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Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study

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Abstract

Knowledge of carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) colonization is important to prevent nosocomial spread but also to start prompt adequate antibiotic therapy in patients with suspicion of infection. However, few studies have examined the incidence and risk factors for CR-KP bloodstream infection (BSI) among rectal carriers. To identify risk factors for CR-KP BSI among carriers, we performed a multicentre prospective matched case–control study of all adult CR-KP rectal carriers hospitalized in five tertiary teaching hospitals in Italy over a 2-year period. Carriers who developed CR-KP BSI were compared with those who did not develop subsequent BSI. Overall, 143 CR-KP BSIs were compared with 572 controls without a documented infection during their hospitalization. Multivariate analysis revealed that admission to the Intensive Care Unit (ICU) (OR, 1.65; 95% CI, 1.05–2.59; p 0.03), abdominal invasive procedure (OR, 1.87; 95% CI, 1.16–3.04; p 0.01), chemotherapy/radiation therapy (OR, 3.07; 95% CI, 1.78–5.29; p <0.0001), and number of additional colonization sites (OR, 3.37 per site; 95% CI, 2.56–4.43; p <0.0001) were independent risk factors for CR-KP BSI development among CR-KP rectal carriers. A CR-KP BSI risk score ranging from 0 to 28 was developed based on these four independent variables. At a cut-off of ≥2 the model exhibited a sensitivity, specificity, positive predictive value and negative predictive value of 93%, 42%, 29% and 93%, respectively. Colonization at multiple sites with CR-KP was the strongest predictor of BSI development in our large cohort of CR-KP rectal carriers.

Keywords: Bloodstream infection, carbapenem resistance, colonization status, rectal carriers
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Introduction

Bloodstream infection (BSI) with carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) is associated with high morbidity and mortality [1]. In-hospital mortality of patients with CR-KP BSI is higher than that of patients with other types of CR-KP infection [2,3]. Timely control of the source and appropriate antibiotic treatment have been associated with better survival [4–7].

CR-KP infection is usually preceded by colonization [8,9]. However, the incidence rate and risk factors for CR-KP BSI among carriers is poorly understood. To date, only two studies have analysed the risk factors for CR-KP infection among rectal carriers. In such studies, patients with several types of conditions were considered to have CR-KP infection, from those with positive clinical samples without signs or

symptoms of infection, to patients with urinary tract infection, ventilator-associated pneumonia, surgical site infection, osteomyelitis and finally BSI [10,11]. Thus we believe that a study focusing only on risk factors for CR-KP BSI among carriers may provide physicians with useful information for managing the most definitively-diagnosed severe manifestation of CR-KP infection.

With the aim of developing a risk assessment for CR-KP BSI among CR-KP carriers, we performed a multicentre prospective case–control study at five large tertiary-care teaching hospitals in Italy over a 2-year study period.

Material and Methods

Study design and population

We performed a multicentre, prospective observational case–control study of all adult (≥18 years) patients with a CR-KP positive rectal swab, hospitalized from 1 January 2012 to 31 December 2013, to identify risk factors for CR-KP BSI.

Cases consisted of patients with at least one episode of CR-KP BSI and a positive rectal swab screening within 90 days before drawing the positive blood cultures (BCs). Each case patient was included only once at the time of the first CR-KP isolation from BCs (index culture), even if more than one CR-KP BSI was reported. The control group consisted of the rectal carriers who did not develop subsequent CR-KP BSI or other relevant infections (pneumonia, intra-abdominal infection or urinary tract infection). Matching was performed at a ratio of 1:4 according to the time of the primary positive CR-KP rectal swab (within the same month) and the time at risk of having a subsequent infection (i.e. controls had to have the same days of CR-KP carriage and follow-up time as their matched cases prior to CR-KP BSI onset).

Setting

The study was carried out in five large tertiary-care teaching hospitals in Italy with a cumulative admission rate of about 200 000 patients per year.

Rectal swabs were routinely performed at each study site for all hospitalized patients with at least one of the following criteria: (i) transfer from another hospital or long-term care facility; (ii) sharing a room with a newly diagnosed CR-KP infection or colonization patient; and (iii) admission to a high-risk unit, including the intensive care unit (ICU), solid organ transplant (SOT) unit and haematology departments. The surveillance of other sites beside stools was not systematically performed either in the ICU or in other settings.

Data

Data were collected prospectively in a standardized case report form. Underlying diseases were recorded according to the Charlson's score [12]. The risk factor variables were considered from the time of diagnosis of colonization to BSI onset (cases) or hospital discharge (controls). Invasive hepatobiliary procedures included hepatic surgery, liver transplantation, endoscopic retrograde cholangiopancreatography, percutaneous biliary drainage and implant of biliary stent; invasive abdominal procedures included open abdominal surgery, endoscopic abdominal surgery and percutaneous drainage; other invasive procedures not mentioned above were also recorded. Corticosteroid therapy was defined by 16 mg prednisone-equivalent per day for >15 days; neutropenia was defined as <500 neutrophil cells per microlitre of blood for ≥7 days; chemotherapy and/or radiation therapy were defined as receipt of cytotoxic antineoplastic drugs or ionizing radiation for cancer cure or palliation. Patients were followed until hospital discharge or in-hospital mortality.

Definitions

Rectal carriers were defined as patients with CR-KP isolation from the rectal swab in the absence of symptoms and signs of invasive infection. In addition, every other sample positive for CR-KP other than blood cultures, including urine samples, respiratory samples, surgical site cultures and other skin cultures, obtained from patients without clinical signs of infection and who had not received a specific antibiotic treatment, were considered as colonization apart from that occurring in stools. CR-KP BSI was defined as a BSI documented by blood culture positivity (at least one specimen) for a CR-KP strain and clinical signs of the systemic inflammatory response syndrome [7]. BSI onset was considered as the date of the index BC collection (i.e. the first BC that yielded the study isolate).

Microbiological study

Rectal swabs were inoculated on a chromogenic agar plate (Oxoid Brilliance CRE; Thermo Fisher Scientific, Cambridge UK) containing a carbapenem antibiotic as selective agent. Blood cultures were incubated using the BacTAlert automated system (bioMérieux, Marcy l'Etoile, France). The Vitek 2 automated system (bioMérieux) was used for isolate identification and carbapenem resistance testing. Minimum inhibitory concentrations (MICs) were classified according to Clinical and Laboratory Standards Institute (CLSI) breakpoints [13]. Bla genes were identified by polymerase chain reaction (PCR) and sequencing according to standard procedures [14].