Asymptomatic rectal carriage of *bla*$_{KPC}$ producing carbapenem-resistant Enterobacteriaceae: who is prone to become clinically infected?

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Abstract

Carbapenem-resistant Enterobacteriaceae (CRE) are emerging extremely drug-resistant pathogens; *bla*$_{KPC}$ is the predominant carbapenemase in Israel. Early detection of asymptomatic rectal carriers is important for infection control purposes. We aimed to determine who among newly identified CRE rectal carriers is prone to have a subsequent clinical specimen with CRE. A matched case-control study was conducted in a tertiary care teaching hospital in Israel. Cases with a primary positive CRE rectal test and subsequent CRE clinical specimens were matched in a 1:2 ratio with CRE rectal carriers who did not develop subsequent CRE clinical specimens (controls). Matching was based on calendar time of primary CRE isolation, whether the primary CRE isolation was ≤48 h or >48 h after hospital admission, and time at risk to have a subsequent clinical specimen. Data were extracted from the patients' medical records and from the hospital's computerized database. One hundred and thirty-two newly identified CRE rectal carriers (44 cases, 88 controls) were included. The median time interval between screening and subsequent clinical specimens was 11 days (range, 3–27); 86% of the clinical specimens were classified as true infections. Independent predictors of subsequent CRE clinical specimens were: admission to the intensive care unit, having a central venous catheter, receipt of antibiotics, and diabetes mellitus. Identification of the risk factors for subsequent infections among CRE-colonized patients can be used to control modifiable risk factors and to direct empirical antimicrobial therapy when necessary.

Keywords: carbapenem-resistant Enterobacteriaceae, infection, Klebsiella pneumoniae carbapenemase, rectal carriage, risk factors
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Introduction

Carbapenem-resistant *Enterobacteriaceae* (CRE) are emerging extremely drug-resistant pathogens [1]. Enteric strains that harbour carbapenemases, which are plasmid-encoded enzymes, show remarkable epidemic success and have been associated with local, regional and intercontinental dissemination. Such strains consist primarily of *Klebsiella pneumoniae* that produce the serine carbapenemase Klebsiella pneumoniae carbapenemase (KPC) or the metallo-beta-lactamases VIM or NDM-1 [2,3]. These organisms are typically resistant to nearly all available antimicrobial agents [4] and infections by them are associated with an increased risk of mortality [5–7]. Thus, the spread of CRE harbouring carbapenemases is a clinical and public health problem.

Strict contact isolation and physical separation of carriers from non-carriers are key components in containing CRE in acute care hospitals [8]. Relying solely on clinical cultures will not detect the majority of CRE carriers [9]; therefore, active surveillance of patients at high risk of CRE carriage is strongly recommended [4,10]. Sites of CRE carriage include the lower gastrointestinal tract, the oropharynx, skin and urine [11]. The primary surveillance screening site, which has been advocated by the US Centers for Disease Control and Prevention

(CDC) and the European Society of Clinical Microbiology and Infectious Diseases, is the stool or rectal swab [4,10]. Indeed, several studies have demonstrated the role of active surveillance in the control of CRE outbreaks [12,13].

While the implications of having a positive CRE surveillance test are clear in terms of infection control strategy (i.e. asymptomatic carriers should be cohorted with clinically infected patients), the impact of detection of asymptomatic colonization on subsequent infection is unclear. In this study we aimed to determine who among newly identified CRE rectal carriers is prone to have a subsequent clinical specimen with CRE.

Methods

Study setting, patient population and definitions

The Tel Aviv Sourasky Medical Centre is a 1200-bed tertiary care teaching hospital in Tel Aviv, Israel. This hospital (like many other Israeli hospitals) has had ongoing CRE outbreaks since 2006 (mainly bla_{KPC} producing *K. pneumoniae* ST258). Cohorting with dedicated staff and strict contact isolation precautions have been enforced for all CRE patients since mid-2007. In addition, screening has been routinely performed for all patients hospitalized in acute or chronic care facilities in the past year and for contacts of newly identified CRE patients [14]. Patients are not cohorted until positive screening results are finalized.

The study population included patients who were identified as CRE carriers by rectal screening tests and had not had prior positive clinical cultures for CRE at the study hospital. Exclusion criteria were age <18 years and affiliation to the obstetrics and gynaecology unit. Data were extracted from the hospital's computerized administrative and laboratory data repositories.

Study design

A matched case-control study was performed. Cases included all patients with a primary positive CRE rectal test and a subsequent positive CRE clinical culture between 1 May 2007 and 30 April 2009. A clinical culture was defined as any culture other than stool or rectal swab; in case of multiple subsequent CRE clinical cultures, the one most proximal to the positive screening test was assessed. For each case, matched controls were selected at a 1:2 ratio from a pool of patients with a primary positive CRE rectal test and no subsequent positive CRE clinical cultures. Matching was based on (i) calendar time (month/year) of the primary positive CRE rectal test; (ii) whether detection of primary CRE rectal carriage was upon admission or later during hospital stay (≤48 h or >48 h from hospital admission); and (iii) follow-up time, defined as the time-at-risk to develop positive clinical samples after the positive screening test (i.e. controls had to have at least the same follow-up time as their matched case and were censored when reaching the same follow-up time as their matched case).

Data collection

Data were extracted from the patients' medical records and from a hospital computerized database according to a pre-prepared questionnaire. Three possible predictors of subsequent positive CRE clinical specimens were measured as continuous variables: age, days in hospital in the 30 days before screening, and days in hospital during the follow-up period. The following possible predictors were measured as categorical variables: sex, admission from a long-term care facility or from another hospital, co-morbid conditions (diabetes mellitus (DM), cardiovascular, renal, lung or neurological disease, malignancy, immunodeficiency, skin ulcers), debilitated functional state, hospital unit at the time of screening, contact with the healthcare system 30 days before screening (hospitalization ≥2 days, mechanical ventilation, exposure to antibiotics >1 day) and during the follow-up period (hospitalization ≥2 days and >7 days, admission to the intensive care unit (ICU), mechanical ventilation, exposure to antibiotics (categorized by class) >1 day, surgery, and presence of invasive devices including permanent urinary catheter, central venous catheter (CVC), enteral feeding tube, drain and endotracheal tube). Two reviewers independently determined whether CRE clinical specimens represented infection or colonization based on definitions outlined by the CDC [15]; in cases of disagreement, a third reviewer was consulted.

Microbiological methods

Rectal swabs were streaked onto selective MacConkey agar plates supplemented with 1 mg/L imipenem. Growing colonies were identified to the species level and tested for carbapenem resistance using the Vitek 2 system (bioMerieux, Marcy l'Etoile, France) and Etest for validation (AB Biodisk, Solna, Sweden). This method has been determined to be adequately sensitive (85%) and specific (94%) for screening purposes [16]. Enterobacteriaceae colonies were also tested for bla_{KPC} using PCR. A CRE screening test was defined as positive if either a CRE isolate was identified and/or bla_{KPC} was detected. Clinical specimens were processed in accordance with the CLSI guidelines [17] and isolates were identified using the Vitek 2 system.

Statistical analysis

The association between presumptive predictors and subsequent CRE clinical specimens for the matched case-control