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Characteristics, risk factors and outcomes of carbapenem-resistant *Klebsiella pneumoniae* infections in the intensive care unit

Konstantinos Z. Vardakas [a,b,*], Dimitrios K. Matthaiou [d], Matthew E. Falagas [a,b,f], Elli Antypa [c], Asimoula Koteli [e], Eleni Antoniadou [c]

[a] *Alfa Institute of Biomedical Sciences, Athens, Greece*
[b] *Department of Internal Medicine-Infectious Diseases, Iaso General Hospital, Iaso Group, Athens, Greece*
[c] *Intensive Care Unit, Gennimatas General Hospital, Thessaloniki, Greece*
[d] *Intensive Care Unit, Attikon University Hospital, Athens, Greece*
[e] *Department of Microbiology, Gennimatas General Hospital, Thessaloniki, Greece*
[f] *Department of Medicine, Tufts University School of Medicine, Boston, MA, USA*

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Summary *Objective:* To study the characteristics, risk factors and outcomes of intensive care unit (ICU) patients with carbapenem-resistant (CRKp) and carbapenem-susceptible (CSKp) *Klebsiella pneumoniae* infections.
Methods: A retrospective cohort of patients with *K. pneumoniae* infections in an eight-bed ICU between January 2006 and October 2009.
Results: During the study period, 104 patients were diagnosed with *K. pneumoniae* infection (80 CRKp and 24 CSKp). Isolation of CRKp increased gradually during the study period, while isolation of CSKp remained constant. The mean age of patients was 66.3 ± 14.3 years. The mean APACHE II score was 17.9 ± 6.9. The median duration of ICU stay until the infection was 15 days. Thirty five patients (33.7%) had primary and 30 (28.8%) had secondary bacteremia. Seventy-two patients (69.2%) died in the ICU. No independent risk factors for development of CRKp infections were identified in the multivariate analysis. Treatment failure ($p = 0.001$) was the only independent predictor of mortality in the multivariate analysis (APACHE II, shock, multi-organ failure, respiratory failure, acute renal failure, acidosis and

* Corresponding author. 9 Neapoleos street, 151 23 Marousi, Athens, Greece. Tel.: +30 6947939600; fax: +30 2106839605.
E-mail address: k.vardakas@aibs.gr (K.Z. Vardakas).

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extensive-drug resistance were included in the model). No difference in mortality was found between patients with CRKp and CSKp isolates.
Conclusions: Infection due to *K. pneumoniae* in the ICU was associated with high mortality. Control of the infection was the most important determinant of the outcome of critically ill patients.

Introduction

Outbreaks due to carbapenem-resistant *Klebsiella pneumoniae* (CRKp) infections are frequently reported both in hospitals and long-term care facilities,[1–4] and their incidence increases worldwide.[4–6] Lately, CRKp were included in the US Centers for Disease Control and Prevention (CDC) list of the most troublesome bacteria along with *Clostridium difficille* and methicillin-resistant *Staphylococcus aureus*. Resistance to carbapenems may be mediated via modifications in the permeability of the outer membrane, up-regulation of efflux pumps with or without hyperproduction of AmpC β-lactamases (cephalosporinases) or extended spectrum β-lactamases (ESBLs), or production of specific carbapenem-hydrolyzing β-lactamases (carbapenemases).[7] The presence of carbapenemases may be accompanied by genes conferring resistance to other β-lactams as well as fluoroquinolones. Hence, treatment options are limited and CRKp infections have been associated with increased mortality and excess cost.[8–10]

In several countries CRKp infections are considered endemic (most hospitals in the country are repeatedly seeing cases from autochthonous sources).[7,11] Most of the available studies have described mixed populations of hospitalized patients receiving treatment in the general medical or surgical wards and the intensive care unit (ICU).[12–15] In this study, we sought to investigate the characteristics, risk factors, and outcomes of ICU patients with CRKp infections.

Methods

This study was reported according to the STROBE recommendations (Strengthening and Reporting of Observational studies in Epidemiology).[16] It was performed from January 2006 till October 2009 at the ICU of Gennimatas General Hospital, Thessaloniki, Greece, which is a 350-bed tertiary centre. The ICU has 8 beds and covers for all medical and surgical cases. Pathogens were identified from the electronic records of the department of Microbiology and the clinical data were collected retrospectively using medical records of the ICU. Patients were followed from ICU admission until discharge from the ICU or death. Approval was granted by the Ethics Committee of the hospital.

Every patient receiving care in the ICU with a positive culture for *K. pneumoniae* was included in the study if the isolate was deemed responsible for infection. A patient was eligible for inclusion if the infection developed during the ICU stay or was admitted to the ICU for this infection. All patients were included in the analysis of mortality, while only patients that developed CRKp infection in the ICU were included in the analysis for risk factors. If more than one episode of *K. pneumoniae* infection occurred in the same patient, only the first episode could be included, regardless the initial susceptibility of the isolate or subsequent changes. Patients with or without other previous or concurrent infections, were eligible for inclusion.

The scope of the study was to study the characteristics of patients with *K. pneumoniae* infections, the risk factors for development of CRKP infections and all cause ICU mortality in the whole cohort and in pre-specified subgroups (effective empirical treatment, bacteremia and resistance pattern). Data regarding demographic characteristics and patients' medical and surgical history (including data from the index ICU stay period prior the *K. pneumoniae* infection), interventions during ICU stay and antibiotic treatment, other bacteria or fungi isolated from the same clinical specimen, different specimens at the same time or variable specimens in different time points soon prior or after the index episode of *K. pneumoniae* infection were collected.

Bacteremia was defined as isolation of *K. pneumoniae* from at least one blood culture in addition to symptoms and signs compatible with systemic inflammatory response syndrome (SIRS, fever or hypothermia, respiratory rate of more than 20 breaths per minute, tachycardia $>$90 beats/min and white blood cell count $>$11000 μl or $<$4000/μl). Primary bacteremia was defined as bacteremia without an identified site of infection, while secondary was defined as the isolation of *K. pneumoniae* from blood and another site of infection or the *K. pneumoniae* strain was isolated from blood and an obvious site of infection was identified (e.g. consolidation in chest X-ray or computer tomography scan, edema of or fluid collection around the gall bladder, edema, rash or fluid drainage from skin or surgical site infection, etc). The Pitt score was used to assess the severity of bacteremia. Breakthrough bacteremia was defined as the one developing while the patient was receiving one of the antibiotics for at least 48 h prior the positive culture.

Empirical treatment was defined as prescription of antibiotics before the culture result was available; empirical treatment was considered appropriate when the isolated pathogen was susceptible *in vitro* to the empirically administered antibiotic according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints at the time of infection. Multi-drug resistance (MDR), extensive-drug resistance (XDR) and pan-drug resistance (PDR) bacteria were defined according to pre-specified criteria.[17] Treatment failure was defined as death due to infection, no change or deterioration of patient's condition despite appropriate antibiotic treatment.