Rate and Risk Factors for Carbapenem Resistant \textit{Acinetobacter baumannii} Clinical Infections in Colonized Patients

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\textbf{ABSTRACT}

\textbf{Background:} Carbapenem-resistant \textit{Acinetobacter baumannii} (CRAB) is an important cause of nosocomial infections. Active surveillance for CRAB carriage to identify and isolate colonized patients is used to reduce transmission.

\textbf{Objectives:} To assess the rate and risks of clinical infection among CRAB-carrier and non-carrier patients.

\textbf{Methods:} Hospitalized patients from whom CRAB screening-cultures were obtained between January and June 2018 were identified retrospectively. All CRAB-carriers were compared to a convenient sample of non-carriers and were followed to detect development of CRAB clinical infection during admission.

\textbf{Results:} We compared 115 CRAB carriers to 166 non-carriers. The median age in the study group was 76 years (IQR 71–87) vs. 65 years (55–79) in the non-carriers group ($P < 0.001$). Residence in a nursing facility, debilitated state, and admission to medical wards vs. intensive care units were more frequent among CRAB-carriers ($P < 0.001$). Mechanically ventilated patients included 51 CRAB carriers (44%) and 102 non-carriers (61%). Clinical infection developed in 49 patients (17%), primarily CRAB pneumonia. Of the CRAB-carriers and non-carriers, 26/115 (23%) and 23/166 (14%), respectively, developed a clinical infection ($P = 0.05$). One-third of the ventilated patients were infected. Debilitated state and antibiotic treatment during hospitalization were linked to higher infection rates ($P = 0.01$). Adjusted analysis showed that mechanical ventilation and CRAB colonization were strongly associated with clinical infection ($P < 0.05$).

\textbf{Conclusion:} The rate of CRAB infection among carriers was high. Mechanical ventilation and CRAB colonization were associated with CRAB clinical infection, primarily pneumonia.

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\textbf{KEY WORDS:} \textit{Acinetobacter baumannii}, antibiotic resistance, carbapenem, carriage, risk factors

\textit{Acinetobacter baumannii} has increasingly been recognized as a healthcare-associated pathogen, which is involved in hospital outbreaks worldwide and in Israel [1,2]. Contamination of hospital environment and persistence on various surfaces, including medical devices, respiratory care equipment, and patient care items has been well documented [3]. Outbreaks have been attributed to both environmental transmission and patient-to-patient transmission of the pathogen. Most affected patients are critically ill [3]. \textit{Acinetobacter baumannii} infection is commonly associated often with ventilator-associated pneumonia (VAP), but skin and soft tissue infections, wound infections, urinary tract infections, and bacteremia may develop as well [4]. Infections caused by Carbapenem-resistant \textit{Acinetobacter baumannii} (CRAB) are a serious threat in many hospital units since treatment often requires the use of last line antibiotics, such as colistin and tigecycline [5].

Limiting the spread of CRAB strains requires multifaceted interventions including isolation precautions, strict adherence to infection control policies, dedicated patient care equipment, identification of the source in outbreaks (sometimes leading to clinical unit closure), environmental cleaning and disinfection, limited use of broad-spectrum antibiotics, and screening and early detection of colonized or infected patients [6].

Colonized patients (CRAB-carriers) may be detected by surveillance cultures from skin, pharyngeal, nostrils, or rectal specimens [7]. Such active patient surveillance may be performed if patients are deemed at-risk or during readmission. Early identification of carriers can provide timely information that allows implementation of strict contact precautions before transmission of infection to other patients but may also predict clinical infection [8].

In this study we determined the risk for development of clinical infection (i.e., pneumonia, bacteremia) in adult patients who had CRAB-positive surveillance rectal swab and/or sputum cultures during their current hospitalization. We hypothesized that the proportion of CRAB clinical infections would be
higher among CRAB-carrier patients compared to non-carriers (control group). Other risk factors for CRAB-associated clinical infection were identified as well.

**PATIENTS AND METHODS**

This retrospective study was conducted at Shaare Zedek Medical Center, a 1000-bed teaching hospital affiliated with the Hebrew University of Jerusalem, Israel. As part of the hospital's infection control program, weekly rectal swabs and, when available, surveillance sputum cultures, are routinely sampled for CRAB in high-prevalence or CRAB-prone departments such as the intensive care unit (ICU) and step-down units in the medical and geriatric departments. Additional screening was performed on patients who were considered to be at high risk for multi-drug resistance (MDR) pathogens. These patients included those who are residing in nursing homes or those who were hospitalized during the previous year. Screening is similar to carbapenem-producing Enterobacteriaceae screening criteria. All CRAB-carrier patients (exposed group) were compared to a convenient sample of CRAB non-carrier patients in terms of rate and risks for the development of CRAB clinical infection.

Results of CRAB surveillance cultures of patients hospitalized from January to June 2018 were retrieved from the hospital's computerized microbiologic database. During this time CRAB-colonized adult patients (aged 18 years or older) detected by rectal swabs and/or surveillance sputum cultures comprised of the initial study group (n=115). The control group included 166 adult patients. The latter constituted a third of all CRAB negative patients who were screened during the same time-frame. Patients were included only once in the study—at the time of admission when the first surveillance culture (positive or negative) was taken. Patients who had a clinical culture with CRAB before the screening culture were excluded. The proportion of patients who developed CRAB-associated clinical infections during admission was assessed in the study group (CRAB-carriers) and was compared to that in the control group (CRAB-non-carriers).

Demographic, clinical, and laboratory data were retrieved from the electronic medical records of all patients. Data included age, sex, residence, previous hospitalization within 90 days, functional capacity (designated as 1 for independent, 2 for partially dependent, and 3 for totally dependent patients), Charlson Comorbidity Score (CCS), type of clinical culture and/or infection, mechanical ventilation, ICU or step-down unit admission, admission and discharge departments, surgical procedure during admission (before clinical infection) including tracheostomy, length of stay, and in-hospital mortality. Factors associated with the development of CRAB-positive infection were evaluated.

**DEFINITIONS**

**Colonized patients / CRAB-carriers:** asymptomatic patients with CRAB-positive rectal swab/sputum cultures

**CRAB-positive sputum cultures:** sputum cultures may indicate either a clinical infection (as one parameter of pneumonia) or colonization. Diagnosis of CRAB pneumonia was based on clinical, laboratory, radiologic and microbiologic criteria [9,10]. Patients with positive sputum cultures, without pneumonia, were classified as colonized patients. Surveillance sputum cultures were classified differently in the microbiological database and were easily distinguished from clinically indicated sputum cultures.

**Clinical cultures:** All cultures obtained for clinical diagnostic purposes rather than for surveillance

**CLINICAL DIAGNOSTIC CRITERIA OF CRAB PNEUMONIA**

CRAB isolated from sputum, deep suction, or bronchoalveolar lavage specimen

- New lung infiltrate on chest X-ray
- Two or more of the following: cough, purulent sputum, abnormal auscultatory findings, signs of respiratory failure, signs of dyspnea, worsening of tracheal aspirate fluid in mechanically ventilated patients
- One of the following: leukocytosis or leukopenia (defined as WBC count > 10,000/mm$^3$ or < 4500/mm$^3$, respectively), band neutrophils > 15%, pulse rate > 120 beats/min or systolic hypotension [11]

HAP was defined as a pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after admission. VAP was defined as a pneumonia occurring > 48 hours after endotracheal intubation [12].

**DATA AND STATISTICAL ANALYSIS**

Demographic, clinical and laboratory variables were entered in an Excel spreadsheet. Quantitative variables were compared using the t-test, for two independent groups, and the Mann-Whitney test for non-normal distribution of the tested variable. For categorical variables a chi-square test or Fisher's exact test was used. Variables found statistically significant (two-sided $P < 0.05$) using univariate analysis for the dependent variable (CRAB clinical infection) were further examined using both, a stepwise forward likelihood ratio and enter multivariate logistic regression model. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA). The study was approved by the institutional review board of Shaare Zedek Medical Center (approval number 0152-18).

**RESULTS**

The study comprised 310 patients who had been screened for CRAB between January and June 2018; 29 patients were excluded, 15 were duplicate cases, and 14 had a clinical infection that pre-dated colonization or diagnosis less than 24 hours since the CRAB-positive surveillance culture. Thus, the final
study group comprised of 115 CRAB-carriers and 166 CRAB non-carriers. Overall, 264 rectal swab cultures were performed. Thirty-two patients had both rectal and sputum surveillance cultures, 17 had surveillance sputum cultures and no rectal swabs [Table 4]. Positive surveillance cultures comprised primarily of rectal swab cultures (n=112, 97%). Demographic and clinical data of the patients are shown in Table 1.

Median patient age was 74 years (IQR 60–83), higher among CRAB-carriers vs. non-carriers (< 0.001). Fifty-seven patients (20%) resided in a nursing home, of them, 45 (79%) were CRAB-carriers. Most patients in the cohort and most CRAB-carriers were admitted to the medical wards (180/281) [Table 1]. The mean Charlson Comorbidity Score (CCS) was significantly higher among CRAB-carriers (P < 0.001) [Table 1]. The cohort included 153 patients who were mechanically ventilated; 51 were CRAB-carriers and 102 were non-carriers (P < 0.001).

Forty-nine patients (17% of the entire cohort) developed a clinical infection with CRAB, which primarily manifested as pneumonia (n=44). One patient had pneumonia and a wound infection and five patients had true bacteremia without a known source.

Clinical CRAB infection developed in 26/115 (23%) CRAB-carriers vs. 23/166 (14%) non-carriers (P = 0.05) [Table 2]. Age, sex, residence, and admitting department were not associated with an increased risk of clinical infection.

The median number of surveillance cultures was similar among non-colonized patients vs. CRAB carriers (1 [IQR 1–2] vs. 1 [IQR 1–1], respectively). Mean number of surveillance cultures was 2 ± 1.6 vs. 1.7 ± 1.8 (P = 0.2, not shown).

Low functional capacity (limited or total dependence) was significantly associated with higher infection rates (P < 0.001) [Table 1]. Antibiotic treatment during hospitalization before detection of clinical CRAB infection was frequent in the CRAB infection group (46/49 vs. 162/224, P < 0.01).

Adjusted analysis revealed that mechanical ventilation and CRAB colonization were strongly associated with clinical infection (P < 0.05) [Table 3].

Patients who had CRAB infection had a significantly longer hospital stay and increased in-hospital mortality (P < 0.001) [Table 2].

**DISCUSSION**

In this study we showed that both mechanical ventilation and CRAB-colonization (as detected by rectal swabs) were significantly associated with the development of a CRAB clinical infection, primarily pneumonia.

*Acinetobacter baumannii* is one of the most significant VAP-causing pathogens [11-13]. Mechanically ventilated patients are especially prone to CRAB infection due to the moist environment associated with ventilator tubing, suction catheters, and humidifiers [14]. Other factors include inadequate hand hygiene or glove-changing when managing airway or contaminated ventilators or contaminated surfaces [3]. Indeed, in this study almost all the patients with CRAB infection were intubated or had been tracheostomized prior infection (45/49, 90%).

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**Table 1. Demographic and clinical characteristics of the study cohort**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRAB-non-carriers n=166</th>
<th>CRAB-carriers n=115</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, IQR)</td>
<td>65 (55–79)</td>
<td>74 (71–87)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex: female, n (%)</td>
<td>75 (45)</td>
<td>59 (51)</td>
<td>0.3</td>
</tr>
<tr>
<td>Residence (n=277), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>152/164 (93)</td>
<td>68/113 (60)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HCF/nursing home</td>
<td>12/164 (7)</td>
<td>45/113 (40)</td>
<td></td>
</tr>
<tr>
<td>Admission department, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical (n=180)</td>
<td>75 (45)</td>
<td>105 (91)</td>
<td></td>
</tr>
<tr>
<td>Surgical (n=11)</td>
<td>8 (5)</td>
<td>3 (3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICU/intermediate care (n=90)</td>
<td>83 (50)</td>
<td>7 (6)</td>
<td></td>
</tr>
<tr>
<td>Charlson Comorbidity Score (mean ± SD)</td>
<td>2.4 ± 2</td>
<td>3.2 ± 2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Charlson Comorbidity Score &gt; 4, n (%)</td>
<td>133 (80)</td>
<td>84 (73)</td>
<td>0.2</td>
</tr>
<tr>
<td>Functional capacity (n=262)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent, n (%)</td>
<td>92/152 (61)</td>
<td>22/110 (20)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Any degree of limitation, n (%)</td>
<td>60/152 (39)</td>
<td>88/110 (80)</td>
<td></td>
</tr>
<tr>
<td>Previous admission (90 days), n (%)</td>
<td>49 (30)</td>
<td>38 (33)</td>
<td>0.6</td>
</tr>
<tr>
<td>Antibiotic treatment during hospitalization until clinical infection or discharge (n=273), n (%)</td>
<td>117/158 (74)</td>
<td>92/115 (80)</td>
<td>0.3</td>
</tr>
<tr>
<td>Surgical procedure during admission (before clinical infection), n (%)</td>
<td>38 (23)</td>
<td>18 (16)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>102 (61)</td>
<td>51 (44)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Aside from 11 patients who were admitted to the surgical ward, 45 patients had a surgical intervention during admission (before clinical infection, excluding tracheostomy); 31 were admitted to the intensive care unit. Surgical interventions included abdominal (n=17, 30%), neurosurgical (n=19, 34%), orthopedic (n=11, 20%), cardiothoracic (n=6, 11%), and other (n=3, 5%) procedures.

ICU = intensive care unit, IQR = interquartile range.
functional capacity, and residence, CRAB-carriers were a sicker population [Table 1]. This finding is consistent with previous reports [15,16] and reflects the practice of targeted screening of at-risk patients prone to colonization with MDR pathogens.

Fecal colonization was previously shown to be linked to subsequent clinical infection [17]. In a report by Blanco et al. [18] CRAB-colonized patients at ICU admission were 15.2 times more likely to develop a subsequent positive clinical culture for and 1.4 times more likely to die during the current hospitalization. Others have demonstrated similar findings in cases of rectal colonization with other highly resistant Gram-negative rods [19,20].

Our results support the practice of active surveillance cultures (specifically rectal screening for CRAB colonization) in select populations (i.e., ventilated patients) where the prevalence of CRAB is high. This routine may prove useful in terms of commencing isolation measures and prevention of the spread of CRAB. Subsequently, it may affect decisions regarding empirical therapy in cases of VAP in these patients. Indeed, 25% of CRAB-carriers and approximately 33% of ventilated patients developed CRAB clinical infection.

Aside from mechanical ventilation and CRAB colonization, other findings in our study deserve consideration. In our cohort, almost all CRAB-infected patients (47/49, 96%) were treated with antibiotics prior infection [Table 2]. In previous reports, long-term use of certain antibiotics and even short-term use of carbapenems increased the risk of CRAB infection [21,22]. Although this association was not demonstrated in the adjusted analysis, we believe that selection pressure driven by antibiotics functional capacity, and residence, CRAB-carriers were a sicker population [Table 1]. This finding is consistent with previous reports [15,16] and reflects the practice of targeted screening of at-risk patients prone to colonization with MDR pathogens.

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may contribute to CRAB infection. The univariate analysis also showed impaired functional capacity to be strongly associated with the development of a clinical infection [Table 2]. Among our study patients, over 50% of those who developed a clinical infection were totally dependent. This reflects the severity of illness of the study population (similar to the high CCS) [Table 2]. Bedridden patients are prone to colonization and infection with CRAB [23]. In point prevalence surveys of 1667 patients in an Israeli hospital, elderly and bedridden patients with dementia comprised 24% of patients and 59% of mechanically ventilated patients. Those patients were twice as likely to be colonized or infected by MDR pathogens (39.3% vs. 18%, $P < 0.001$) [24]. As expected, these patients are also exposed to multiple courses of antibiotic [23].

Last, it is worth noting that the length of stay and the in-hospital mortality were both significantly increased among CRAB infected patients. Although the study was not aimed to assess those outcomes, the findings are in line with previous reports [25].

**LIMITATIONS**

Several limitations should be noted. The retrospective design of the study has inherent limitations such as missing data and selection bias. The study population was quite ill (almost 25% had CCS > 4, and 40% were totally dependent) and most of the patients were screened for CRAB. However, this study describes real-life practice where CRAB screening is targeted to select population. Screening healthy or young patients would be unjustified in terms of cost-effectiveness. Another important limitation is the over-representation of patients who were admitted to the ICU. As CRAB prevalence at the Shaare Zedeck ICU is a priori rather low due to strict infection control measures in the ICU, ICU admission was not associated with clinical CRAB infection.

Finally, our data were based mainly on only one screening site (rectal swabs), as the fraction of sputum cultures was small, which may reduce sensitivity regarding identifying colonized patients. We did not screen other sites such as axilla, groin, or nostrils. Although increased sensitivity was previously shown when different sites were screened [9] (55% for six different body sites versus 14–29% for one site), screening multiple sites is demanding and less applicable.

**CONCLUSIONS**

The two most important parameters associated with CRAB infection were mechanical ventilation and positive CRAB surveillance cultures. Screening ventilated patients may prove useful, especially in departments with high prevalence of CRAB. Frequent screening may help with early selection of appropriate empiric antimicrobial therapy, in addition to applying infection control precautions. Assessing cost-effectiveness of this practice demands further studies.

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**References**

Xie et al. used national healthcare databases from the US Department of Veterans Affairs to build a cohort of 153,760 individuals with coronavirus disease 2019 (COVID-19), as well as two sets of control cohorts with 5,637,647 (contemporary controls) and 5,856,411 (historical controls) individuals, to estimate risks and 1-year burdens of a set of pre-specified incident cardiovascular outcomes. The authors showed that, beyond the first 30 days after infection, individuals with COVID-19 are at increased risk of incident cardiovascular disease spanning several categories, including cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease. These risks and burdens were evident even among individuals who were not hospitalized during the acute phase of the infection and increased in a graded fashion according to the care setting during the acute phase (non-hospitalized, hospitalized, and admitted to intensive care units). These results provide evidence that the risk and 1-year burden of cardiovascular disease in survivors of acute COVID-19 are substantial. Care pathways of those surviving the acute episode of COVID-19 should include attention to cardiovascular health and disease.

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