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Post-surgical mediastinitis due to carbapenem-resistant Enterobacteriaceae: Clinical, epidemiological and survival characteristics☆

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ABSTRACT

Invasive infections due to carbapenem-resistant Enterobacteriaceae (CRE), including polymyxin-resistant (PR-CRE) strains, are being increasingly reported. However, there is a lack of clinical data for several life-threatening infections. Here we describe a cohort of patients with post-surgical mediastinitis due to CRE, including PR-CRE. This study was a retrospective cohort design at a single cardiology centre. Patients with mediastinitis due to CRE were identified and were investigated for clinically relevant variables. Infecting isolates were studied using molecular techniques. Patients infected with polymyxin-susceptible CRE (PS-CRE) strains were compared with those infected with PR-CRE strains. In total, 33 patients with CRE mediastinitis were studied, including 15 patients (45%) with PR-CRE. The majority (61%) were previously colonised. All infecting isolates carried bla_{KPC} genes. Baseline characteristics of patients with PR-CRE mediastinitis were comparable with those with PS-CRE mediastinitis. Of the patients studied, 70% received at least one agent considered active in vitro and most patients received at least three concomitant antibiotics. Carbapenem plus polymyxin B was the most common antibiotic combination (73%). Over 90% of patients underwent surgical debridement. Overall, in-hospital mortality was 33% and tended to be higher in patients infected with PR-CRE (17% vs. 53%; $P = 0.06$). In conclusion, mediastinitis due to CRE, including PR-CRE, can become a significant challenge in centres with CRE and a high cardiac surgery volume. Despite complex antibiotic treatments and aggressive surgical procedures, these patients have a high mortality, particularly those infected with PR-CRE.

1. Introduction

Post-sternotomy mediastinitis is a life-threatening infection that occurs in a small proportion (0.5–2.7%) of patients undergoing cardiothoracic surgery [1–4], resulting in longer hospital stay, higher medical costs, additional surgical procedures and, finally, increased mortality. Recent studies showed that 14–32% of patients who developed post-surgical mediastinitis died, indicative of a higher risk of morbidity and mortality compared with patients who do not experience infectious complications [1–5]. Although the main micro-organisms implicated are Gram-positive bacteria (e.g. staphylococci), Gram-negative pathogens can also be a relevant cause of mediastinitis at some centres [5]. Importantly, compared with other micro-organisms, mediastinitis associated with Gram-negative pathogens was shown to have higher rates of in-hospital death [5].

Invasive infections associated with carbapenem-resistant Enterobacteriaceae (CRE) pose a serious challenge to clinicians. Treatment with drugs such as polymyxins (polymyxin B or colistin), carbapenems or their combinations are basically supported

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by observational studies [6–8]. The emergence of resistance to polymyxins further complicates the situation [9–11]. Whilst there is an increasing body of evidence on the clinical characteristics of patients with more common CRE infections (e.g. bloodstream infections) [6,7], we are faced with a lack of clinical information in the case of less frequent but otherwise severe CRE infections such as post-surgical mediastinitis. To the best of our knowledge, this is the first study describing a cohort of patients with post-surgical mediastinitis due to CRE, including patients infected with strains resistant to polymyxins.

Given the lack of evidence described above and the potential occurrence of polymyxin resistance in CRE, this study intended to describe the clinical characteristics of a significant post-sternotomy mediastinitis CRE outbreak population and to compare survival outcomes among polymyxin-resistant and -susceptible isolates.

2. Materials and methods

2.1. Study population and setting

This retrospective cohort study was conducted at Instituto Dante Pazzanese de Cardiologia (São Paulo, Brazil) between December 2010 and June 2014. This is a 350-bed hospital specialising in cardiology and cardiovascular surgery that serves as a referral centre for 300 000 patients, 90% of whom are from São Paulo. Patients undergoing surgical procedures at the institution are followed by the institutional teams until the patient recovers or is clinically stable, allowing for external follow-up. For the purpose of this study, patients aged ≥18 years diagnosed with mediastinitis due to CRE were identified. Mediastinitis was defined as the presence of at least one of the following: (i) organisms cultured from mediastinal tissue or fluid obtained during a surgical operation or needle aspiration; (ii) evidence of mediastinitis seen during a surgical operation or histopathological examination; and (iii) fever (>38 °C), chest pain or sternal instability, and at least one of the following: purulent discharge from mediastinal area, organisms cultured from blood or discharge from mediastinal area, or mediastinal widening on the chest radiograph [12].

Patients were considered to be infected with CRE if such isolates were obtained from either blood cultures, surgical specimens or by needle aspiration from the sternal area and/or mediastinum. For the duration of the study, all patients with mediastinitis were under the care of the same infectious diseases and cardiovascular surgical staff members. Patient charts were reviewed to capture both demographic and clinically relevant data, including co-morbidities, prior cardiovascular procedures, immunosuppressant drugs, previous infections, colonisation and prior antibiotic use. The Society of Thoracic Surgeons (STS) score, indicative of operative mortality and morbidity of adult cardiac surgery, was calculated [13]. Surgical information, such as type and duration of the procedure, blood loss, perfusion time, extracorporeal circulation and re-operation, was also collected. All relevant information regarding antibiotic treatments was reviewed. This study was approved by the Ethical Committee of Instituto Dante Pazzanese de Cardiologia.

2.2. Microbiology

All Gram-negative strains recovered from patients with mediastinitis were submitted to the local microbiology laboratory for identification and determination of antimicrobial susceptibility profiles by VITEK® 2 system using AST-N238 and AST-N239 cards (bioMérieux, Marcy-l'Étoile, France). Based on the results of the routine antimicrobial susceptibility testing and phenotypic tests (VITEK® 2 system and modified Hodge test), the clinical isolates were classified as CRE. Carbapenem (imipenem and meropenem) resistance was defined as a minimum inhibitory concentration (MIC) of ≥4 μg/mL according to Clinical and Laboratory Standards Institute (CLSI) breakpoints. Resistance to polymyxins was defined by a colistin MIC ≥4 μg/mL. Molecular testing was conducted at Laboratório Especial de Microbiologia Clínica (LEMC) of Universidade Federal de São Paulo (UNIFESP) (São Paulo, Brazil) and included a real-time multiplex PCR assay for bla_{KPC}, bla_{GES}, $bla_{OXA\text{-}48\text{-}like}$, bla_{NDM}, bla_{IMP} and bla_{VIM} carbapenemase genes [14]. The genetic relatedness for each group of CRE clinical strains was evaluated by pulsed-field gel electrophoresis (PFGE) using the restriction enzyme *Spe*I (New England Biolabs Inc., Ipswich, MA) and the results were analysed using BioNumerics v.6.6 (Applied Maths, Sint-Martens-Latem, Belgium). Multilocus sequence typing (MLST) for *Klebsiella pneumoniae* strains was performed as described by Diancourt et al. [15], and the Institut Pasteur MLST database was used to assign allelic numbers and sequence types (http://bigsdb.web.pasteur.fr/klebsiella/klebsiella.html; accessed 11 November 2015).

2.3. Antibiotic dosing

The following intravenous [16] antimicrobial doses were used at the institution for the treatment of patients with CRE mediastinitis, according to the antimicrobial stewardship programme of the hospital: polymyxin B, 25 000 UI/kg/day; amikacin, 15 mg/kg/day; gentamicin, 5 mg/kg/day; meropenem, 1 g every 8 h; imipenem, 500 mg every 6 h; tigecycline, 100 mg initial dose followed by 50 mg every 12 h; and ciprofloxacin, 400 mg every 12 h. The doses were adjusted according to the patient's renal function. In the case of patients with a body mass index (BMI) >40 (kg/m^2), the dose of meropenem was increased to 6 g day (2 g every 8 h).

2.4. Statistics analysis

Each subject was included only once (index infection) in the analysis. Descriptive statistics were used to describe the overall characteristics of the whole cohort. Patients infected with polymyxin-resistant CRE (PR-CRE) strains were compared with those infected with polymyxin-susceptible CRE (PS-CRE) strains using either Fisher's exact test or χ^2 test as appropriate for categorical variables, and Wilcoxon rank-sum test for continuous variables. Patients were followed during their hospital stay after the diagnosis of mediastinitis was made, and charts were reviewed up to October 2014 (3 months after the end of the study period) to determine the survival status following discharge. If the information was not available in the chart, it was retrieved by telephone contact. A survival analysis to compare survival between groups was performed using the log-rank test. The effect of PR-CRE on mortality was evaluated with a Cox proportional hazard model to determine the hazard ratio (HR) and 95% confidence interval (CI).

A multivariate model was performed to take into account differences between the PS-CRE and PR-CRE groups. Significance was defined as a *P*-value of ≤0.05 (two-tailed). IBM SPSS Statistics for Windows v.19.0 software package (IBM Corp., Armonk, NY) was utilised for the statistical analyses.

3. Results

From December 2010 to June 2014, 5933 cardiac surgeries were performed at this single institution. During this period 92 patients (1.6%) were diagnosed with mediastinitis, among which Gram-positive and Gram-negative pathogens were isolated from 45% and 55% of the patients, respectively. Enterobacteriaceae were isolated in 88% of patients infected with Gram-negative pathogens, including 36 patients infected with CRE strains. Three patients were