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Enterobacteriaceae bacteremias among cancer patients: an observational cohort study

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SUMMARY

Background: *Enterobacteriaceae* bacteremia is a common complication in patients with neoplasm. The cancer itself, chemotherapy-induced immunosuppression, and other cancer-related procedures play a role as predisposing factors for this condition. However, despite the clear association between cancer and *Enterobacteriaceae* bacteremia, the distinctive clinical characteristics of patients with cancer presenting with *Enterobacteriaceae* bacteremia have not been well established.

Methods: The population studied was a prospective cohort of adult hospitalized patients with *Enterobacteriaceae* bacteremia in a tertiary care hospital. We compared the clinical variables and microbiological features between patients with an underlying neoplasm ($n = 203$) and those without ($n = 259$). STATA software was used for statistical association analysis.

Results: In a bivariate analysis, older age, prior exposure to aminopenicillins, fewer days of symptoms, biliary source of bacteremia, greater severity of APACHE II score, lower white blood cell and platelet counts, and the presence of *Klebsiella pneumoniae* were more common in the neoplasm group. In a multivariable analysis, *K. pneumoniae* bacteremia (odds ratio (OR) 6.13, 95% confidence interval (CI) 1.65–22.71; $p = 0.007$), APACHE II score (OR 1.18, 95% CI 1.05–1.34; $p = 0.007$), and exposure to aminopenicillins (OR 28.84, 95% CI 1.94–429.3; $p = 0.015$) were associated with neoplasm. *K. pneumoniae* bacteremia was more commonly present in patients with lung and gastrointestinal cancers.

Conclusions: We have confirmed the association of *K. pneumoniae* bacteremia with underlying neoplastic disease, especially with gastrointestinal malignancies, which may allow stratification for initial empiric antibiotic therapy in this subset of patients. Prior exposure to aminopenicillins in the neoplasm group might contribute to this finding.

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1. Introduction

Sepsis is one of the leading causes of morbidity and mortality in the USA.[1] The proportion of sepsis caused by Gram-negative bacilli (*Enterobacteriaceae*) is epidemiologically significant, and carries an overall increase in mortality.[2,3] Sepsis itself is a spectrum that spans presentation of localized infection with transient bacteremia and rapid recovery to multi-organ failure and death. The population affected by this condition is heterogeneous due to different demographic factors, causative organisms, infection sources, host genetic diversity, etc. Importantly, host predisposition factors play a role in the acquisition of bacteremia and the development of sepsis; among these are age, underlying medical illness, immunosuppression, and breach of integrity of the natural host barriers. Neoplasm is a common finding in this setting as one of the predisposing factors, and it has been postulated that the relative risk of sepsis is almost 10 times greater in patients with cancer compared to the general population.[4] Chemotherapy-induced neutropenia and mucositis, long-term catheter placements, and immune system dysfunction are among the neoplasm-related conditions that place those patients at greater risk of developing bacteremia and sepsis.[5]

Due to this great heterogeneity in the patient population and the dramatic variety in outcomes, it is important to establish clinical strategies to identify patients at greater risk for worse outcomes or with underlying undiagnosed risk factors, to provide more specific evaluation and therapy. The possible distinctive clinical characteristics of Gram-negative sepsis in this subgroup of patients that would allow for a better risk stratification have not yet been fully established. The aim of this study was to identify clinical characterizing factors of the subset of patients with *Enterobacteriaceae* bacteremia and an underlying neoplasm.

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2. Materials and methods

2.1. Patients and data collection

We performed a database analysis of a prospective cohort study in a tertiary care hospital that included adult hospitalized patients with *Enterobacteriaceae* sepsis and bacteremia. The study participants consisted of subjects selected from the Sepsis Registry at the Duke University Medical Center, Durham, North Carolina. The data collection took place from 2002 to 2007. Inclusion criteria for the study were defined as adults (≥18 years) with culture-confirmed *Enterobacteriaceae* bacteremia. Exclusion criteria were negative blood cultures, outpatient status, and isolation of any pathogen other than *Enterobacteriaceae* from blood culture. The study collected clinical variable data and microbiological features among 468 patients. We performed a statistical analysis of clinical variables in patients with neoplasm vs. those without; clinical variables included demographics (age, sex, and gender), risk factors (presence or absence of diabetes mellitus, use of corticosteroids at presentation, surgery in the previous 30 days, transplanted organ recipient status, exposure to antibiotics over the last 30 days, exposure to aminopenicillins over the same period of time, and hemodialysis), symptoms (presence or absence of fever, temperature ≥38 °C, and days of symptoms before presentation), route of acquisition (community vs. healthcare associated), main known sources of bacteremia (urinary, biliary, pneumonia, or indwelling intravascular catheter-related bacteremia), laboratory data (white blood cell (WBC) count, platelet count, and serum creatinine and albumin), sepsis severity score (APACHE II), complications (presence or absence of organ injury (kidney or lung), septic shock, disseminated intravascular coagulation (DIC), mechanical ventilation, or all-cause attributable mortality), total days of effective antibiotic therapy, and the microbiology characteristics (type of *Enterobacteriaceae* in the blood culture and presence of polymicrobial bacteremia).

Blood cultures were processed using the BACTEC 9240 automated culturing system. Antibiotic exposure was defined as any antibiotic therapy >24 h but <30 days prior to the time when the positive blood cultures were drawn. Neoplasm included any type of cancer: hematologic or solid organ. Aminopenicillin exposure was defined as previous treatment with amoxicillin or ampicillin. Indwelling intravascular catheter included any peripheral, central, peripherally inserted, tunneled, or arterial intravascular catheters. Infection of a catheter line was defined as having simultaneous positive blood cultures from the line and from a peripheral site, with first positivity arising from the line. Polymicrobial bacteremia was considered as the presence of more than one *Enterobacteriaceae* or one *Enterobacteriaceae* and another different organism. Total days of effective antibiotic therapy was defined as the time an effective antibiotic was started based on antibiogram susceptibility results of the isolate to the time at which therapy was completed.

2.2. Statistical analysis

We performed an initial bivariate analysis and compared the categorical variables using Chi-square tests. Analyses were performed excluding missing values. We determined whether our continuous variables followed a normal distribution using the Shapiro–Wilk test. We used the *t*-test to compare these variables between patients with and without neoplasm. We included all variables whose tests for association with neoplasm rendered a *p*-value of ≤0.25 in a forward, stepwise, multivariate logistic regression model. A two-sided *p*-value of <0.05 was considered to indicate a statistically significant difference. All analyses were performed using STATA software.

3. Results

3.1. Clinical characteristics of the Enterobacteriaceae bacteremia cohort

A total of 468 patients with *Enterobacteriaceae* bacteremia were analyzed. The mean age was 56.9 ± 16.3 years; 255 patients were male (54.5%), 312 were Caucasian (66.7%), and 132 (28.2%) were African-American. Fever was present in 410 of 456 (89.9%) of the patients. We identified a total of 169 (37.0%) healthcare-associated bacteremias and 288 (63.0%) community-acquired bacteremias in 457 observations. From the analyzed cohort, 189 of 453 (41.7%) patients had previously received antibiotic therapy and 155 of 456 (34.0%) had undergone a surgical procedure over the last 30 days before presentation. Regarding co-morbidities, 130 of 463 (28.1%) patients had a diagnosis of diabetes mellitus, 57 of 461 (12.4%) were transplant recipients, and 52 of 461 (11.3%) had received hemodialysis. Of 436 patients, the three most common known sources of bacteremia were genitourinary with 111 patients (25.5%), catheter-related blood stream infection (CRBSI) with 73 (16.7%), and biliary tract with 23 (5.3%). Laboratory data were (mean ± standard deviation): WBC count $10.7 \pm 8.5 \times 10^9$/l, platelet count $175.3 \pm 126.7 \times 10^9$/l, albumin 2.8 ± 0.8 mg/dl, and creatinine 2.02 ± 2.39 mg/dl. The most common bacterial species isolated among 461 patients were *Escherichia coli* with 146 (31.7%) and *Klebsiella pneumoniae* with 99 (21.5%). The mean APACHE II score was 13.42 ± 5.92, with a portion of 305 patients developing septic shock (90; 29.5%), acute lung injury (39; 12.8%), acute kidney injury (30; 9.8%), DIC (21; 6.9%), and death (10.2%; 47 of 459).

3.2. Clinical characteristics of the subset of patients with neoplasia compared to those without neoplasia

A total of six patients were excluded because of missing data regarding neoplasm status. Of the 462, we identified 203 patients with a diagnosis of neoplasm. Of patients with neoplasm, the mean age was 59.6 ± 15.3 years; 120 (59.1%) patients were male, 158 (77.8%) were Caucasian, and 39 (19.2%) were African-American. The most common species isolated in this group was *K. pneumoniae* (62/201, 30.8%). Compared to patients without neoplasm (Table 1), patients with neoplasm were older (59.6 ± 15.3 vs. 54.8 ± 16.9; $p = 0.002$), had a smaller proportion of African-American subjects (19.2% vs. 35.3%; $p = 0.0001$), had fewer days of symptoms (3.15 ± 4.45 vs. 4.77 ± 9.62; $p = 0.03$), had more healthcare-associated infections (42.5% vs. 32.3%; $p = 0.03$), and greater exposure to aminopenicillins (10.5% vs. 2.1%; $p = 0.018$). A biliary source of infection was more common among patients with underlying neoplasia (8.2% vs. 3.2%; $p = 0.03$). Conversely, CRBSI (12.0% vs. 20.2%; $p = 0.02$) and urinary source (16.3% vs. 32.4%; $p = 0.0001$) were less common in this population. Diabetes mellitus (17.2% vs. 36.7%; $p = 0.0001$) and previous transplantation (5.4% vs. 17.4%; $p = 0.0001$) were also less common in this group. The APACHE II score was higher in this group (14.3 ± 5.2 vs. 12.7 ± 6.4; $p = 0.004$), in contrast to WBC count (10.7 ± 8.6 vs. 11.7 ± 7.8; $p = 0.005$), platelet count (174.6 ± 127.1 vs. 196.6 ± 119.5; $p = 0.0001$), and serum creatinine (1.4 ± 1.3 vs. 2.5 ± 2.9; $p = 0.0001$). The serum creatinine discrepancy is explained in part due to the lower proportion of patients in this group receiving hemodialysis (4 (2.0%) vs. 48 (18.7%); $p = 0.0001$).

In a multivariate analysis (Table 2), *K. pneumoniae* bacteremia (odds ratio (OR) 6.13, 95% confidence interval (CI) 1.65–22.71; $p = 0.007$), APACHE II score (OR 1.18, 95% CI 1.05–1.34; $p = 0.007$), and previous exposure to aminopenicillins (OR 28.84, 95% CI 1.94–429.3; $p = 0.015$) were associated with underlying neoplasm.

Table 1
Comparison of patients with and without neoplasm ($N = 462$)

Variables	N	Neoplasm		p-Values
		No ($n = 259$)	Yes ($n = 203$)	
Age	462	54.8 ± 16.9	59.6 ± 15.3	0.002[a]
Race	461	$n = 258$	$n = 203$	0.0001[a]
Caucasian		150 (58.1%)	158 (77.8%)	
African-American		91 (35.3%)	39 (19.2%)	
Gender, male	462	133/259 (51.4%)	120/203 (59.1%)	0.1
Fever	453	224/252 (88.9%)	183/201 (91.0%)	0.45
Days of symptoms, mean ± SD	444	4.77 ± 9.62	3.15 ± 4.45	0.03[a]
Route	451	$n = 251$	$n = 200$	
Healthcare		81 (32.3%)	85 (42.5%)	0.03[a]
Community-acquired		170 (67.7%)	115 (57.5%)	0.03[a]
Antibiotic exposure in the last 30 days	452	105/254 (41.3%)	83/198 (41.9%)	0.90
Exposure to aminopenicillins	173	2/97 (2.1%)	8/76 (10.5%)	0.018[a]
Source	431	$n = 247$	$n = 184$	
Urinary		80 (32.4%)	30 (16.3%)	0.0001[a]
CRBSI		50 (20.2%)	22 (12.0%)	0.02[a]
Biliary		8 (3.2%)	15 (8.2%)	0.03[a]
Pneumonia		10 (4.1%)	8 (4.4%)	0.88
Other/unknown		99 (40.1%)	109 (59.2%)	
Surgery in last 30 days	450	79/250 (31.6%)	74/200 (37.0%)	0.23
Diabetes mellitus	462	95/259 (36.7%)	35/203 (17.2%)	0.0001[a]
Transplant recipient	460	45/258 (17.4%)	11/202 (5.4%)	0.0001[a]
Corticosteroids	459	65/256 (25.4%)	40/203 (19.7%)	0.15
Septic shock	300	49/178 (27.5%)	37/122 (30.3%)	0.6
APACHE II score, mean ± SD	462	12.7 ± 6.4	14.3 ± 5.2	0.004[a]
WBC count, $\times 10^9$/l, mean ± SD	459	11.7 ± 7.8	10.7 ± 8.6	0.005[a]
Platelet count, $\times 10^9$/l, mean ± SD	457	196.6 ± 119.5	174.6 ± 127.1	0.0001[a]
Albumin, mean ± SD	203	2.8 ± 0.9	2.8 ± 0.8	0.77
Creatinine, mean ± SD	456	2.5 ± 2.9	1.4 ± 1.3	0.0001[a]
Bacteremia				
Escherichia coli	455	88/254 (34.6%)	56/201 (27.9%)	0.12
Klebsiella pneumoniae	455	36/254 (14.2%)	62/201 (30.8%)	0.0001[a]
Polymicrobial bacteremia	410	36/235 (15.3%)	32/175 (18.3%)	0.42
Enterobacteriaceae + *Pseudomonas aeruginosa*	462	10/259 (3.9%)	9/203 (4.4%)	0.76
Days of effective antibiotic therapy	397	17.4 ± 12.5	15.8 ± 9.8	0.16
Acute lung injury	300	22/178 (12.4%)	16/122 (13.1%)	0.84
Disseminated intravascular coagulation	300	12/178 (6.7%)	9/122 (7.4%)	0.83
Mechanical ventilation	446	23/251 (9.2%)	14/195 (7.2%)	0.45
Hemodialysis	460	48/257 (18.7%)	4/203 (2.0%)	0.0001[a]
Death (all causes)	453	28/252 (11.1%)	18/201 (9.0%)	0.45

CRBSI, catheter-related blood stream infection; SD, standard deviation; WBC, white blood cell.
[a] p-Values < 0.05.

3.3. *Klebsiella* bacteremia and type of neoplasm

Patients who developed *K. pneumoniae* bacteremia ($n = 98$) had a greater proportion of underlying neoplasm when compared to 357 individuals who had bacteremia caused by other *Enterobacteriaceae* (62 (63.3%) vs. 139 (38.9%); $p = 0.0001$). Previous antibiotic exposure over the last 30 days (38 (39.6%) vs. 150 (42.7%); $p = 0.57$) and healthcare acquisition (38 (38.4%) vs. 129 (36.8%); $p = 0.77$) of the bacteremia were not statistically different. According to the type of underlying neoplasm (Table 3), *K. pneumoniae* was most frequently observed in patients with lung (3/7; 42.9%) and gastrointestinal cancers (24/57; 42.1%), followed by genitourinary (8/22; 36.4%) and hematologic malignancies (22/76; 28.9%).

4. Discussion

We found that the subgroup of patients with neoplasm presenting with *Enterobacteriaceae* bacteremia were more

Table 2
Multivariable analysis results for variables associated with neoplasm

Variables	OR	95% CI	p-Value
Klebsiella pneumoniae	6.13	1.65–22.71	0.007
APACHE II	1.18	1.05–1.34	0.007
Diabetes mellitus	0.19	0.06–0.65	0.008
Aminopenicillin	28.84	1.94–429.3	0.015
Days of symptoms	0.87	0.75–1.01	0.06
Age	1.02	0.99–1.06	0.171
WBC count	0.93	0.87–1.00	0.048
Community-acquired	2.69	0.90–7.99	0.075
Transplant recipient	0.25	0.04–1.55	0.137

CI, confidence interval; OR, odds ratio; WBC, white blood cell.

Table 3
Distribution of *Klebsiella pneumoniae* bacteremia cases per cancer type

Type of cancer	Number of patients	*Klebsiella pneumoniae* bacteremia
Lung	7	3 (42.9%)
Gastrointestinal	57	24 (42.1%)
Genitourinary	22	8 (36.4%)
Hematologic	76	22 (28.9%)
Gynecologic	10	1 (10%)
Breast	11	0 (0%)
Central nervous system	2	0 (0%)
Other	16	4 (25%)
Total	201	62

likely to be infected with *K. pneumoniae*. This association may be explained in part due to host and pathogen associated factors. Previous reports have identified underlying malignancy of between 14% and 34% among patients with *K. pneumoniae* bacteremia and up to 53% in *K. pneumoniae* nosocomial bacteremia.[6–9] In our cohort, this number was significantly higher (63%), which could be explained in part by the higher proportion of healthcare-associated cases identified. Other bacteremias such as those caused by *Pseudomonas aeruginosa*, *Enterobacter spp*, and *Streptococcus bovis* have also been associated with malignancies,[10,11] most commonly of gastrointestinal origin.

Pathogen-related factors, such as different capsular, pili, lipopolysaccharide (LPS), and siderophore determinants,[12] may confer an adaptive advantage in patients with underlying malignancy and increase the potential for gastrointestinal translocation or biofilm formation in indwelling intravascular catheters, thus resulting in *K. pneumoniae* bacteremia over other intestinal commensals or colonizers. These are some of the potential explanations for the association we observed in our cohort. *K. pneumoniae* has been described colonizing the oropharynx among ill hospitalized patients and the gastrointestinal tract in long-term care facility residents.[13,14] Moreover, the nosocomial acquisition of *K. pneumoniae* bacteremia in cancer patients has been linked to higher mortality and to previous antibiotic exposure and antibiotic resistance.[9,15,16] In our cohort, healthcare-associated bacteremia was more frequently observed in patients with neoplasm; interestingly neither healthcare-related nor previous antibiotic exposure over the last 30 days were associated with *K. pneumoniae* bacteremia. Those risk factors may be more important in resistance antibiotic selection rather than invasiveness capabilities.

Exposure to aminopenicillins in the group of patients with neoplasm was significantly different to that of those without cancer; this may contribute to the selection of *K. pneumoniae* in this population. It is known that the presence of a chromosomal gene encoding a penicillin-specific beta-lactamase confers *K. pneumoniae* resistance to ampicillin.[17] In contrast, albeit with some geographic variation, human isolates of *E. coli* in the USA have a 16.5% rate of resistance to ampicillin.[18] Despite controlling for this type of exposure, there was still an association of *K. pneumoniae* bacteremia in patients with underlying malignancy, suggesting that there may be a role for other intrinsic potential virulent factors. However, other associated factors conferring a potential advantage for invasiveness in this setting are not known.

Host-related factors may also vary depending on the type of underlying malignancy, since demographics, the degree of gastrointestinal mucositis, chemotherapy-induced neutropenia, surgical interventions, and long-term devices may differ significantly among the different malignancies. Some other possible variations in outcomes may also be associated with the different antibiotic susceptibility of the bacteria, device colonization capabilities, and selection related to the particular procedures for each type of cancer.

It is important to note that there are some limitations to the findings drawn from this study. The clinical characteristics delineated from patients with cancer in our study may not apply to other cohorts with different underlying co-morbidities. This cohort included only bacteremia due to *Enterobacteriaceae*, which excluded important healthcare-related Gram-negative pathogens such as Pseudomonas and Acinetobacter. We were also unable to control for other potential important variables, including among others, the type of chemotherapy, degree of mucositis, and time since device placement, which may have confounded the findings. This study confirms that the subgroups of patients with cancer are more prone to develop *K. pneumoniae* bacteremia due to their intrinsic demographic and epidemiological characteristics.

In conclusion, sepsis and bacteremia are dynamic processes with great diversity and heterogeneity in different patient populations. In the subpopulation of patients with underlying malignancy there may be a specific predisposition for *Enterobacteriaceae* bacteremia to be caused by *K. pneumoniae*. This may allow the targeting of initial empiric antibiotic therapy based on local institutional antibiotic susceptibility patterns.

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Ethical approval: The present project is in compliance with the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects). Written informed consent was obtained from participants in accordance with protocols approved by the Institutional Review Board (IRB) at Duke University Hospital. Analyses of clinical data were performed under an approved protocol at the University of Colorado Denver.

Conflict of interest: No conflicts of interest are reported by Andrés F. Henao-Martínez, Guido R. González-Fontal, José R. Castillo-Mancilla, and Ivana V. Yang.

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