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Clinical and microbiological features of resistant gram-negative bloodstream infections in children

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Summary
Background: Bloodstream infections (BSIs) caused by Gram-negative (GN) bacteria cause significant morbidity and mortality. There is a worldwide increase in the reported incidence of resistant microorganisms; therefore, surveillance programs are important to define resistance patterns of GN microorganisms causing BSIs. The objective of this study was to describe the clinical and microbiological features of resistant GN BSIs in a tertiary pediatric hospital in Turkey.
Methods: Patients between 1 month and 18 years of age hospitalized between January 2005 and December 2012 were included in this study. The presence of ESBL and AmpC type beta-lactamase activity were evaluated using the Clinical and Laboratory Standards Institute (CLSI) disk diffusion and double-disk synergy tests.
Results: A total of 209 resistant GN bacterial BSI episodes were identified in 192 patients. Of 192 children, 133 (69.2%) were aged ≤48 months of age. Sixty-six (31.6%) of the BSIs were considered community-acquired and 143 (68.4%) were hospital-acquired infections. The most common isolates were non-fermenting GN bacteria ($n = 117$, 55.9%). The major causative pathogens were *Pseudomonas* spp. in non-fermenting GN bacteria. The resistance rates to imipenem for *Pseudomonas* spp. and *Acinetobacter* spp. were 40.5% and 41.6%, respectively. The most common isolates in fatal patients were *Pseudomonas* spp. followed by *Escherichia coli*. The overall 28-day mortality rate was 16.3%.

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Conclusions: Although our study was performed at a single center and represents a local population, based on this study, it is concluded that surveillance programs and studies of novel antibiotics for resistant GN bacteria focusing on pediatric patients are required.

Introduction

Bloodstream infection (BSI) is a clinical syndrome defined as the presence of bacteria in the blood, and it is associated with high morbidity and mortality. The epidemiology of microbial pathogens causing BSI has changed over the years, with an increase in the incidence of Gram-negative (GN) organisms [1,2]. Prompt and appropriate empirical treatment plays a critical role in GN BSIs. However, the increasing prevalence of resistant GN bacteria makes the empirical treatment of BSIs more difficult [3,4]. Although the use of antibiotics and, therefore, infections due to resistant organisms are highly common in hospital settings, and antibiotic resistance has recently emerged as an important cause of community-acquired BSIs [5,6]. This increase has also reduced the number of appropriate antibiotics available for the treatment of serious life-threatening GN BSIs. By contrast, it is worrisome that this increase has progressed much faster than the development of new antibiotics. Moreover, antibiotics that were developed and those currently under development are generally focused on adults. Studies investigating the clinical and epidemiological features of pediatric BSIs are lacking, and most of these studies are focused on specific age groups, particular microorganisms, or underlying diseases [7—9]. The objective of this study is to describe the clinical and microbiological features of community- and hospital-acquired BSIs and to investigate their causative pathogens and antibiotic resistance profiles, as well as mortality caused by BSIs, in a tertiary pediatric hospital in Turkey.

Methods

This retrospective study included clinical records of hospitalized patients aged between 1 month and 18 years who had blood culture positivity for resistant GN bacteria at Dr. Sami Ulus Maternity and Children's Training and Research Hospital between January 2005 and December 2012. Neonatal patients, outpatients, patients with a hospital stay shorter than 24 h and patients who were referred to our hospital from other health-care facilities were excluded from the study. Age, gender, department of hospitalization, underlying diseases, history of hospitalization within the last 3 or 6 months, history of parenteral or oral antibiotic use, and 30-day history of corticosteroid or other immunosuppressive or anticarcinogenic drug use, surgical operations, administration of hemodialysis, peritoneal dialysis, or plasmapheresis, and use of a mechanic ventilator and central venous catheter were recorded. In addition, the peripheral leukocyte count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels that were assessed on the day when the positive blood culture was obtained were recorded. BSI was defined as the isolation of a pathogen microorganism from >1 blood culture bottle. BSIs were classified as community- and hospital-acquired infections and were compared accordingly. Pathogens were defined as community-acquired BSIs if detected within the first 48 h of hospitalization, and they were defined as hospital-acquired BSIs if detected after 48 h of hospitalization. The recovery of different species 72 h after the previous positive blood culture in a single patient was considered to be a distinct episode. Isolation of the same microorganism from a single patient was considered to be a single episode even if the culture was obtained after 72 h.

The blood cultures were incubated in a BacT/Alert automated culture system at 37 °C for 24—48 h (bioMérieux®, France) and then Gram-stained and subcultured onto plates containing 5% sheep blood agar, eosin methylene blue agar, and chocolate agar. A control passage was performed for cultures that did not grow for 10 days. Confirmation of bacterial identification was achieved using conventional methods, such as a Gram stain test, oxidase test, lactose fermentation, urea test, indole test, and motility test, with an API 20E (bioMérieux®, France) in fermenting GN bacteria

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and an API 20NE (bioMérieux®, France) in non-fermenting GN bacteria between 2004 and 2009. However, by using this method, some of the non-fermenting GN bacteria could not be identified at the species level. The tests were performed with a Phoenix™-100 (BD, Diagnostic Instrument System, Sparks, USA) between 2009 and 2011 and with a VITEK 2 ID-AST (bioMérieux, France) automated system after 2011. The antibiotic susceptibility of blood isolates was assessed using an automated system as well as the Kirby-Bauer Disk Diffusion method and an extended-spectrum beta-lactamase (ESBL) assay. The AmpC beta-lactamase activity was detected using double-disk synergy and disk diffusion methods according to the Clinical Laboratory Standard Institute (CLSI) guidelines.

Statistical analysis

Data were analyzed using SPSS 15.0. Categorical variables were evaluated by the chi-square test, and continuous variables were evaluated by the Mann—Whitney U test and *t*-test. A p value of <0.05 was considered significant.

Results

Throughout the study, a total of 209 resistant GN BSI episodes were identified in 192 patients. The patients comprised 112 (58.3%) males and 80 (41.7%) females, with a mean age of 42.5 ± 52.6 months (median, 15; range, 1—204 months). The patients were classified into three age groups as follows: 1—12 months (n = 83, 43.2%), 13—48 months (n = 50, 26%), and 49—216 months (n = 59, 30.7%). Most of the patients were hospitalized in the general pediatrics department (n = 168, 80.4%), followed by pediatric surgery (n = 22, 10.5%) and the pediatric intensive care unit (n = 19, 9.1%). Underlying diseases were present in 162 (84.4%) patients, and the most common underlying disease was neurological disease (n = 30; 14%), followed by congenital or acquired heart disease (n = 23, 12%) and solid tumor (n = 23, 12%). The hospitalization rate and history of antibiotic use within the last 3 months were 65.6% (n = 137) and 75.6% (n = 158), respectively, and the hospitalization rate and history of antibiotic use within the last 6 months were 70.8% (n = 148) and 78.5% (n = 164), respectively. Within the 30 days before the diagnosis of GN BSI, 34 (16.3%) patients underwent chemotherapy administration, 19 (9.1%) underwent surgery, 6 (2.9%) used corticosteroid, and 6 (2.9%) underwent hemodialysis or peritoneal dialysis. At the time of diagnosis, twenty-six (12.4%) patients were being followed-up by mechanical ventilation, and a central venous catheter was present in 24 (11.5%) patients. The results are presented in Table 1. The mean hospital stay following the diagnosis of GN BSI was 22.6 ± 32.4 days (median, 14; range, 0—240 days).

Table 1 Underlying diseases of the patients with gram-negative bacteremia.

	n	%
Underlying disease	162	77.5
Neurological disease	30	14.4
Cardiac disease	23	11
Solid tumor	23	11
Gastrointestinal system disease	21	10
Hematologic disease	14	6.7
Nephrologic and rheumatologic disease	12	5.7
Respiratory tract disease	11	5.3
Others	28	13.4

The resistant GN BSIs comprised 66 (31.6%) community- and 143 (68.4%) hospital-acquired infections. The CRP level was higher in hospital-acquired infections (p = 0.000). The presence of underlying diseases, antibiotic use, chemotherapy administration, presence of a central venous catheter, and ongoing ventilation treatment were more common in hospital-acquired infections. The overall 28-day mortality was higher in hospital-acquired infections (Table 2). Non-fermenting GN bacilli accounted for 117 (55.9%) of the causative agents. Table 3 presents the distribution of microorganisms detected for community- and hospital-acquired BSIs. Non-fermenting species, except for *Pseudomonas* and *Acinetobacter*, were more common in community-acquired BSIs (p = 0.01), whereas *Klebsiella* spp. were more common in hospital-acquired BSIs (p = 0.035). Underlying diseases were present in 57.8% (11/19) of the patients with community-acquired BSIs caused by *Pseudomonas* spp. and in 66.6% (18/27) of the patients with community-acquired BSIs caused by non-fermenting GN bacilli other than *Pseudomonas* and *Acinetobacter* spp. One patient had cystic fibrosis associated with a BSI caused by *Acinetobacter baumannii*. This isolate was susceptible to carbapenem. In hospital-acquired isolates, the resistance of *Acinetobacter* spp. to imipenem was 41.6%, and all *Acinetobacter* spp. were susceptible to colistin. In community- and hospital-acquired *Pseudomonas* spp., imipenem resistance was 15.7% and 53%, respectively, and half of the isolates were susceptible to colistin. In non-fermenting GN

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Table 2 The distribution of the gram-negative microorganisms responsible from bacteremia.

Microorganism	Total (n = 209)	
	n	%
Non-fermenting bacilli[a]	55	26.3
Brevundimonas vesicularis	6	
Flavimonas oryzihabitans	5	
Burkholderia cepacia	4	
Burkholderia gladioli	3	
Sphingomonas paucimobilis	3	
Raltsonia picketii	2	
Cryseomonas luteola	2	
Elizabethkingia meningoseptica	2	
Stenotrophomonas maltophilia	1	
Pastorella pneumotropica	1	
Shewanella putrefaciens	1	
Alcaligenes xylosoxidans	1	
Cupriavidus pauculus	1	
Comomonas testosteroni	1	
Achromobacter denitrificans	1	
Pseudomonas spp.	49	23.4
P. aeroginosa	23	
K. pneumonia	32	15.3
***Enterobacter* spp.**	30	14.4
E. cloaca	19	
E. coli	25	12
***Acinetobacter baumannii* complex**	13	6.2
Serratia marcescens	3	1.5
C. freundii	2	1

[a] Non-fermenting Gram-negative bacilli excluding *Pseudomonas* and *Acinetobacter* spp.

bacilli other than *Pseudomonas* and *Acinetobacter* spp., imipenem resistance was remarkably low (0% and 3.5%, respectively), colistin resistance was considerably high (85% and 85.7%, respectively), and ciprofloxacin resistance was low (7.6% and 10.7%, respectively). In *Klebsiella* spp., imipenem resistance was 0% and 3.7% and ciprofloxacin resistance was 20% and 14.5%, respectively. No colistin resistance was detected. More than half of the hospital-acquired *Klebsiella* spp. (66.6%) was resistant to gentamicin. In community- and hospital-acquired *Enterobacter* spp., imipenem resistance was 0% and 31.8% and ciprofloxacin resistance was 0% and 4.5%, respectively. No colistin resistance was detected. Additionally in these species, aminoglycoside resistance was low. In *Escherichia coli* isolates, imipenem resistance was low, whereas half of the hospital-acquired isolates were resistant to ciprofloxacin and no colistin resistance was detected. In these species, gentamicin resistance was remarkably high (100% and 60%, respectively). *Serratia* and *Citrobacter* spp. showed no resistance to imipenem, ciprofloxacin, and colistin. Table 3 presents the resistance profiles of ESBL- and AmpC beta-lactamase-producing microorganisms to aztreonam, imipenem, ciprofloxacin, trimethoprim-sulfamethoxazole (TMP-SMX), colistin, gentamicin, and amikacin.

Table 3 The gram-negative microorganisms isolated from fatal patients.

Pathogen	Mortality	
	n	%
Pseudomonas spp.	13	38.2
E. coli	6	17.6
Non-fermenting[a] bacilli	4	11.7
Enterobacter spp.	4	11.7
Klebsiella spp.	3	8.8
Acinetobacter spp.	3	8.8
Serratia spp.	1	2.9
C. freundii	0	0
Total	34	

[a] Non-fermenting gram-negative bacilli excluding *Pseudomonas* and *Acinetobacter* spp.

The overall 28-day mortality was 16.3% (n = 34). In these patients, the most commonly isolated strains were *Pseudomonas* spp. followed by *E. coli* spp.

Discussion

In this study, the clinical and microbiological features of BSIs caused by resistant GN bacteria in pediatric patients and their resistance profiles were evaluated. The BSIs caused by GN bacteria were more common in the youngest age group. A study based on hospital discharge data obtained from various hospitals in 7 states of the USA reported that the annual age- and gender-adjusted incidence of sepsis was 0.56/1000 in all pediatric cases, and the highest age-adjusted incidence was in infants (5.16/1000), which decreased to 0.20/1000 in patients aged 10—14 years [10]. In a population-based study, 56 children were identified with GN BSI, and the annual gender-adjusted incidence rate of GN BSI per 100,000 persons was 129.7 in infants; this rated significantly decreased to 14.6 and 7.6 in children aged 1—4 and 5—18 years, respectively [7].

Pediatric studies on community- and hospital-acquired BSIs reported various rates of underlying diseases, which vary according to the population of the health-care facility. Common underlying diseases include preterm delivery, malnutrition, hydrocephaly, meningomyelocele, convulsive diseases, neutropenia, organ transplantation, use of

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steroids or other immunosuppressive drugs, cancer, liver failure, congenital heart disease, neurogenic bladder, chronic kidney disease, cystic fibrosis, and malaria [7,11–14]. In our study, underlying diseases were present in approximately three-quarters of our patients, and the most common diseases were neuromuscular.

The role of GN bacteria in community- and hospital-acquired BSIs has been reported with varying rates [4,15,16]. In our study, hospital-acquired infections accounted for approximately three-quarters of the resistant GN BSIs.

AmpC beta-lactamase-producing non-fermenting bacilli were the most common resistant GN bacteria in community- and hospital-acquired BSIs. A retrospective study investigated the epidemiological and clinical outcomes of bacteremia caused by multidrug-resistant *Enterobacteriaceae* and non-fermenting bacilli in a European tertiary pediatric hospital during a 12-month period. The study identified 136 blood cultures in 119 patients and reported that 86.3% of the patients presented with an underlying disease. The median age of the patients was 1.1 years; the most commonly isolated strains were *Klebsiella pneumoniae*, *E. coli* and *Pseudomonas aeruginosa*; the percentage of multidrug-resistant organisms was 39%; and 67.6% of the infections were acquired in hospital settings [17].

Non-fermenting GN bacilli are important agents of infections acquired in hospital settings, particularly in intensive care units. However, recent reports demonstrated that these pathogens also play a role in community-acquired infections. In a study on the clinical impact of GN non-fermenters in adults with community-onset bacteremia, non-fermenting GN bacilli were detected in 31 (6%) of 565 adults with community-acquired bacteremia [6]. In our study, these agents were responsible for over half of the BSIs detected in our patients. In a population-based study that investigated the BSIs caused by GN bacilli in children over a 10-year period, *P. aeruginosa* was the second most common pathogen after *E. coli* [7]. In the SENTRY Antimicrobial Surveillance Program (1997–2002), the prevalence of *P. aeruginosa* was two-fold higher in hospital-acquired infections than in community-acquired infections and multidrug resistant *P. aeruginosa* was relatively more common in hospital settings and intensive care units (community-acquired, 3.4%; hospital-acquired, 9%) [18]. In our study, *Pseudomonas* spp. were detected at high rates in community-acquired infections. This is attributed to underlying diseases leading to secondary immunosuppression, such as diabetes mellitus and chronic kidney disease, or primary immunodeficiency diseases. In the SENTRY Antimicrobial Surveillance Program (1997–2007), the resistance of *P. aeruginosa* to imipenem was 20% [19]. In our study, the prevalence of imipenem-resistant *Pseudomonas* was considerably high (40.5%). In the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) program, which investigates the *in vitro* susceptibility of bacterial isolates to meropenem worldwide, the intensive care units in Turkey had the highest rate of multidrug resistant *P. aeruginosa* spp. (50%) [20]. In our study, the resistance of *Pseudomonas* spp. to carbapenem was remarkably high compared to the lower resistance to aminoglycoside and ciprofloxacin.

A. baumannii has recently emerged as an important agent of infections acquired in hospital settings, particularly in intensive care units [21]. In the SENTRY Antimicrobial Surveillance Program (1997–2002), *Acinetobacter* spp. were responsible for 2.9% of hospital-acquired BSIs and 1.2% of community-acquired BSIs [18]. In our study, BSI caused by *A. baumannii* was present in only one patient who had cystic fibrosis. Although carbapenems are the first-line treatment for BSIs caused by *Acinetobacter* spp., colistin has also become an important treatment option worldwide due to the increasing resistance to carbapenem. The rate of imipenem-resistant *A. baumannii* spp. in patients treated in intensive care units increased five-fold between 2001 and 2008 [22]. In the 2011 report by the Turkish National Nosocomial Infections Surveillance Network, the resistance to carbapenem for *A. baumannii* spp. isolated from hospital-acquired infections was 74% [23]. In our study, resistance to carbapenem was higher than 40% and no colistin resistance was detected.

Klebsiella spp. is the second most common pathogens of both community- and hospital-acquired GN BSIs after *E. coli* [16,24]. In our study, *Klebsiella* spp. was the most common pathogens in hospital-acquired BSIs. *K. pneumoniae* is the most frequent ESBL-producing organism of the *Enterobactericea* [21,25]. Carbapenems are the most effective agents for the treatment of ESBL-producing *K. pneumoniae* infections. However, the widespread use of carbapenems has led to the emergence of carbapenemase-producing strains [26]. In our study, the resistance of *Klebsiella* spp. to imipenem was 4.3%. In a study that investigated BSIs caused by ESBL-producing *Klebsiella* spp. in children in Turkey over a 4-year period, the prevalence of ESBL-producing isolates was 57.1% and carbapenem resistance was 0% [27]. Studies showed that the frequent use of quinolones, particularly for the treatment of GN bacilli infections

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in adults, results in a number of mechanisms that lead to resistance to quinolones and the emergence of plasmid-mediated resistance in ESBL-producing *Klebsiella* spp. [28]. In this study, the resistance of *Klebsiella* spp. to ciprofloxacin was 16.6%, which was lower than the rates reported in other adult studies. We propose that this outcome is attributed to the limited use of quinolones in children compared to adults and therefore is the reason for the low-level of quinolone resistance.

E. coli is the most frequently isolated GN bacilli both in community- and hospital-acquired BSIs [4,29]. In our study, *E. coli* was the fifth most common pathogen in all infections, and it was more frequently detected in hospital-acquired BSIs compared to community-acquired BSIs. Moreover, ESBL production was detected in all *E. coli* isolates. ESBL-producing *E. coli* isolates are generally resistant to fluoroquinolones, TMP-SMX, and aminoglycosides. A study identified 95 ESBL-producing *E. coli* isolates and reported the rates of resistance to ciprofloxacin, TMP-SMX, amikacin, and imipenem as 36%, 37%, 85%, and 100%, respectively [30]. In our study, the rates of resistance to ciprofloxacin, TMP-SMX, and amikacin were similar to these previously reported rates (52%, 25%, and 76%, respectively), whereas resistance to imipenem was significantly lower (5.2%).

In a surveillance study by the Centers for Disease Control and Prevention (CDC), *Enterobacter* was reported as the fifth most common pathogen isolated from patients treated at intensive care units (5—8.6%) [31]. In our study, *Enterobacter* spp. were the fourth most common microorganisms isolated from infections. During treatment, *Enterobacter* spp. is likely to exhibit rapid resistance to third-generation cephalosporins *via* the production of AmpC Beta-lactamase. In a study on the clinical features of BSIs caused by *Enterobacter cloacae*, 3.5% of the isolates were ESBL-producers, whereas 59.6% and 31.6% of the isolated included inducible and derepressed AmpC enzymes, respectively, and all of the isolates were susceptible to imipenem, meropenem, gentamicin, and ciprofloxacin [32]. In our study, *Enterobacter* spp. were most susceptible to aminoglycosides and ciprofloxacin. *Enterobacter* spp. become resistant to carbapenems by producing carbapenemase [33]. In a study on the molecular epidemiology of carbapenem resistance in *E. cloacae* strains, 3.55% (35/986) of the strains were carbapenem-resistant isolates [34]. In our study, imipenem resistance in *E. cloacae* strains was found in one-third of the isolates.

Mortality in patients with BSI may be associated with a number of factors, including the severity of infection, underlying diseases, age, and inappropriate empirical antibiotic therapy. The overall 28-day mortality reported in patients with GN BSI varies between 11 and 26.2% [4,7]. In our study, the overall 28-day mortality was 16.3%. In these patients, *Pseudomonas* spp. was the most frequently isolated pathogens. Moreover, BSIs caused by *Pseudomonas* spp. lead to high mortality. In a study previously conducted in our hospital that excluded patients in intensive care units, the mortality rate for 171 patients was 27.5%, and similar to our study, *P. aeruginosa* was associated with high mortality [35].

Our study has several limitations. First, the sample size was small because the study was conducted at a single center. Second, most of the patients had an underlying disease making them prone to infection. Finally, neonatal patients, who have a high rate of hospitalization, were excluded from this study.

Conclusion

Studies of pathogens responsible for bloodstream infections and their antibiotic resistance patterns are critically important for defining prompt and appropriate treatments. Antibiotic resistance surveillance programs and studies of novel antibiotics for resistant GN bacteria focusing on pediatric patients are required.

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Competing interests

None declared.

Ethical approval

Not required.

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