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Risk factors for mortality among carbapenem-resistant enterobacteriaceae carriers with focus on immunosuppression

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SUMMARY

Objectives: To identify risk factors for mortality in a cohort of carbapenem-resistant enterobacteriaceae (CRE) carriers, focusing on immunosuppression and other risk factors known at the time of CRE carriage detection.

Methods: We prospectively followed all new and known CRE carriers admitted between June 2016 and June 2017 to a single tertiary center in Israel. Patients were included in the study after confirmation of the carrier state. Demographic and clinical data were documented on admission or CRE acquisition and patients were followed prospectively post-discharge until January 2018 or death. Risk factors for mortality known at the time of the first encounter with a CRE carrier were sought. Adjusted hazard ratios (HR) for mortality at end of follow-up with 95% confidence intervals (CI) were assessed using Cox regression analysis.

Results: A total of 115 patients were included in the analysis. During the study period, 66 (57.4%) patients died. Immunosuppression was associated with mortality (HR 1.95, CI 95% 1.12–3.44), adjusted to the Charlson co-morbidity score, functional status, chronic renal disease and *Klebsiella pneumonia* CRE, the latter three also significantly associated with mortality. CRE bacteremia occurred among 24 (20.9%) carriers during follow up, more frequently among immunosuppressed patients and was significantly associated with mortality at end of follow-up ($p = 0.015$).

Conclusion: Immunosuppression is independently associated with mortality among CRE carriers, possibly related to CRE bacteremia that is frequent among these patients. Further research is needed on interventions to prevent deaths among CRE carriers.

Background

The appearance and spread of carbapenem-resistant enterobacteriaceae (CRE) poses a major health hazard.[1,2] Common risk factors for acquisition of these resistant bacteria include long-term healthcare residency, past/present antibiotic use, organ transplantation, severe illness, chronic comorbidities, mechanical ventilation and indwelling devices.[3–7] Colonization (i.e., carrier state) has been shown as a risk factor for infection, thus exposing the patient to an increased risk of death.[1,2,7–10]

It has been our observation that clinical infections with CRE are more common among immunosuppressed CRE carriers than among carriers with other comorbidities, especially in neutropenic hemato-oncological patients. Possible reasons include frequent antibiotic treatment that selects preferentially for resistant bacteria and a decrease in host barriers, which in turn might lead to higher CRE translocation through the gut resulting in bacteremia.

Our aim was to prospectively search for risk factors for mortality among CRE carriers, focusing on data known at the time CRE carriage is identified, and to test the hypothesis that immunosuppression is a risk factor for CRE bacteremia and death among these patients. Identification of risk factors for mortality might aid in triage and early interventions in CRE carriers.

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Methods

Study design, setting and participants

We prospectively followed adult (≥18 years) CRE carriers admitted between June 2016 and June 2017 to a single tertiary center in Israel (Rambam Health Care Campus). Patients with new acquisition and those with known carriage on admission were included on their first admission to our hospital after confirmation of their carrier state. The start of follow-up was the acquisition date for new acquisitions and the date of admission of known carriers. All patients were prospectively followed until January 2018 or death.

Study variables

The exposure variable was immunosuppression defined by either immunosuppressive therapy (defined as use of corticosteroids (prednisone equivalent >20 mg/day) for at least 14 days, chemotherapy or radiotherapy, hematopoietic stem cell transplantation (HSCT) or other recognized immunosuppressive therapy) or a disease state related to immunosuppression (mainly hematologic malignancy).[11] The outcome assessed was mortality from start to end of follow-up. A set of confounders and other risk factors was collected at admission and at the time of CRE carriage identification, including demographic and clinical data. To describe comorbidity we used the revised Charlson score.[12] For risk prediction, we focused on variables known at the time of the observed encounter with a CRE carrier during the study period.

Data sources

Data were collected from the hospital's electronic medical record system that alerts the infectious control personnel of every acquisition or admission of a CRE carrier. National infectious disease control registries were contacted to confirm the first CRE acquisition date for each carrier. Deaths outside the hospital are updated in the system from the national Health Ministry.

Microbiology methods

Carriage was defined by at least one positive rectal swab. Rectal swab screening samples were cultured on PD420 CHROM agar KPC plates (Hy Laboratories Ltd, Rehovot, Israel). CRE was defined as enterobacteriaceae of any type resistant to all tested carbapenems using the Clinical and Laboratory Standards Institute (CLSI) M100S guidelines definition of MIC > 1.[13] DNA was extracted from suspected CRE colonies using the Qiamp DNA mini kit (QIAgen, Hilden, Germany) in accordance with the manufacturer's instructions. Carbapenemase genetic mechanism, i.e., $bla_{KPC}/bla_{NDM}/bla_{OXA-48}/bla_{VIM}$, was detected using polymerase chain reaction (PCR)-based multiplexed assays specific for these genes.[14,15]

Statistical analysis

Factors associated with mortality at end of follow-up were assessed by univariate analysis. Categorical variables were compared using Chi square or Fisher exact test and continuous variables by *t*-test or the Mann–Whitney-U test, as appropriate. Adjusted analysis for mortality was performed using Cox regression analysis. All variables significant on univariate analysis ($p < 0.05$) were included in multivariate analysis together with immunosuppression as exposure variable. Immunosupression was forced into the Cox model regardless of statistical significance on univariate analysis because of our interest in it as our exposure variable. Analyses were conducted using SPSS version 21.

The study was approved by the institute review board (IRB no. 0236-16-RMB).

Results

One hundred and fifteen known/new CRE carriers were included in the analysis. Of the 115 study participants, 42 (36.5%) were female, the mean age was 65.55 years (SD ± 16), the functional status of 58 (50.4%) was independent and 37 (32.3%) were immunosuppressed. Data on CRE resistance mechanism was available for 84 patients and KPC dominated (Table 1). During the study follow-up, 24 (20.9%) developed CRE bacteremia and 66 (57.4%) patients died.

Of the variables known at the time of carriage acquisition/carrier admission, dependent functional status, Charlson score, chronic renal disease and *Klebsiella pneumoniae* strains were significantly associated with mortality (Table 1). Dependent functional status, chronic renal disease and *Klebsiella pneumoniae* strains were independently associated with mortality at end of follow-up. Adjusted to these, immunosuppression was significantly associated with mortality (HR 1.95, 95% CI 1.12–3.44, $p = 0.02$) (Fig. 1). Categorizing the immunosuppressed population to malignancy/ HSCT (29 patients total, 22 hematological cancer) and others, malignancy remained significantly associated with mortality (HR 1.96, 95% CI 1.03–3.72). Other immune suppression followed the same survival curve, but was not statistically significant.

Immunosuppressed patients had a higher rate of bacteremia caused by CRE than other patients during the follow-up (11/37 (29.7%) vs. 13/78 (16.7%), respectively) though the difference was not statistically significant ($p = 0.11$). CRE bacteremia, in turn, was significantly associated with mortality at end of follow-up; 19/24 (79.2%) of patients with bacteremia died vs. 47/91 (51.6%) without bacteremia, $p = 0.02$ (Table 2).

Discussion

In this study, we report on risk factors for mortality known at the time of the first encounter with a CRE carrier in the hospital, whether if admitted as a known carrier or acquiring CRE during hospitalization. The factors identified were poor functional status, immunosuppression, chronic renal disease and *Klebsiella pneumoniae* CRE strains. The immunosuppressed population in our study were mainly hemato-oncological patients, who experience prolonged severe neutropenia and mucositis while receiving broad-spectrum antibiotics, which exposes them to translocation of CRE from the bowel. Indeed, we observed that the risk for death among immunosuppressed patients might be mediated by bacteremia of the colonizing CRE strain.

Risk factors for death among CRE carriers might be common to other very sick populations similar to the population of patients carrying CRE and might be mediated by CRE. The latter were of interest to us. Independent risk factors identified for CRE bacteremia among CRE carriers included intensive care unit (ICU) admission, abdominal invasive procedure, chemotherapy/radiation therapy (similar to the immunosuppressed factor in our study) and multiple colonization sites in a multicenter study in Italy.[16] In another multicenter study in Italy, multisite colonization and ICU stay were similarly associated with CRE bacteremia, in addition to a previous BSI and younger age.[17] From one hospital in Israel risk factors for any type of CRE infection included again ICU admission, diabetes mellitus, presence of a central venous catheter and receipt of antibiotics.[18] The risk factors identified depend on the case mix, the risk factors investigated and their definitions. The risk factors

Table 1
Risk factors for all-cause mortality at end of follow-up—univariate analysis.

Variable	Alive ($n=49$)	Dead ($n=66$)	P value
Age in years, mean ± SD	62.0 ± 15.5	67.2 ± 16.3	0.093
Female sex (%)	18 (36.7)	24 (36.4)	0.967
Functional status, independent (%)	32 (65.3)	26 (39.4)	0.006
Immunosuppression[a] (%)	12 (24.5)	25 (37.9)	0.129
Malignancy/HSCT	10 (20.4)	19 (28.8)	
Other immunosuppression/ steroids	2 (4.1)	6 (9.1)	
Heart failure (%)	9 (18.4)	13 (19.7)	0.858
Dementia (%)	2 (4.1)	8 (12.1)	0.185
Chronic pulmonary disease (%)	1 (2)	8 (12.1)	0.076
Diabetes with chronic complications (%)	16 (32.7)	19 (28.8)	0.656
Chronic renal disease (%)	11 (22.4)	27 (40.9)	0.037
Revised Charlson score, median (IQR)	2 (0–4)	3 (2-5)	0.026
Mechanical ventilation (%)	5 (10.2)	16 (24.2)	0.054
Urinary catheter (%)	13 (26.5)	28 (42.4)	0.078
Central line (%)	14 (28.6)	24 (36.4)	0.380
Surgical drain (%)	4 (8.2)	6 (9.1)	1
Naso-gastric tube/gastrostomy (%)	6 (12.2)	14 (21.2)	0.210
KCP resistance gene (%)	27/35 (77.1)	41/49 (83.6)	0.575
Klebsiella pneumoniae strain (%)	27 (55.1)	51 (77.3)	0.012
Known CRE carriage at admission (%)	11 (22.4)	16 (24.2)	0.822
Clinical culture positive for CRE at presentation (%)	15 (30.6)	14 (21.2)	0.251

[a] Immunosuppression defined as: malignancy with chemotherapy or radiotherapy, hematopoietic stem cell transplantation (HSCT), use of corticosteroids (prednisone equivalent > 20 mg/day) for at least 14 days, or other recognized immunosuppressive therapy.

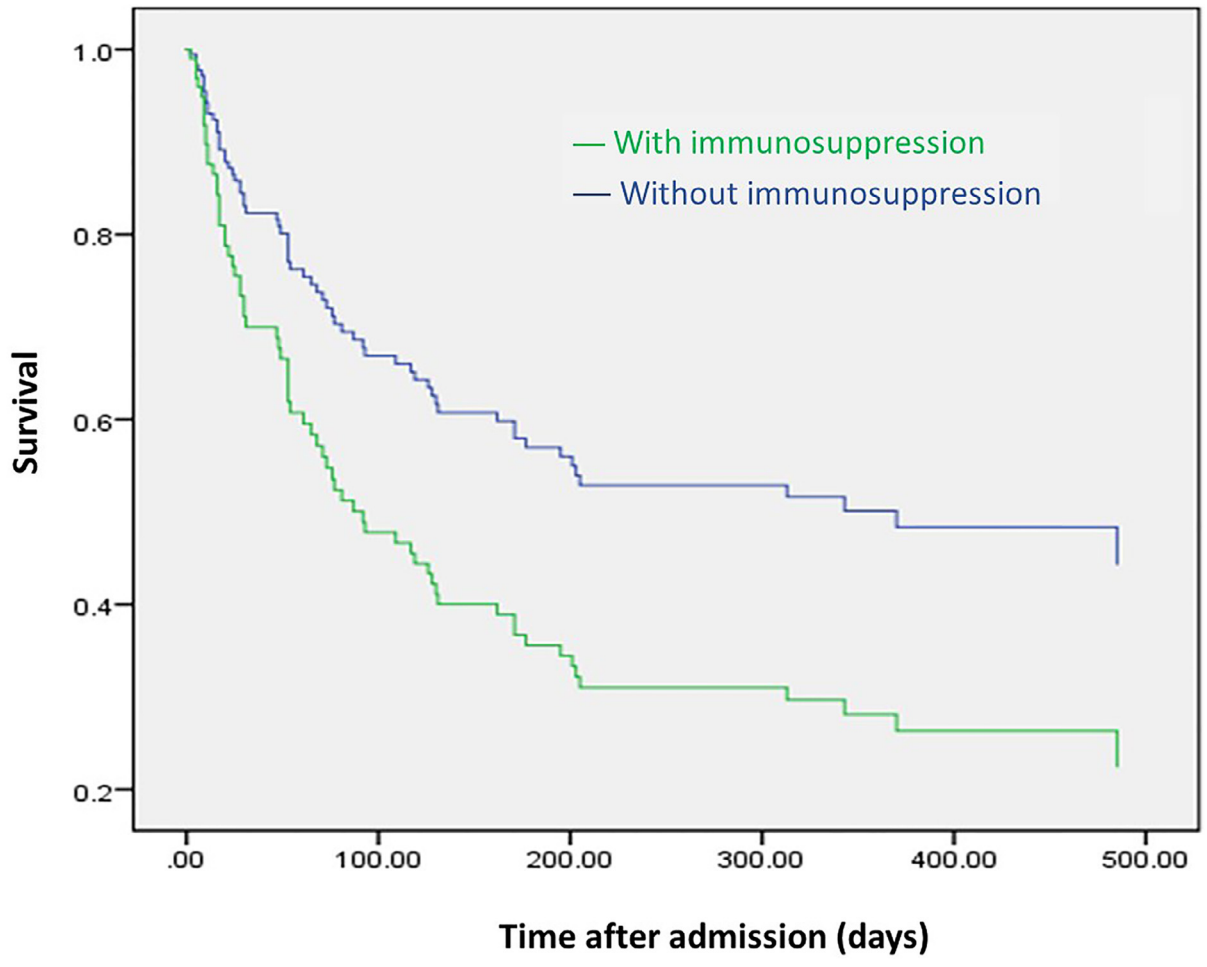

Fig. 1. Cox regression survival plot by immunosuppression status.

Table 2
Cox regression analysis for mortality.

Variable	HR (95% CI)	*P* value
Functional status, independent	0.34 (0.20–0.59)	<0.001
Immunosuppression	1.95 (1.11–3.44)	0.021
Chronic renal disease	1.83 (1.04–3.20)	0.035
Klebsiella pneumoniae strain	2.18 (1.22–3.90)	0.009
Revised Charlson score	0.97 (0.86–1.10)	0.623

for death we identified were not identical to previous studies for these reasons and because they combine the risk for infection and for death with infection. In addition, our focus was on risk factors available at the time of the first encounter with a patient carrying CRE in the hospital; to be implemented at this time. Other studies, focusing on the haematological cancer population, reported on very high mortality rates of CRE bacteremia among these patients and an association between carbapenem resistance and mortality in patients with bacteremia.[19,20]

Our results regarding immunosuppressed patients have two implications. The first is the importance of avoiding CRE acquisitions among immunosuppressed patients. This mandates strict separation of immunosuppressed patients from CRE carriers, including the transfer of CRE carriers from high-level care oncology wards to other wards. The second relates to the management immunosuppressed patients who are identified as CRE carriers. These patients might benefit from decolonization of CRE carriage before intense chemotherapy. We previously reviewed the literature and described five studies that utilized non-absorbable antibiotics for CRE eradication.[21] Most regimens included gentamicin and colistin, alone or in combination. The only randomized trial was small and had short term follow up, and reported successful CRE eradication in 61.1% in the intervention group vs. 16.1% the placebo group after 1 week after 7 day therapy.[22] However, none of the studies had long enough follow-up to show the long-term effects of decolonization. An emerging option for eradication of CRE colonization is fecal microbiota transplantation (FMT). Recently, 20 hematologic patients, carriers of multi drug resistant (MDR) Enterobacterceae (7 of which CRE) were treated with FMT via nasogastric tube (total of 25 transplantations). Complete MDR decolonization was achieved in 15/20 (75%) of the participants. There were no severe adverse events.[23] Furthermore, when immunosuppressed patients develop severe sepsis or Gram-negative bacteremia, they might benefit from anti-CRE coverage for empiric antibiotic therapy.

This study has limitations. Since CRE carriage is prevalent in patients with multiple co-morbidities, multiple factors that were not documented can impact mortality. The small sample size might have masked other risk factors for death. As this is a single-center study, results might not be applicable to other centers. Yet, the prospective data collection, post discharge follow-up, adjustment for multiple risk factors and the plausibility of our findings supports our risk stratification.

To conclude, our data suggest several risk factors for mortality known at the time of acquisition/admission among CRE carriers, among them immunosuppression. Mortality might be driven by CRE bacteremia. Special attention and further research is needed on prevention of CRE acquisition, management and decolonization of carriers and early directed treatment for sepsis among them.

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Conflicts of interests

None.

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