High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality

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Abstract

Carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) is becoming a common cause of healthcare-associated infection in Italy, with high morbidity and mortality. Prevalent CR-KP clones and resistance mechanisms vary between regions and over time. Therapeutic approaches and their impact on mortality have to be investigated. We performed a prospective study of patients with CR-KP isolation, hospitalized in nine hospitals of Rome, Italy, from December 2010 to May 2011, to describe the molecular epidemiology, antibiotic treatment and risk factors for mortality. Overall, 97 patients (60% male, median age 69 years) were enrolled. Strains producing *bla*KPC-3 were identified in 89 patients, *bla*VIM in three patients and *bla*CTX-M-15 plus porin defects in the remaining five patients. Inter-hospital spread of two major clones, ST512 and ST258, was found. Overall, 36.1% and 20.4% of strains were also resistant to colistin and tigecycline, respectively. Infection was diagnosed in 91 patients who received appropriate antibiotic treatment, combination therapy and removal of the infectious source in 73.6%, 59.3% and 28.5% of cases, respectively. Overall, 23 different antibiotic regimens were prescribed. In-hospital mortality was 25.8%. Multivariate analysis adjusted for appropriate treatment, combination therapy and infectious-source removal, showed that Charlson comorbidity score, intensive-care unit onset of infection, bacteraemia and infection due to a colistin-resistant CR-KP strain were independent risk factors for mortality. The spread of clones producing *K. pneumoniae* carbapenemases, mainly ST258, is currently the major cause of CR-KP infection in central Italy. We observed a high rate of resistance to colistin that is independently associated with worse outcome.

Keywords: Carbapenem resistance, carbapenemase, colistin resistance, in-hospital mortality, *Klebsiella pneumoniae*
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Introduction

Carbapenem resistance represents the current challenge in the treatment of infections caused by Gram-negative bacteria [1]. In Italy, since the first detections of resistance to carbapenems in *Acinetobacter baumannii* and *Pseudomonas aeruginosa* during the late 1990s [2,3], concern has risen for the detection of

carbapenem-resistant Enterobacteriaceae, especially *Klebsiella pneumoniae* [4–7].

Carbapenem resistance can be the result of various mechanisms including the production of a carbapenemase enzyme, such as metallo-β-lactamases, *K. pneumoniae* carbapenemases (KPCs), and OXA-48; and the combination of porins defect plus extended spectrum β-lactamase (ESBL) or AmpC enzyme production [8]. Strains producing carbapenemases are more resistant to carbapenems compared with those with other mechanisms of resistance, and their genes may be achieved horizontally, allowing them to spread widely. In Italy, carbapenem-resistant *K. pneumoniae* (CR-KP) strains showing the combination of porins defect plus ESBL production were becoming common in some centres [9], whereas in others carbapenemase-producing strains were prevalent and, in most cases, they were clonally related [10].

The therapeutic armamentarium against infection by CR-KP is limited to antibiotics with high potential toxicity, such as colistin and gentamicin, or with a poor pharmacokinetic/pharmacodynamic profile, as tigecycline. The use of these antibiotics has been associated with the emergence of resistance against them [11]. For these reasons, most authors recommend using combination therapy with different classes of antibiotics to improve the efficacy and to prevent the emergence of further resistance [12]. However, the evidence about which combination is optimal is far from clear, and the impact of resistance to the last antimicrobial choices available in clinical practice is unknown.

We performed a prospective multicentre study in nine hospitals in Rome, Italy, to assess which are the current prevalent clones and mechanisms of resistance among CR-KP isolates, to describe the characteristics of patients colonized or infected by such strains, and to analyse the therapeutic management of patients with CR-KP infection and the predictors of mortality in these patients.

Methods

Study design and setting

We performed a multicentre prospective observational study based on an alert system provided by nine microbiology laboratories belonging to the SEERBIO-GRAB network. These laboratories serve a population of *c.* 2.5 million people in Rome, and analyse clinical samples collected in one teaching institution, six tertiary hospitals, one clinical and research institute, and one long-term care facility, with a total of 4000 beds, ranging from 100 to 1200 beds per centre.

During December 2010 through to May 2011, the clinical and microbiological data of all consecutive patients with isolation of a *K. pneumoniae* strain showing reduced susceptibility to ertapenem (MIC $\geq$ 1 mg/L), from different specimens, were collected. An investigator contacted the participating centres to monitor the inclusion of all eligible cases. The completeness and consistency of the protocols were systematically reviewed before data were entered into the database.

Diagnostic and therapeutic management for all patients, including the need to obtain surveillance cultures, was not standardized and decisions were made at the discretion of the attending physician.

The study involved the analysis of existing clinical and laboratory data that were anonymous (an alphanumeric code, composed of a letter identifying the hospital of origin and the number indicating the clinical history, was assigned to each patient) before being entered in the database. Hence, according to local and national regulations, this analysis was exempt from formal approval by the Ethics Committee.

Clinical data and definitions

The medical charts of the patients were reviewed according to a pre-established protocol including the following variables: age, sex, diabetes, chronic obstructive pulmonary disease, renal insufficiency (with or without dialysis), liver cirrhosis, active cancer, human immunodeficiency virus infection, solid organ transplantation, haematological disease with or without stem cell transplantation, and corticosteroid therapy ($\geq$ 10 mg/day of prednisone during $\geq$ 15 days).

Data on prior healthcare exposure included: admission from other hospital or long-term care facility, previous hospitalization in the past 12 months, prior admission to intensive-care unit (ICU) or major surgery in the past 30 days, and receipt of any antibiotic during $\geq$ 48 h in the past 30 days.

Dates of hospital admission and of CR-KP isolation, ward of stay, and presence of devices including central venous catheter (CVC), mechanical ventilation and urinary catheter at the time of CR-KP isolation were recorded.

Infection was established according to standard definitions [13], the probable infectious source was determined on the basis of the microbiological results and physician's judgment. Bloodstream infections (BSI) were defined as low-risk BSI if the portal of entry was the CVC or urinary tract, and as high-risk BSI in the other cases [14].

Data on therapeutic management included: type, dosage, route of administration and dates of start and of end for any antibiotic. Appropriate antimicrobial therapy was defined as treatment with at least one *in vitro* active antibiotic for a minimum of 48 h [15]. Removal of the infectious source was also recorded.

Outcome was evaluated using the following: development of septic shock; in-hospital death; and length of hospitalization from the CR-KP isolation.