and the detection of carbapenemases genes (blaKPC,
blaNDM, blaIMP, blaVIM, blaGES and blaOXA-48-like) was
determined using real-time PCR12 for all isolates recovered.

Therapy management was performed at the discretion of the infectious diseases (ID) attending physician, and
the present study considered the real-world evidence of the
prescribed regimens. To categorize the antimicrobial combination into groups, we separated the combination regimens into
two distinct risk groups: (a) regimens containing polymyxin B and
aminoglycosides ± other antimicrobials and (b) regimens
containing polymyxin B ± other antimicrobials (but without
aminoglycosides).

The following intravenous antimicrobial doses were
used at the institution for the treatment of CRE medi-
astinitis: polymyxin B 25,000 UI/kg/day (no loading dose),
amikacin 15 mg/kg/day q24h, gentamicin 5 mg/kg/day q24h,
meropenem 1 g q8h, imipenem 500 mg q6h, tigecycline
100 mg loading dose followed by 50 mg q12h, and ciprofloxacin
400 mg q12 h.13

Each subject was included only once in the analysis.
Descriptive statistics was used to describe the overall char-
acteristics of the cohort. All 30 patients included in the two
regimen groups were analyzed using the log rank test to esti-
mate the time to evolution to AKI according to the RIFLE
criteria.7 Categorical variables were compared using the Fisher
or Chi-square test, and quantitative variables using t-Student
or Mann–Whitney tests, as appropriate. p-Value ≤0.05 was
considered statistically significant.

The statistical package SPSS 19 (IBM, New York, USA) was
used for dataset management and analysis.

This study was approved by the Ethical Committee of Insti-
tuto Dante Fazzanese de Cardiologia.

Results and discussion

The most common surgical procedures performed were coro-
nary artery bypass grafting (CABG) and/or valve replacement
(70%). The demographic and clinical characteristics found in
both treatment groups are reported in Table 1.

CRE mediastinitis was most commonly due to Klebsiella
pneumoniae (n = 20), Enterobacter aerogenes (n = 8), and Enterobac-
ter cloacae (n = 2); blaKPC was the only gene detected and
present in all CRE strains. Among the 30 patients, three (10%)
were treated with double antimicrobial therapy, and 90% were
treated with triple, quadruple or even quintuple antimicro-
bials according to the clinical judgment of the severity and/or
resistance of the CRE to polymyxin B.

Any degree of AKI occurred in 26 (86.6%) patients. Of
these, 20 (77%) were classified as risk, injury or failure and
six (23.1%) as end-stage renal disease. In the polymyxin
B/aminoglycosides treatment group, the mean time to AKI
was six days, compared to 27 days in the polymyxin B-other
antimicrobials (without aminoglycosides) treatment group
(p = 0.03). Fig. 1 shows the estimate of AKI-free days survival
risk stratified by the log-rank test between the treatment
groups of polymyxin B-aminoglycoside and polymyxin B-
other antimicrobials regimens.

Among the 20 patients who had no end-stage renal disease,
9/20 (45%) had creatinine ≥1.5 mg/dL at the end of treatment,
4/12 (33.3%) in the polymyxin-aminoglycoside group and 5/8
(62.5%) in the polymyxin-other combination group (p = 0.36).

Among the 12 polymyxin-resistant-CRE patients
(PR-CRE), 10 (83.3%) were in the group treated with
polymyxin/aminoglycoside (p = 0.121). Duration, assessed
in days, of polymyxin treatment was significantly shorter
in the group that used aminoglycosides compared to the
polymyxin/other antimicrobials group (25 × 44 days, p = 0.019),
which was most likely due to progression to renal failure
and the option by the clinician to reduce damage. Hospital
mortality was higher in the polymyxin B/aminoglycoside
group, p = 0.023, which could have been due to the multi-
factorial risks involved, including more PR-CRE cases in this
group. Although the difference in the number of PR-CRE
cases was not significant, it was clearly more difficult to treat
the infection and more aggressive procedures were used
leading to loss of renal function with subsequent need for
hemodialysis.
This unique case series highlights the difficulties in the treatment of CRE mediastinitis with prolonged use of polymyxin B-based combination regimens. Treating mediastinitis after cardiac surgery is rather challenging, which is even more difficult if CRE or PR-CRE are involved. The occurrence of PR-CRE in Brazil is increasing and is becoming a public health concern given the dearth of viable therapeutic options available. The benefit of treatment with polymyxin combined with carbapenems for CRE infections has previously been reported, but in cases of PR-CRE, the number of clinical studies has been limited. Our case series is limited in its ability to determine the causes of renal dysfunction, but it is reasonable to assume that among the factors related to progression to renal dysfunction, the concomitant use of polymyxin B and aminoglycosides is an important factor due to higher propensity to cause any degree of AKI.

Regimens containing polymyxin B and aminoglycosides should be observed with caution, particularly in this patient population due to increased potential for nephrotoxicity, but in some cases, this regimen is the only treatment available for difficult to treat infections.

The main limitations of this single-center study were its sample size and the retrospective nature of the study design.

Table 1 - Demographic and clinical characteristics of patients with mediastinitis in both treatment groups.

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>Total n = 30</th>
<th>Polymyxin B plus other antimicrobials n = 11</th>
<th>Polymyxin B plus aminoglycoside/other n = 19</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, n (%)</td>
<td>12 (40)</td>
<td>4 (36.4)</td>
<td>8 (42.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Race White, n (%)</td>
<td>23</td>
<td>8 (72.7)</td>
<td>15 (79)</td>
<td>1.00</td>
</tr>
<tr>
<td>Body mass index (BMI) mean (SD)</td>
<td>30</td>
<td>31.44 (8.10)</td>
<td>30.41 (7.68)</td>
<td>0.735</td>
</tr>
<tr>
<td>BMI &gt; 30, n (%)</td>
<td>12 (40)</td>
<td>4 (36.3)</td>
<td>8 (42.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>APACHE Index (AI) when CRE treatment starts/No. patients (P)</td>
<td>13 (%)</td>
<td>12 (AI)</td>
<td>15.78 (AI)</td>
<td>0.414</td>
</tr>
<tr>
<td>Creatinine (mg/dL) before surgery mean (SD)</td>
<td>30</td>
<td>0.90 (0.30)</td>
<td>1.11 (0.44)</td>
<td>0.268</td>
</tr>
<tr>
<td>ICU stay before CRE mediastinitis, n (%)</td>
<td>14 (46.6%)</td>
<td>4 (36.4%)</td>
<td>10 (52.6%)</td>
<td>0.466</td>
</tr>
<tr>
<td>CRE mediastinitis</td>
<td>30</td>
<td>11</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymyxin B, n (%)</td>
<td>30</td>
<td>11</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Length of treatment (days)</td>
<td>30 (P)</td>
<td>44 days</td>
<td>25 days</td>
<td>0.019</td>
</tr>
<tr>
<td>Total doses/day IU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1,500,000</td>
<td>1,500,000</td>
<td>1,500,000</td>
<td>0.215</td>
</tr>
<tr>
<td>Minimal</td>
<td>750,000</td>
<td>1,300,000</td>
<td>750,000</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>3,200,000</td>
<td>3,200,000</td>
<td>2,200,000</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides, n (%)</td>
<td>19 (63.3)</td>
<td>–</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Length of treatment median mean range (days)</td>
<td>–</td>
<td>–</td>
<td>20 (6–45)</td>
<td></td>
</tr>
<tr>
<td>Patients any AKI degree – n</td>
<td>26</td>
<td>9 (9.1%)</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>End Stage Renal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time to AKI in days</td>
<td>–</td>
<td>27 days</td>
<td>6 days</td>
<td>0.03 (CI 95% 3–14)</td>
</tr>
<tr>
<td>Complete renal function recovery after treatment (SCR &lt; 1.5 mg/dL), n (%)</td>
<td>9 (45)</td>
<td>5 (62.5)</td>
<td>4 (33)</td>
<td>0.36</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>11</td>
<td>1 (9.1%)</td>
<td>10 (52.6%)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Fig. 1 – Kaplan–Meier curve stratified by polymyxin B plus aminoglycoside treatment and polymyxin B plus other antimicrobial combinations in patients with mediastinitis due to carbapenem-resistant Enterobacteriaceae (CRE).

Thus, definite conclusions are precluded due to low statistical power. Despite the limitations, limited data are available on polymyxin B and prolonged periods of treatments, and
thus, our results provide useful clinical information to better understand extended periods of use of polymyxin B and other antimicrobial combinations with respect to AKI development.

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Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES