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Research note

Antimicrobial treatment and outcomes of critically ill patients with OXA-48-like carbapenemase-producing Enterobacteriaceae infections

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Running title: Antimicrobial therapy, clinical characteristics and outcomes of critically ill ICU patients, with severe OXA-48-like infections.

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Keywords: OXA-48, carbapenemase-producing Enterobacteriaceae (CPE), intensive care unit, mortality, treatment
Abstract

We report on the clinical characteristics, antimicrobial therapy and outcomes of 20 critically ill patients with severe OXA-48-like infections. Carbapenem-based therapy demonstrated improved survival (OR = 5.0) as compared with non-carbapenem therapy. Risk factors for mortality included APACHE III score and length of stay, highlighting the significant influence of comorbidities and severity of underlying illness on outcomes.
Optimal antimicrobial management of carbapenemase-producing Enterobacteriaceae (CPE) infections remains a contentious issue. Moreover the majority of clinical studies have reported on infections associated with KPC-producing and metallo-ß-lactamase (MBL) producing Enterobacteriaceae. OXA-48-like carbapenemases are class D carbapenem-hydrolyzing ß-lactamases, first identified in Turkey in 2001, and have subsequently emerged as a significant cause of CPE-related infections and outbreaks (Poirel, Potron, & Nordmann, 2012). The management of OXA-48-like CPE infections is complicated by varied ß-lactam susceptibility and difficulties in laboratory detection. Antimicrobial therapy of serious infections in critically ill patients is further complicated by organ dysfunction and other pathophysiological disturbances that impact on the optimal pharmacodynamic and pharmacokinetic exposures (Roberts & Lipman, 2009). Thus management of serious OXA-48-like infections in critically ill patients is a difficult and challenging scenario. We report on the clinical management and outcomes of critically ill patients who developed serious infections secondary to OXA-48-like Enterobacteriaceae.

The Wits Donald Gordon Medical Centre is a 220 bed hospital that serves as a referral hospital for complicated colorectal and hepatobiliary surgery, oncology and liver, kidney and pancreas transplant patients. The Intensive Care Unit (ICU) comprises a 15-bed multi-disciplinary intensive care unit and 14-bed high care unit. In October 2012 the first OXA-48-like isolate was identified and subsequently a retrospective review of all patients with OXA-48-like infections admitted to and managed in the ICU between October 2012 and May 2013 was conducted.

Retrospective collection of data included: demographics; duration of ICU/ hospital stay (LOS); timing of admission relative to positive cultures; comorbidities; immunosuppression; source of
infection; APACHE III score (Knaus, et al., 1991); device usage; invasive procedures (surgery; radiological); carbapenem MIC; empiric and targeted antimicrobial therapy (type; duration); outcome. Ethical approval obtained from HREC, University of the Witwatersrand (M140206)

Continuous variables reported as median (range) and categorical variables reported as frequencies. Student t-test and Fishers exact test used as appropriate. Odds ratio used to compare outcomes between different treatment groups.

Classification of healthcare-associated infections, immunosuppression and infection-type all defined according to standard CDC criteria (Horan, Andrus, & Dudeck, 2008). Unidentified source of bloodstream infection (BSI) defined as a primary bacteraemia. Any isolate with reduced carbapenem susceptibility, as defined by CLSI guidelines, was investigated for the presence of six different carbapenemase genes: \( \text{bla}_{\text{NDM}}; \text{bla}_{\text{KPC}}; \text{bla}_{\text{OXA-48like}}; \text{bla}_{\text{VIM}}; \text{bla}_{\text{IMP}}; \text{bla}_{\text{GES}} \) (CLSI, 2013). Appropriate empiric therapy defined as the use of at least one antimicrobial agent to which the isolate was susceptible (CLSI breakpoints). Definitive treatment defined as the antimicrobial agent(s) initiated on the basis of susceptibility results.

We report on the clinical and microbiological characteristics of 20 patients (table 1). Isolates included \textit{Klebsiella pneumoniae} (n=18), \textit{Klebsiella oxytoca} (n=1) and \textit{Citrobacter freundii} (n=1). Isolates were confirmed \textit{OXA-48like} positive by PCR and no other carbapenemase genes were detected (18/20 phenotypically confirmed ESBL-producers)(Lowman, Marais, Ahmed, & Marcus, 2014). The MIC\textsubscript{50}/MIC\textsubscript{90} to meropenem for all isolates tested (n=15) and \textit{K. pneumoniae} isolates tested (n=13) was 2/32 µg/ml and 2/8 µg/ml, respectively. Seven (87.5%) of the immunosuppressed patients were neutropaenic. Complicated intra-abdominal infections
accounted for 7 (35%) infections, and a bacteraemia (primary and secondary) was documented in 9 (45%) patients. Three of the primary bacteraemias occurred in neutropaenic patients and one each in a patient with subacute liver failure (autoimmune hepatitis) and renal failure (hepato-renal syndrome). Eighteen patients had either a central venous catheter (CVC) and/or a urinary catheter. APACHE III score and an inverse relationship between LOS were the only significant risk factors associated with mortality, \( p = 0.04 \). Comparing bacteraemic to non-bacteraemic patients the only significant difference identified was duration of time between first isolation of OXA-48-like isolate and outcome, \( p = 0.02 \). Nineteen patients formed part of the definitive therapy analysis as one patient’s treatment was withdrawn. Combination therapy was administered in 13 patients, with 9 of these receiving a carbapenem. Carbapenem-based definitive therapy demonstrated a survival benefit as compared to non-carbapenem therapy (OR for survival = 5.0, 95% CI 0.7–38). No difference in mortality was demonstrated for monotherapy versus combination therapy.

Tzouvelakis and colleagues, in their review of clinical studies of KPC-producing and metallo-β-lactamase-producing *Klebsiella pneumoniae* found that carbapenem-based combination therapy was superior to alternative agents (Tzouvelekis, Markogiannakis, Psychogiou, Tassios, & Daikos, 2012). Combination therapy appears to be superior for KPC-producing *K. pneumoniae* bloodstream infections but the exact combination and role of carbapenems is unknown (Munoz-Price, et al., 2013). A recent study on bacteraemias due to OXA-48 CPE demonstrated a mortality rate of 50% with no significant differences between definitive treatment groups (Navarro-San Francisco, et al., 2013). Carbapenem therapy was used in only 7 of 34 patients, yet the authors concluded that high-dose β-lactams (meropenem if MIC ≤ 4µg/ml) should be
included as part of combination therapy. Our data suggests improved survival with carbapenem-based therapy and we support the use of high-dose carbapenems (meropenem 2g tds in our cohort, adjusted accordingly for patients with renal dysfunction where continuous haemodialysis not utilized). The choice of carbapenem should be MIC-based and whether or not an additional agent is necessary is unknown. We did not find any trend towards improved survival between the monotherapy and combination therapy groups. It is acknowledged that the retrospective nature and small sample size of this study is a limitation and further studies are necessary to confirm these findings. The only significant difference between bacteraemic and non-bacteraemic patients was the LOS from time of first isolation of OXA-48-like isolate, to outcome. This most likely serves as a proxy for death as 6 of 9 bacteraemic patients died within a short timeframe, suggesting that isolation of an OXA-48-like CPE from blood is associated with early increased mortality. A short hospital LOS and high APACHE III score was shown to be a risk factor for death. This data suggests that patients admitted with a poor prognosis were likely to succumb to infection within a shorter time period highlighting the importance of prognostic assessment and the influence of patient comorbidities on outcomes. Although antimicrobial resistance in Gram negatives may impact on outcomes in the ICU, it is unclear to what extent other confounding factors influence the association (Shorr, 2009). It has been demonstrated that KPC-producing K. pneumoniae are less virulent in non-human in vivo models (Lavigne, et al., 2013; McLaughlin, et al., 2014). The apparent high mortality associated with CPE-related infections may be attributable more to the underlying illness and patient status than to the micro-organism itself.

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Conflict of interests

The authors have none to declare

References


### Table 1. Clinical characteristics of 20 ICU patients with OXA-48-like infections

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Gender</th>
<th>Underlying condition</th>
<th>APACHE III score</th>
<th>Immuno-suppressed</th>
<th>Infection type &amp; Organism</th>
<th>Empirical therapy (Carbapenem MIC, µg/ml)†</th>
<th>Definitive therapy (Carbapenem MIC, µg/ml)†</th>
<th>Hospital LOS (days)</th>
<th>Outcome (time from specimen to outcome, days)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>M</td>
<td>Liver transplant</td>
<td>65</td>
<td>Yes</td>
<td>SSI* K. pneumoniae</td>
<td>Meropenem (2)</td>
<td>Ceftriaxone + Amikacin</td>
<td>42</td>
<td>Died (12)</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>M</td>
<td>Colon carcinoma</td>
<td>53</td>
<td>No</td>
<td>SSI* K. pneumoniae</td>
<td>Meropenem (4) + Amikacin</td>
<td>Tigecycline</td>
<td>31</td>
<td>D/C (16)</td>
</tr>
<tr>
<td>3**</td>
<td>21</td>
<td>F</td>
<td>Aplastic anemia/ Bone marrow transplant</td>
<td>92</td>
<td>Yes</td>
<td>Pneumonia <em>C. freundii</em></td>
<td>Imipenem (NT) + Amikacin</td>
<td>Tigecycline + Ciprofloxacin</td>
<td>48</td>
<td>Died (20)</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>F</td>
<td>Rheumatoid arthritis/ Diverticular abscess</td>
<td>60</td>
<td>Yes</td>
<td>UTI &amp; clAI K. pneumoniae</td>
<td>Ciprofloxacin</td>
<td>Ciprofloxacin</td>
<td>38</td>
<td>D/C (22)</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>F</td>
<td>Sarcoma</td>
<td>80</td>
<td>Yes</td>
<td>Primary bacteraemia K. pneumoniae</td>
<td>Ertapenacim (NT)</td>
<td>Treatment withdrawn</td>
<td>13</td>
<td>Died (2)</td>
</tr>
<tr>
<td>6**</td>
<td>43</td>
<td>F</td>
<td>Chronic liver disease (cirrhosis)</td>
<td>41</td>
<td>No</td>
<td>Pneumonia K. oxytoxa</td>
<td>Ertapenacim (&gt;32)</td>
<td>Meropenem (&gt;32) + Ceftazidime</td>
<td>41</td>
<td>D/C (21)</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>F</td>
<td>Cholangiocarcinoma</td>
<td>69</td>
<td>Yes</td>
<td>clAI/Liver abscess K. pneumoniae</td>
<td>Ertapenacim (8)</td>
<td>Meropenem (4) + Cotrimoxazole</td>
<td>28</td>
<td>D/C (17)</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>M</td>
<td>Cholangiocarcinoma</td>
<td>68</td>
<td>No</td>
<td>SSI K. pneumoniae</td>
<td>Tigecycline + Amikacin</td>
<td>Meropenem (2) + Amikacin</td>
<td>75</td>
<td>D/C (65)</td>
</tr>
<tr>
<td>No.</td>
<td>Age</td>
<td>Sex</td>
<td>Diagnosis</td>
<td>Location/Complication</td>
<td>cIAI*</td>
<td>Cause of Infection</td>
<td>Initial Antibiotic Treatment</td>
<td>Final Outcome</td>
<td>LOS†</td>
<td></td>
</tr>
<tr>
<td>-----</td>
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<td>----------------------------------------</td>
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<td></td>
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<tr>
<td>9</td>
<td>59</td>
<td>F</td>
<td>Biliary leak</td>
<td>post-cholecystectomy</td>
<td>No</td>
<td>cIAI* K. pneumoniae</td>
<td>Meropenem (8) + Amikacin</td>
<td>Died (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>64</td>
<td>M</td>
<td>Cholangiocarcinoma/Chronic renal failure</td>
<td></td>
<td>No</td>
<td>Primary bacteraemia K. pneumoniae</td>
<td>Nil</td>
<td>Died (9)</td>
<td></td>
<td></td>
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<tr>
<td>11</td>
<td>63</td>
<td>F</td>
<td>Rectal carcinoma</td>
<td></td>
<td>Yes</td>
<td>Primary bacteraemia K. pneumoniae</td>
<td>Meropenem (NT) + Ciprofloxacin</td>
<td>Died (1)</td>
<td></td>
<td></td>
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<tr>
<td>12</td>
<td>37</td>
<td>F</td>
<td>Autoimmune hepatitis</td>
<td></td>
<td>No</td>
<td>Primary bacteraemia K. pneumoniae</td>
<td>Ertapenem</td>
<td>Died (13)</td>
<td></td>
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<tr>
<td>13</td>
<td>46</td>
<td>M</td>
<td>Colon carcinoma</td>
<td></td>
<td>Yes</td>
<td>SSI K. pneumoniae</td>
<td>Tigecycline + Ertapenem</td>
<td>D/C (33)</td>
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<tr>
<td>14</td>
<td>98</td>
<td>M</td>
<td>Pneumonia</td>
<td></td>
<td>No</td>
<td>Pneumonia K. pneumoniae</td>
<td>Ciprofloxacin + Cotrimoxazole</td>
<td>Died (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>55</td>
<td>F</td>
<td>Colon carcinoma</td>
<td></td>
<td>No</td>
<td>UTI K. pneumoniae</td>
<td>Tigecycline + Ertapenem</td>
<td>D/C (14)</td>
<td></td>
<td></td>
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<tr>
<td>16</td>
<td>64</td>
<td>F</td>
<td>Intestinal fistula post-surgery complication</td>
<td></td>
<td>No</td>
<td>cIAI K. pneumoniae</td>
<td>Piperacillin-tazobactam + Amikacin</td>
<td>D/C (32)</td>
<td></td>
<td></td>
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<tr>
<td>17</td>
<td>62</td>
<td>M</td>
<td>Pancreatic carcinoma</td>
<td></td>
<td>No</td>
<td>cIAI K. pneumoniae</td>
<td>Ertapenem (8)</td>
<td>D/C (11)</td>
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</tr>
<tr>
<td>18</td>
<td>68</td>
<td>M</td>
<td>Cholangiocarcinoma</td>
<td></td>
<td>No</td>
<td>cIAI K. pneumoniae</td>
<td>Ertapenem (8)</td>
<td>D/C (4)</td>
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<td></td>
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<tr>
<td>19</td>
<td>73</td>
<td>M</td>
<td>Cholangitis</td>
<td></td>
<td>No</td>
<td>cIAI* K. pneumoniae</td>
<td>Piperacillin-tazobactam</td>
<td>D/C (7)</td>
<td></td>
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<tr>
<td>20</td>
<td>48</td>
<td>M</td>
<td>Liver transplant</td>
<td></td>
<td>Yes</td>
<td>Primary bacteraemia K. pneumoniae</td>
<td>Ertapenem (4)</td>
<td>D/C (18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*bacteraemic infection
†carbapenem MIC for isolate where known
‡time from culture-diagnosis of infection to final outcome

LOS – length of stay; SSI – surgical site infection; UTI - urinary tract infection; cIAI – complicated intra-abdominal infection; D/C – discharged from hospital; NT – not tested.
Highlights:

2. Comparison of carbapenem versus non-carbapenem based therapy
3. Comparison of monotherapy versus combination therapy
4. Survival benefit for carbapenem-based therapy which is MIC-dependent
5. Underlying conditions and patient-specific factors impact on outcomes