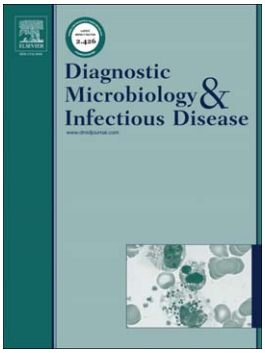

Antimicrobial treatment and outcomes of critically ill patients with OXA-48_{like} carbapenemase-producing Enterobacteriaceae infections

Warren Lowman, Gunter Schleicher

PII: S0732-8893(14)00403-9
DOI: doi: 10.1016/j.diagmicrobio.2014.09.023
Reference: DMB 13696

To appear in: *Diagnostic Microbiology and Infectious Disease*

Received date: 5 March 2014
Revised date: 22 September 2014
Accepted date: 26 September 2014

Please cite this article as: Lowman Warren, Schleicher Gunter, Antimicrobial treatment and outcomes of critically ill patients with OXA-48_{like} carbapenemase-producing Enterobacteriaceae infections, *Diagnostic Microbiology and Infectious Disease* (2014), doi: 10.1016/j.diagmicrobio.2014.09.023

Research note

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

Authors:

Warren Lowman[a,b]; Gunter Schleicher[b]

Microbiology Department, Pathlink Laboratories, Gauteng, South Africa[a]; Wits Donald Gordon Medical Centre, Johannesburg, South Africa[b]

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

#Address correspondence to Warren Lowman:

Pathlink Laboratories, 8 Sturdee Avenue, Rosebank, Johannesburg, Gauteng, South Africa

Tel: +27 (082) 922 0834 Fax: +27 (086) 6725745

warren.lowman@wits.co.za

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: bla_{NDM}; bla_{KPC}; $bla_{OXA\text{-}48\textit{like}}$; bla_{VIM}; bla_{IMP}; bla_{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 *Klebsiella pneumoniae* (n=18), *Klebsiella oxytoca* (n=1) and *Citrobacter freundii* (n=1). Isolates were confirmed OXA-$48_{\textit{like}}$ positive by PCR and no other carbapenemase genes were detected (18/20 phenotypically confirmed ESBL-producers)(Lowman, Marais, Ahmed, & Marcus, 2014). The MIC_{50}/MIC_{90} to meropenem for all isolates tested (n=15) and *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-ß-lactamase-producing *Klebsiella pneumoniae* found that carbapenem-based combination therapy was superior to alternative agents (Tzouvelekis, Markogiannakis, Psichogiou, 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 ß-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.

Funding

No funding source

Acknowledgements

We would like to thank Ronel Senekal for her assistance in collecting and collating data.

Conflict of interests

The authors have none to declare

References

CLSI (2013) Performance Standards for Antimicrobial Susceptibility Testing; Twenty Third Informational Supplement, M100-S23. In. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania, 19087-1898 USA.

Horan, TC, Andrus, M, & Dudeck, MA (2008) CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *American journal of infection control, 36*, 309-332.

Knaus, WA, Wagner, DP, Draper, EA, Zimmerman, JE, Bergner, M, Bastos, PG, Sirio, CA, Murphy, DJ, Lotring, T, Damiano, A, & et al. (1991) The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest, 100*, 1619-1636.

Lavigne, JP, Cuzon, G, Combescure, C, Bourg, G, Sotto, A, & Nordmann, P (2013) Virulence of Klebsiella pneumoniae isolates harboring bla KPC-2 carbapenemase gene in a Caenorhabditis elegans model. *PloS one, 8*, e67847.

Lowman, W, Marais, M, Ahmed, K, & Marcus, L (2014) Routine active surveillance for carbapenemase-producing Enterobacteriaceae from rectal swabs: diagnostic implications of multiplex polymerase chain reaction. *J Hosp Infect*.

McLaughlin, MM, Advincula, MR, Malczynski, M, Barajas, G, Qi, C, & Scheetz, MH (2014) Quantifying the clinical virulence of Klebsiella pneumoniae producing carbapenemase Klebsiella pneumoniae with a Galleria mellonella model and a pilot study to translate to patient outcomes. *BMC Infect Dis, 14*, 31.

Munoz-Price, LS, Poirel, L, Bonomo, RA, Schwaber, MJ, Daikos, GL, Cormican, M, Cornaglia, G, Garau, J, Gniadkowski, M, Hayden, MK, Kumarasamy, K, Livermore, DM, Maya, JJ, Nordmann, P, Patel, JB, Paterson, DL, Pitout, J, Villegas, MV, Wang, H, Woodford, N, & Quinn, JP (2013) Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. *Lancet Infect Dis, 13*, 785-796.

Navarro-San Francisco, C, Mora-Rillo, M, Romero-Gomez, MP, Moreno-Ramos, F, Rico-Nieto, A, Ruiz-Carrascoso, G, Gomez-Gil, R, Arribas-Lopez, JR, Mingorance, J, & Pano-Pardo, JR (2013)

Bacteraemia due to OXA-48-carbapenemase-producing Enterobacteriaceae: a major clinical challenge. *Clin Microbiol Infect, 19*, E72-79.

Poirel, L, Potron, A, & Nordmann, P (2012) OXA-48-like carbapenemases: the phantom menace. *J Antimicrob Chemother, 67*, 1597-1606.

Roberts, JA, & Lipman, J (2009) Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med, 37*, 840-851; quiz 859.

Shorr, AF (2009) Review of studies of the impact on Gram-negative bacterial resistance on outcomes in the intensive care unit. *Crit Care Med, 37*, 1463-1469.

Tzouvelekis, LS, Markogiannakis, A, Psichogiou, M, Tassios, PT, & Daikos, GL (2012) Carbapenemases in Klebsiella pneumoniae and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev, 25*, 682-707.

Table 1. Clinical characteristics of 20 ICU patients with OXA-48$_{like}$ infections

Patient No.	Age	Gender	Underlying condition	APACHE III score	Immuno-suppressed	Infection type & Organism	Empirical therapy (Carbapenem MIC, µg/ml)†	Definitive therapy (Carbapenem MIC, µg/ml)†	Hospital LOS (days)	Outcome (time from specimen to outcome, days)‡
1	55	M	Liver transplant	65	Yes	SSI* *K. pneumoniae*	Meropenem (2)	Ceftriaxone + Amikacin	42	Died (12)
2	68	M	Colon carcinoma	53	No	SSI* *K. pneumoniae*	Meropenem (4) + Amikacin	Tigecycline	31	D/C (16)
3**	21	F	Aplastic anemia/ Bone marrow transplant	92	Yes	Pneumonia *C. freundii*	Imipenem (NT) + Amikacin	Tigecycline + Ciprofloxacin	48	Died (20)
4	78	F	Rheumatoid arthritis/ Diverticular abscess	60	Yes	UTI & cIAI *K. pneumoniae*	Ciprofloxacin	Ciprofloxacin	38	D/C (22)
5	41	F	Sarcoma	80	Yes	Primary bacteraemia *K. pneumoniae*	Ertapenem (NT)	Treatment withdrawn	13	Died (2)
6**	43	F	Chronic liver disease (cirrhosis)	41	No	Pneumonia *K. oxytoca*	Ertapenem (>32)	Meropenem (>32) + Ceftazidime	41	D/C (21)
7	37	F	Cholangio-carcinoma	69	Yes	cIAI/ Liver abscess *K. pneumoniae*	Ertapenem (8)	Meropenem (4) + Cotrimoxazole	28	D/C (17)
8	57	M	Cholangio-carcinoma	68	No	SSI *K. pneumoniae*	Tigecycline + Amikacin	Meropenem (2) + Amikacin	75	D/C (65)

9	59	F	Biliary leak post-chole-cystectomy	53	No	cIAI* *K. pneumoniae*	Meropenem (8) + Amikacin	Meropenem (8) + Ciprofloxacin	19	Died (3)
10	64	M	Cholangio-carcinoma/ Chronic renal failure	62	No	Primary bacteraemia *K. pneumoniae*	Nil	Cefepime	19	Died (9)
11	63	F	Rectal carcinoma	89	Yes	Primary bacteraemia *K. pneumoniae*	Meropenem (NT) + Ciprofloxacin	Meropenem + Ciprofloxacin	9	Died (1)
12	37	F	Autoimmune hepatitis	121	No	Primary bacteraemia *K. pneumoniae*	Ertapenem	Tigecycline	21	Died (13)
13	46	M	Colon carcinoma	66	Yes	SSI *K. pneumoniae*	Tigecycline + Amikacin	Tigecycline	57	D/C (33)
14	98	M	Pneumonia	105	No	Pneumonia *K. pneumoniae*	Ertapenem	Ciprofloxacin + Cotrimoxazole	23	Died (14)
15	55	F	Colon carcinoma	62	No	UTI *K. pneumoniae*	Tigecycline + Ertapenem	Meropenem (1) + Amikacin	42	D/C (14)
16	64	F	Intestinal fistula post-surgery complication	59	No	cIAI *K. pneumoniae*	Piperacillin-tazobactam + Amikacin	Colistin + Amikacin	60	D/C (32)
17	62	M	Pancreatic carcinoma	39	No	cIAI *K. pneumoniae*	Ertapenem (8)	Meropenem (0.5) + Amikacin	18	D/C (11)
18	68	M	Cholangio-carcinoma	49	No	cIAI *K. pneumoniae*	Ertapenem (8)	Ertapenem (8)	20	D/C (4)
19	73	M	Cholangitis	95	No	cIAI* *K. pneumoniae*	Piperacillin-tazobactam	Meropenem (4) + Ciprofloxacin	7	D/C (7)
20	48	M	Liver transplant	65	Yes	Primary bacteraemia *K. pneumoniae*	Ertapenem (4)	Meropenem (0.5) + Ceftazidime	22	D/C (18)

*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:

1. Clinical characteristics and outcomes of critically ill patients with serious OXA-48 infections.
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