Infections caused by carbapenem-resistant *Klebsiella pneumoniae* among patients in intensive care units in Greece: a multi-centre study on clinical outcome and therapeutic options

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Abstract

Infections due to carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) have emerged as a public health problem worldwide given their spread dynamics and the limited therapeutic options. Our aim was to study the clinical outcome of patients with CR-KP infections in relation to antimicrobial treatment. CR-KP infections that occurred in a 10-month period (September 2009 to June 2010) in patients admitted to 19 intensive care units all over Greece were studied. A total of 127 CR-KP infections were reported. Central venous catheter bacteraemia was the most frequent infection, followed by ventilator-associated pneumonia (39 (30.7%) and 35 (27.6%) cases, respectively). Resistance to colistin, tigecycline, gentamicin and amikacin was detected in 20%, 33%, 21% and 64% of isolates, respectively. Regarding treatment, 107 cases received active treatment, including 1 or ≥2 active antibiotics in 65 (60.7%) and 42 (39.3%) cases, respectively. The most frequent combination was colistin plus aminoglycoside and tigecycline plus aminoglycoside (17 and 11 cases, respectively). Forty-eight (45.2%) of the cases that received active treatment were considered clinical failures, with 23.5% mortality at 14 days. Logistic regression analysis revealed that age ≤55 years, non-immunocompromised patients and patients who received colistin had higher successful response rates, while patients ≤55 years old had lower mortality rates at 14 days after the introduction of active treatment. CR-KP infections are associated with a significant clinical failure rate. Colistin remains a valuable antimicrobial agent for treating these infections, while the rise of resistance to the last available antibiotics further limits treatment options.

Keywords: Carbapenem-resistance, intensive care unit, *Klebsiella pneumoniae*, KPC, mortality
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Introduction

Carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) is an emerging threat both for the patient and the healthcare system globally. Infections due to CR-KP strains usually concern critically ill patients and are associated with high morbidity, mortality, prolongation of hospitalization and costs [1–5]. Treatment options are limited and include aminoglycosides, colistin, tigecycline and fosfomycin [6,7]. However, the activity of the latter agents against CR-KP seems to also depend on pk/pd parameters, which are still under evaluation [8–10]. Additionally, the increasing use of these antibiotics has been followed by reports describing the emergence of Gram-negative isolates resistant to these agents [11–13].

In Greece at the beginning of the past decade VIM-1-producing *K. pneumoniae* became endemic in intensive care units

(ICUs) [14]. Subsequently, the emergence in 2007 and the monoclonal spread of KPC-producing *K. pneumoniae* strains displaced VIM-producing strains and dominated across the country during the last 2 years [2,15]. Infections due to these multidrug-resistant pathogens are a new reality and their treatment constitutes a challenge, given that experience in treating infections caused by KPC-producing isolates is limited and the optimal treatment either as monotherapy or as combination therapy has not yet been established. The aim of this study was to investigate the characteristics of patients with infections due to CR-KP pathogens, as well as their outcome in relation to antimicrobial treatment.

Material and Methods

In December 2009 the Hellenic Center for Disease Control and Prevention invited all (69) ICUs in the country to participate in this multicentre study. Of them, 19 ICUs agreed to participate. These were ICUs providing services to both medical and surgical patients and had a mean number of eight beds (range, 5–12 beds).

From September 2009 through to June 2010, all ICU patients with a microbiologically confirmed infection due to CR-KP were recorded. Data were collected retrospectively during September–December 2009 and prospectively during January–June 2010. The following data were collected using one form per case: demographic, underlying and epidemiologic characteristics, microbiological data and clinical response to therapeutic schemes. Data were collected by one trained physician per ICU. The forms were sent to the Hellenic Center for Disease Control and Prevention for statistical analysis. The study has been performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Bloodstream infection, ventilator-associated pneumonia (VAP), urinary tract infection, intra-abdominal infection and surgical site infection were defined in accordance with the CDC/NHSN definitions [16]. APACHE II score was determined as follows: low severity (0–14 score), medium severity (15–19 score) and high severity (≥20 score). Active antimicrobial treatment was defined as antimicrobial therapy with ≥1 active agent according to the susceptibility test administered for ≥48 h. Active monotherapy was defined as therapy with one active agent according to the susceptibility test, whereas active combined treatment was defined as a combination with >1 active agent according to the susceptibility test. We determined the clinical outcome at 14 days after the introduction of active antimicrobial treatment for the CR-KP infection (successful response or failure) and the ICU mortality as the final outcome during ICU hospitalization (discharge or death). Successful response was defined as the absence or improvement of clinical signs and/or symptoms of the patient at 14 days after the introduction of active antimicrobials. Failure was defined as the worsening or persistence of clinical signs and/or symptoms, the relapse of infection, and/or the death of the patient at 14 days after the introduction of active treatment. Colistin was given every 8–12 h for a total daily dose of 9×10^6 IU. The loading dose was used with tigecycline, which was administered every 12 h (100–200 mg/day). Gentamicin was administered every 24 h (total daily dose 4–5 mg/kg) and meropenem was administered by extended infusion at a dose of 2 g every 8 h. Drug dosages were adjusted on the basis of creatinine clearance.

The clinical samples collected from the patients were tested for CR-KP using the following methods. (i) Identification and routine susceptibility testing was performed using various automated systems, mainly the Vitek-2 system (Biomerieux, Marcy l Etoile, France). Tigecycline MIC was determined using E-test methodology. Antimicrobial agent MICs were evaluated according to the Clinical and Laboratory Standards Institute guidelines (CLSI) [17] whereas colistin and tigecycline MICs were interpreted in accordance with European Committee on Antimicrobial Susceptibility Testing breakpoints (EUCAST) [18]. (ii) In most cases, boronic acid and EDTA test methodologies were used for detecting isolates producing KPC or MBL carbapenemases, respectively [19,20].

Statistical analysis

The chi-square test was applied to test the association between categorical variables. Multiple logistic regression (forward likelihood ratio election) was applied, with entry criterion based on the significance of the score statistic and removal criterion based on the probability of a likelihood ratio statistic defined by the partial likelihood estimates, in order to investigate the association between the outcome and the characteristics of the patients. Multiple logistic regression was also applied in order to investigate the association of VAP or central venous catheter (CVC)-related bacteraemia with the characteristics of patients. p-Values of ≤0.05 were considered statistically significant. Statistical analysis was performed using the SPSS software (v.13; SPSS Inc., Chicago, IL, USA).

Results

Nineteen ICUs reported 127 CR-KP microbiologically documented infections. Data were collected retrospectively in