Pediatric Gram-Negative Bacteremia: Hidden Agenda

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Abstract

Background Recently, new types of community-onset bacteremia have been introduced as healthcare associated (HCA) in which the infection onset started outside the hospital and there were interactions with the healthcare system. Little data exist differentiating community-acquired (CA) and HCA bacteremia from hospital-acquired bacteremia (HA).

Objectives This article determines differences in the epidemiological characteristics and bacteriology of community-onset (i.e., CA and HCA) and HA gram-negative bacteremia in Saudi pediatric patients.

Methods We conducted a prospective cohort of all pediatric patients diagnosed with gram-negative bacteremia at the King Khalid University Hospital over a year (2015). We received daily electronic notifications of all blood culture positive cases for gram-negative bacilli.

Results A total of 92 children were hospitalized with gram-negative bacteremia; among these 64 (71.1%) were with HA bacteremia, 20 (21.1%) with CA bacteremia, and 8 (7.8%) with HCA bacteremia. Urinary tract infection was common clinical presentation (50%) in the patients diagnosed with CA and HCA bacteremia. Up to 92% of HA bacteremia and 2% of CA bacteremia were presented with septic shock. The most common gram-negative bacteria causing bacteremia is *Klebsiella pneumoniae*, constituting almost 29.3% of all organisms, and was only isolated from HA bacteremia. The antimicrobial susceptibility among the 92 isolates showed that the organisms were nonextended spectrum β-lactamase (non-ESBL) in 90%, and 10% of the isolates were ESBL. There was a significant difference in the total frequency of isolates between CA and HA incidences, regardless of ESBL or non-ESBL ($p < 0.001$).

Conclusion The most common type of gram-negative bacteremia is HA bacteremia followed by the CA and HCA bacteremia.

Keywords
- bacteremia
- community-acquired
- healthcare-associated
- hospital-acquired

Introduction

Bacteremia is a major pediatric health care problem. Despite great developments in therapy and supportive care, bacteremia still represents a major cause of morbidity and mortality.[1,2] In particular, gram-negative bacteremia has increasingly been reported among the pediatric population.[3] Recently, community-onset bacteremia was reclassified, due to increasing numbers of clinical outpatient treatments, into healthcare-associated (HCA) and community-acquired (CA) bacteremia.[4–8] Previous studies that made a comparison between hospital-acquired nosocomial (HA) gram-negative

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bacteremia and CA bacteremia found that there was an increased rate of bacteremia due to drug-resistant pathogens.[9–11] Studying the varying microbiological patterns of bacteremia in children, gram-negative septicemia was categorized in two studies to be up to 71.87 and 73%, respectively, of the culture-positive cases.[12,13] Furthermore, recently, there has been an increase in the number of HCA gram-negative bacteremia among hospitalized patients with high rate of multidrug-resistant (MRO) bacteremia.[14,15] The objective of this study was to analyze the differences between the three types of gram-negative bacteremia with regard to the comorbidities, clinical characteristics, etiology, and outcomes among Saudi children in the King Khalid University Hospital.

Methods

Study Design

This study was conducted at the King Khalid University Hospital, a 1,100-bed hospital with 135 monthly admissions in pediatric wards. It is a major teaching hospital in Riyadh, Saudi Arabia, providing both primary and tertiary medical care. The study was conducted between January 11, 2015, and December 27, 2015. Data were purposely collected from pediatric patients below 15 years of age with gram-negative blood infections, using daily computerized laboratory data and medical record information system. Standardized data forms were used to record demographic details, including underlying diseases, hospital unit, and exposure to the healthcare system in the previous years.

Statistical Analysis

All data were collected in an Excel sheet and were analyzed using the analysis of variance (ANOVA) method for finding differences among the three types of bacteremia. Results were considered significant if $p < 0.05$. Ethical approval for the study was obtained from the ethics committee of the hospital.

Definitions

Gram-negative bacteremia is defined as the isolation of gram-negative bacilli in a blood culture specimen. Clinically, significant bacteremia is defined as at least one positive blood culture, together with clinical features compatible with systemic inflammatory response syndrome. Patients were diagnosed with CA, gram-negative bacteremia if their first positive blood culture results were obtained from blood samples drawn within 48 hours after hospital admission. Cases of HCA bacteremia were diagnosed if one or more of the following criteria was fulfilled: outpatient treatment (patient treated in the clinic or emergency room) hemodialysis or intravenous chemotherapy during the past 30 days; hospitalization for at least 1 day during the past 90 days; home intravenous therapy or wound care during the past 30 days; or residence in a long-term care facility.

In addition, HA infection was defined as an infection that occurred more than 48 hours after admission to the hospital.

Identification and Antimicrobial Susceptibility Testing

Isolates of gram-negative bacteria were identified by standard microbiologic methods in the microbiology laboratory using an automated identification system (Vitek System; bioMerieux, Marcy l'Etoile, France). Susceptibilities to antimicrobial agents were determined by the use of an automated susceptibility testing system (Vitek System; bioMerieux). Extended spectrum β-lactamase (ESBL) production was confirmed by double disk synergy testing, in accordance with the Clinical and Laboratory Standards Institute (CLSI) standards .[15]

Results

Ninety-two children were diagnosed with gram-negative bacteremia, 64 (71.1%) with HA bacteremia, 20 (21.1%) with CA bacteremia, and 8 (7.8%) with HCA bacteremia. The most recorded criteria found in HA bacteremia were outpatient treatment in the past 30 days, intravascular chemotherapy in the past 30 days, and hospitalization for $>$ 1 day in the past 90 days. Most of the patients' age was less than 1year (►**Table 1**). There was no gender difference, and for the underlying comorbidities, there were 12 cases of renal disorder, 12 cases of gastrointestinal disorder, 8 cases of oncology diseases, 6 cases of respiratory disorder, and 13 patients with premature immune deficiency, and there were 3 patients with endocrine disorder (►**Table 2**) Fever was significantly more common in HA type. Urinary tract infection constituted the major clinical presentation for CA and HCA bacteremia. On the other hand, septic shock/hypotension was the main clinical

Table 1 Age range of pediatric patients with gram-negative bacteremia

Age range (y)	Community acquired	Health care associated	Hospital acquired	*p*-Value
<1 (No. 26)	4 (15.4%)	1 (3.8%)	21 (80.8%)	0.1770
1–3 (No. 33)	10 (30.3%)	3 (9.1%)	20 (60.6%)	0.9870
3–6 (No. 16)	3 (18%)	2 (12.5%)	11 (68.6%)	0.2774
6–12 (No. 15)	3 (20%)	1 (6.7%)	11 (73.3%)	0.2150
12–14 (No. 2)	1 (6.6%)	1 (6.7%)	0 (0%)	0.1
Total (No. 92)	20 (21.1%)	8 (7.8%)	64 (71.1%)	0.7801

Table 2 Comorbidities and clinical characteristics of 92 pediatric patients with community-acquired and health-associated and hospital-acquired gram-negative bacteremia

Characteristics	Community acquired ($n = 20$)	Health associated ($n = 8$)	Hospital acquired ($n = 64$)	*p*-Value
Underlying disease				
Hematological/malignancy[8]	4 (25%)	4 (25%)	4 (50%)	0.4795
Renal disease[12]	4 (17.5%)	4 (17.5%)	8 (67%)	0.6162
Gastroenterology[12]	8 (67%)	0 (0%)	4 (33%)	0.6162
Respiratory[6]	2 (33%)	0 (0%)	4 (67%)	0.9352
Endocrine[3]	0 (0%)	0 (0%)	3 (100%)	
Immune deficiency[1]	0 (0%)	0 (0%)	1 (100%)	
Prematurity[13]	0 (0%)	0 (0%)	13 (100%)	
Clinical presentation				
Fever[54]	18 (22%)	6 (11%)	36 (67%)	0.0375
Septic shock/hypotension[26]	2 (8%)	0 (0%)	24 (92%)	0.0279
Urinary tract infection[12]	10 (50%)	4 (33%)	2 (17%)	0.3006

presentation in HA bacteremia indicating that the gram-negative bacteremia is clinically significant. The most common gram-negative bacteria causing bacteremia was *Klebsiella pneumoniae* (29.3%), which was isolated in cases with HA bacteremia. This was followed by *Escherichia coli* (isolated in two types: HA and CA bacteremia, ►**Table 3**). In CA type bacteremia, 25% of the isolated organisms were *E. coli*. The antimicrobial susceptibility of the isolated organisms of CA/HCA, and HA bacteremia showed that majority of the organisms were non-ESBL in 90%, and 10% of the isolates were ESBL. Three isolates were multi-resistant organism (MRO) among HA bacteremia (►**Table 4**). In comparing the difference between ESBL and non-ESBL isolate among the three types of bacteremia, there was no significant difference in the percentage of ESBL and non-ESBL in CA and HA bacteremia ($p = 0.928$). However, there was a significant difference in the total frequency of isolates between CA and HA bacteremia, regardless whether they were in the ESBL or non-ESBL groups ($p < 0.001$, ►**Table 5**). However, there was a high mortality rate constituting 17 mortality cases (18.7%), 14 cases for HA bacteremia and 3 for CA bacteremia (►**Table 6**).

Table 3 Classification of 92 patients with gram-negative bacteremia among community-acquired, healthcare-associated, and hospital-acquired bacteremia

Organism	Community acquired $n = 20$ (%)	Healthcare associated $n = 8$ (%)	Hospital acquired $n = 64$ (%)	Total $n = 92$ (%)
Acinetobacter baumannii	1 (5)	2 (25)	2 (3.1)	5 (5.4)
Acinetobacter lwoffii	0 (0)	1 (12.5)	0 (0)	1 (1.1)
Brucella	2 (10)	0 (0)	0 (0)	2 (2.2)
Burkholderia cepacia	0 (0)	0 (0)	1 (1.5)	1 (1.1)
Escherichia coli	5 (25)	0 (0)	10 (15.6)	15 (16.3)
Enterobacter cloacae	1 (5)	2 (25)	4 (6.2)	7 (7.6)
Haemophilus influenzae	3 (15)	0 (0)	0 (0)	3 (3.3)
Klebsiella pneumoniae	0 (0)	0 (0)	27 (42.1)	27 (29.3)
Pseudomonas aeruginosa	0 (0)	2 (25)	12 (18.7)	14 (15.2)
Pseudomonas flourescens	0 (0)	0 (0)	1 (1.5)	1 (1.1)
Salmonella species	6 (30)	2 (25)	0 (0)	8 (8.6)
Salmonella typhi	1 (10)	0 (0)	0 (0)	1 (1.1)
Serratia marcescens	0 (0)	0 (0)	5 (7.8)	5 (5.4)
Stenotrophomonas maltophilia	0 (0)	0 (0)	2 (3.1)	2 (2.2)
Total	20	8	64	92 (100%)

Table 4 The antimicrobial susceptibility of the isolated organisms among community-acquired/health-associated, and hospital-acquired bacteremia ($n = 92$)

Antibiotics	Resistance $n = 92$ (%)	Community acquired and health associated $n = 28$ (%)	Hospital acquired $n = 64$ (%)	*p*-Value
Pipracillin/tazobactam TAZ	5 (5.5)	0 (0)	5 (7.8)	0
Bactrim/cotrimoxazole SXT	18 (19.8)	5 (18.5)	13 (20.3)	0.5657
Meropenem MEP	5 (5.5)	2 (7.41)	3 (4.7)	0.0674
Imipenem IMP	6 (6.6)	5 (18.5)	1 (1.6)	0.2793
Gentamicin GM	14 (15.4)	10 (37)	4 (6.3)	0.6201
Amikacin AK	4 (4.4)	2 (7.4)	2 (3.1)	0.0405
Augmentin AMC	16 (17.6)	4 (14.8)	12 (18.8)	0.5663
Ampicillin/Ampiclox AMP	48 (52.7)	6 (22.2)	42 (65.6)	0.1128
Cephradine CRD	14 (15.4)	4 (14.8)	10 (15.6)	0.4338
Ciprofloxacin CIP	11 (12.1)	4 (14.8)	7 (10.9)	0.4447
Aztreonam ATM	4 (4.4)	2 (7.41)	2 (3.1)	0.0406
Cefoxitin FOX	13 (14.3)	3 (11.1)	10 (15.6)	0.4597
Cefuroxime/Zinacef CXM	12 (13.2)	0 (0)	12 (18.8)	0
Cephaloridine CPL	4 (4.4)	0 (0)	4 (6.3)	0
Chloramphenicol CHL	2 (2.2)	0 (0)	2 (3.1)	0

Table 5 Difference between ESBL and non-ESBL isolate among community-acquired, healthcare-associated, and hospital-acquired bacteremia

Organism	Community acquired ($n = 13$) and healthcare associated ($n = 7$)	Hospital acquired ($n = 46$)	Total ($n = 66$)	*p*-Value
ESBL	5 (25.0%)	11 (23.9%)	16 (24.2%)	0.928
non-ESBL	15 (75.0%)	35 (76.1%)	50 (75.8%)	
Total	20 (30.3%)	46 (69.7%)	66 (100%)	<0.001

Abbreviations: ESBL, extended spectrum β-lactamase; non-ESBL, nonextended spectrum β-lactamase.
Note: There is no significant difference in the percentage of ESBL and non-ESBL in community-acquired and hospital-acquired bacteremia ($p = 0.928$).However, there is a significant difference in the total frequency of isolates between community-acquired and hospital-acquired bacteremia, regardless of ESBL or non-ESBL ($p < 0.001$).

Discussion

Recent data exist on the differentiation of HCA bacteremia from HA bacteremia and CA bacteremia.[16] In this study, comparing the epidemiology of CA, HCA, and HA bloodstream infections, it was found that health-associated bacteremia (7.8%) was of low incidence unlike other studies in which there were higher incidences of HCA bacteremia. This is similar to a study performed in Spain that found that 18% were CA, 24% were HCA, and 58% were HA.[17] Hoenigl et al found that of the total 1,143 patients diagnosed with bacteremia, HCA accounted for 63.7% and CA for 36.3% cases.[18] Similarly, Friedman's group reported that 50.9% of their 159 cases of gram-negative bacteremia were HCA.[9] Unlike this study, in the study by Hoenigl et al, the study cohort had slightly more male subjects (56.1 vs. 50.2%, $p = 0.044$) than females.[18] In this study, analyzing the causative pathogens, we found that the most common gram-negative bacteria

Table 6 Difference between the mortality rate in hospital-acquired and community-acquired bacteremia

Hospital acquired ($n = 64$)	Community acquired ($n = 20$)	Total	*p*-Value
14 (82.4%)	3 (17.6%)	17	0.1228

causing bacteremia was *K. pneumoniae* and was found to be significantly associated with the HA bacteremia. The causative pathogens were comparable between patients with CA and those with HCA bacteremia. In a recent prospective cohort study, in 672 patients enrolled with positive peripheral blood cultures (192 CA, 85 HCA, and 395 HA), *E. coli* was found to be the most frequently isolated pathogens. *Escherichia coli* was isolated more frequently in patients with community-onset bacteremia, and *Pseudomonas* species were isolated more frequently among those with HA bacteremia.[18] In agreement with previous reports, the most frequently seen underlying diseases in patients with gram-negative bacteremia were malignancies.[19] Compared with patients with HCA bacteremia and CA bacteremia for patients with HA bacteremia, the clinical presentation of urinary tract infection was higher in HCA bacteremia and CA bacteremia–4 (50%) and 10 (50%), respectively, versus 2 (1.3%) for HA bacteremia. Marschall et al reported contradicting results with findings of 38 (28.8%) versus 13 (14.4%) cases of bacteremia for the urinary tract when compared with HA bacteremia and HCA bacteremia.[20] This finding is in accordance with the previous study that reported that HCA bacteremia was associated with increased 30- and 90-day mortality rates when compared with CA bacteremia.[21]

In other studies, the mortality rate of HCA infection seemed to be generally higher than that of CA infection and was similar to that of hospital infection.[10]

In this study, all the isolates of HCA were multisensitive, contrary to a study from Korea in which a total of 240 patients were infected with community-onset *K. pneumoniae* bacteremia, 140 (58.3%) were defined as HCA infection cases, and the remaining 100 patients were classified as CA infections. Patients infected with HCA bacteremia showed significantly different clinical and microbiological characteristics compared with those infected with CA bacteremia. HCA *K. pneumoniae* bacteremia was characterized by more antibiotic-resistant pathogens (ciprofloxacin resistance, 12.9 [18/140] vs. 4.0% [4/100], $p = 0.02$) and ESBL production (12.1 [17/140] vs. 4.0% [4/100], $p = 0.03$) than CA bacteremia.[22]

A recent study from Saudi Arabia reported their experience of HA catheter-related blood stream infections (CRBSIs). CRBSI resulted in 60 admissions with a median of 182 days of hospital stay and 74 changes of central venous catheters. The rate of CRBSI was 2.9 per 1,000 catheter days. *Staphylococcus* species were the most prevalent pathogens (32%), followed by *K. pneumoniae* (5%).[23]

Conclusion

This study concluded that the epidemiology, causative pathogens, and mortality differed markedly between community-onset and HA bacteremia, while differences between CA and HCA bacteremia were by far less pronounced. HA bacteremia was associated with an increase in the risk of mortality when compared with CA bacteremia.

Our study had some limitations. One is the small sample size, a larger study should be performed to validate the findings of this study. Future studies should focus on recognizing CA and HCA bacteremia due to resistant organisms. Nonetheless, to the best of our knowledge, this is the first study comparing the clinical and bacteriological characteristics of HCA, HA, and CA gram-negative bacteremia in Saudi pediatric patients.

Conflict of Interest
None.

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