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ORIGINAL ARTICLE

Epidemiology of community-acquired bacteremia among infants in a medical center in Taiwan, 2002—2011

Yung-Tien Ting [a], Chun-Yi Lu [a], Pei-Lan Shao [b], Ping-Ing Lee [a], Jong-Min Chen [c], Po-Ren Hsueh [c,d], Li-Min Huang [a], Luan-Yin Chang [a,*]

[a] *Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan*
[b] *Department of Pediatrics, Hsin-Chu Branch, National Taiwan University Hospital, Hsin-Chu, Taiwan*
[c] *Department of Laboratory Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan*
[d] *Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan*

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Objective: To investigate the etiologies and antibiotic susceptibility of community-acquired bacteremia in infants in a medical center in northern Taiwan.
Methods: We conducted a retrospective analysis of all blood cultures from infants in the National Taiwan University Hospital from 2002 to 2011 to find community-acquired bacteremia. Common pathogens, antibiotic resistance, and outcome were analyzed.
Results: During the study period, 25,628 blood cultures were collected, and 3.4% of the cultures were positive, of which 15.9% were categorized as community-acquired bacteremia. In the age group of 0—6-days, the leading causative organisms were group B streptococcus (41.7%) and *Escherichia coli* (30.6%). In the 7—90-days and 4—6-months groups, the most common pathogens were *E. coli* (44.1%, 45.5%, respectively) and group B streptococcus (32.4%, 13.6%, respectively). For infants aged 7—12 months, the most common pathogens were *Salmonella* species (51.1%) and *E. coli* (12.8%). The overall mortality rate of community-acquired bacteremia was 6%. Urinary tract infection was the concomitant diagnosis among 52.4% of infants with *E. coli* bacteremia. Meningitis was found in 33.3% of infants with group B

* Corresponding author. Division of Pediatric Infectious Diseases, Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Number 8, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail addresses: ly7077@tpts6.seed.net.tw, lychang@ntu.edu.tw (L.-Y. Chang).

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streptococcus bacteremia. *Listeria monocytogenes* bacteremia was identified in three infants, one of whom had meningitis. Penicillin resistance was found in 4% of group B streptococcus and ampicillin resistance in 71% of *E. coli*.
Conclusion: Our study provides updated etiological data on community-acquired bacteremia in infants in northern Taiwan. Group B streptococcus and *E. coli* remained the leading pathogens in infants aged 6 months or younger and *Salmonella* species for those older than 6 months.

Introduction

Bacteremia is a frequent and important cause of neonatal and infant morbidity and mortality.[1–3] The currently recommended treatment is ampicillin and gentamicin for young infant bacteremia and third-generation cephalosporins for older infants with suspected sepsis.[1,4–6] The evidence to recommend empirical antibiotics in infants with community-acquired bacteremia in Taiwan has been limited because of a lack of comprehensive data on common bacterial pathogens and antimicrobial resistance after 2003.

To investigate the etiologies and antibiotic susceptibility of community-acquired bacteremia in neonates and infants, we thus reviewed microbiological data from blood cultures taken from infants aged 12 months or younger during a 10-year period (2002–2011) at the National Taiwan University Hospital (NTUH), a tertiary medical center with 2500 beds located in Northern Taiwan.

Methods

Patient and bacterial isolates

We performed a retrospective analysis of all blood cultures from infants at NTUH during 2002–2011. All the electronic medical records of infants with positive blood cultures were analyzed. We reviewed the demography, underlying diseases, date of blood sampling, date of hospitalization, laboratory data, clinical presentations, and outcomes.

For antimicrobial susceptibility, isolates were classified as being either susceptible or resistant to an antimicrobial agent using the disc diffusion method and/or minimum inhibitory concentration. The results were interpreted according to Clinical and Laboratory Standards Institute guidelines.

The number of deliveries every year in our hospital was obtained from the obstetrics department to calculate the rate of neonatal early-onset group B streptococcus (GBS) infection in our hospital.

Definitions

Bacteremia was defined as the isolation of at least one non-contaminant bacteria from the blood culture. *Bacillus* species, micrococci, or *Corynebacterium* species grown alone in a single culture were categorized as contaminants,[7–9] and were thus excluded in this study. Coagulase-negative staphylococcus species (CoNS) would be considered true pathogens among neonates and premature babies if there was one or more clinical signs of neonatal sepsis (temperature instability, cardiorespiratory signs, gastrointestinal disturbance, lethargy, or irritability) in infants who had an isolation of CoNS (same species and/or identical antimicrobial susceptibility results) from two or more blood cultures or from one blood culture and a sterile body site.[10] Infections were classified as nosocomial episodes, which would be excluded in this study if they first appeared 48 hours or more after hospitalization or within 14 days after discharge.[10–12] We also excluded the bacteremic neonates whose mothers had been admitted to our hospital for delivery, and the bacteremic premature babies with prolonged hospital stay.

To assess concomitant urinary tract infection (UTI), meningitis, and gastroenteritis, urinary, cerebrospinal fluid (CSF), and stool culture results were evaluated if the aforementioned cultures were obtained within 2 days of blood culture sampling in all infants with clinically significant bacteremia.[2,3] UTI was defined as voiding urine culture with $\geq$100,000 colony-forming units of a single organism per milliliter and catheterized urine culture $\geq$ 10,000 colony-forming units of a single organism per milliliter, respectively. Bacterial meningitis was defined as a positive CSF culture or a positive blood culture with CSF pleocytosis. Gastroenteritis was defined as increased frequency or amount of stool passage with positive results of rotaviral or noroviral antigen by enzyme-linked immunosorbent assay or stool cultures.

The age groups of patients were divided as follows: 0–6-days, 7–90-days, and 4–6-months (91–180 days old) and 7–12-months (181–365 days old) groups. Leukopenia was defined as leukocyte count less than 4000/μL, thrombocytopenia was defined as platelet count less than 100,000/μL, and extremely low birth weight was defined as birth body weight (BBW) less than 1000 g. Fatality was defined as death within 14 days of a positive blood culture.

Statistics

Data were shown with medium (range), percentages, and numbers. We used the Chi-square test to calculate the p values of risk factors associated with mortality. A p value <0.05 was considered statically significant.

Results

Study population and patient characteristics

During the 10-year study period, 25,628 blood cultures were performed on infants. A total of 1224 organisms were

recovered from blood samples. Of these, 339 isolates were categorized as contaminants (27.7%), whereas 139 clinically significant episodes of community-acquired bacteremia (11.4%) were identified. The other 746 (60.9%) episodes were nosocomial infections.

Of these 139 patients with community-acquired bacteremia, 35% of patients were female, and the male-to-female ratio was 1.8 (90:49). Regarding the age group, the 0–6-days group consisted of 36 patients (26%), the 7–90-days group had 34 patients (24%), the 4–6-months group had 22 patients (16%), and the 7–12-months group had 47 patients (34%; Table 1). The most frequent underlying conditions were prematurity in 25 patients (18%), biliary atresia in 13 patients (9.4%), and congenital heart disease (CHD) in 7 patients (5%). No patient had immunodeficiency or hematology-oncology diseases.

The overall fatality rate was 6% (9/139). There was no significant difference in the mortality rates between 2002–2006 and 2007–2012. Early-onset infection (infant age younger than 7 days) was a risk factor of mortality (6/9 vs. 30/100, $p = 0.01$). Other risk factors of mortality included prematurity with gestational age less than 36 weeks (3/9 vs. 13/124, $p = 0.04$), BBW lower than 1,500 g (3/9 vs. 9/120, $p = 0.01$), no fever (6/9 vs. 32/130, $p = 0.006$), leukopenia (leukocyte count<4000/μL; 3/9 vs. 10/118, $p = 0.02$), and thrombocytopenia (platelet count<100,000/μL; 3/5 vs. 9/124, $p < 0.001$).

Clinical features of important pathogens

All the episodes were monomicrobial infections. Gram-positive pathogens predominated the community-acquired bacteremia only in the 0–6-days group (55.6%) and then decreased in proportion as the patients' age increased. In the age group of 0–6 days of life, group B streptococcus (GBS; also known as *Streptococcus agalactiae*) was the most common agent, accounting for 41.7% of all episodes, followed by *E. coli* (30.6%) and *Listeria monocytogenes* (8.3%; Fig. 1). For patients aged 7–90 days and 4–6 months, *E. coli* was the leading cause of bacteremia (44.1% and 45.5%, respectively), and GBS was the second most common agent (32.4% and 13.6%, respectively). *Salmonella* species accounted for half of the episodes in the 7–12-months age group (51.1%), which

Table 1 Characteristics and underlying comorbidities by age group

	N (%)			
Age group	0–90 d	4–6 mo	7–12 mo	Overall
	70 (50)	22 (16)	47 (34)	139 (100)
Male	50 (71)	13 (59)	27 (57)	90 (65)
Prematurity	16 (23)	5 (23)	4 (9)	25 (18)
CHD	3 (4)	3 (14)	1 (2)	7 (5)
GI abnormality	1 (1)	5 (23)	9 (19)	15 (11)
BA	0 (0)	5 (23)	8 (17)	13 (9)
Others	1 (1)	0 (0)	1 (2)	2 (1)
Others	1[a] (1)	0 (0)	0 (0)	1 (0.7)

[a] Perinatal asphyxia, hypoxic ischemic encephalopathy.
BA = biliary atresia; CHD = congenital heart disease; GI = gastrointestinal.

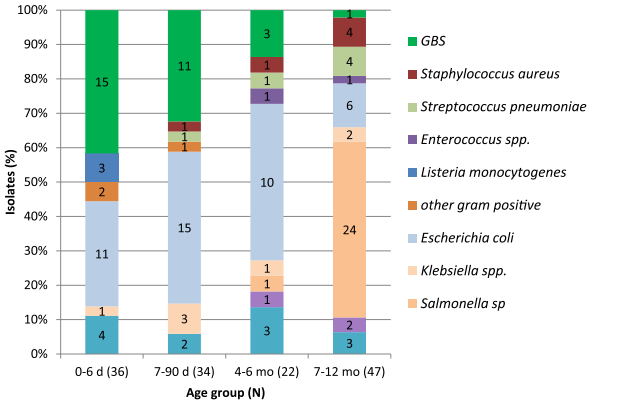

Figure 1. Causes of community-acquired bacteremia by age group.

was four times the second most common organism, *E. coli* (12.8%), in this age group. *Staphylococcus aureus* and *Streptococcus pneumoniae* were the next most common pathogens in this group (8.5% and 8.5%, respectively).

Regardless of the patients' age, *E. coli* bacteremia eventually predominated these community-acquired episodes (42/139, 30%). Of the 42 infants with *E. coli* bacteremia, 23 (54.8%) and 5 (12%) had concomitant UTI or meningitis (Table 2). Cases with concomitant UTI had a significantly lower rate of gestational age <28 weeks (0/24 vs. 4/17, $p = 0.01$), a significantly higher rate of fever (24/24 vs. 0/18, $p < 0.0001$), and a significantly higher rate with C-reactive protein over 5 mg/dL (13/23 vs. 0/17, $p = 0.0002$). Seventy-four percent (17/23) of the patients with UTI were male. The mortality rate of *E. coli* bacteremia was 4.8% (2/42). Extreme low birth weight (BBW < 1000 g; 1/2 vs. 1/39, $p = 0.002$), no fever (2/2 vs. 6/40, $p = 0.003$), and leukopenia (1/2 vs. 1/37, $p = 0.003$) were risk factors of mortality in cases of *E. coli* bacteremia.

Of 30 cases with GBS bacteremia, 15 (50%) were early-onset neonatal bacteremia, and 11 (36.7%) had concomitant meningitis. In the cases with concomitant meningitis, lower rate of prematurity (either gestational age less than 36 weeks or 32 weeks; 0/11 vs. 7/19, $p = 0.02$; 0/11 vs. 6/19, $p = 0.04$, respectively), more febrile patients (10/11 vs. 7/19, $p = 0.004$), higher rates of leukopenia (5/11 vs. 2/19, $p = 0.03$) and elevated serum C-reactive protein level (>5 mg/dL: 6/11 vs. 0/19, $p = 0.0003$; >10 mg/dL: 4/11 vs. 0/19, $p = 0.005$) were noted. Two patients (7%) died.

Salmonella was the most common in the 7–12-months age group. Among the 25 cases with *Salmonella* bacteremia, 15 cases (60%) had concomitant gastroenteritis and no death occurred. Female babies with *Salmonella* bacteremia had a higher rate of gastroenteritis than males according to our data ($p = 0.045$).

There were one case of *Haemophilus influenzae* type B bacteremia and one case with *Neisseria meningitidis* bacteremia. Both cases had concomitant bacterial meningitis.

Drug susceptibility

Thirty (71%) of 42 *E. coli* isolates were ampicillin resistant and 6 (42%) were gentamicin resistant. Five of six

Table 2 Bacterial pathogens in 139 infants with community-acquired bacteremia

	N (%)	Median age in d (range)	UTI	Concomitant meningitis	AGE/colitis	Mortality
Gram-positive	50 (36)					
GBS	30 (22)	6 (0—197)	1 (3)	10 (33)	0 (0)	5 (17)
Staphylococcus aureus	6 (4)	232.5 (79—340)	0 (0)	0 (0)	0 (0)	0 (0)
Streptococcus pneumoniae	6 (4)	246 (52—297)	0 (0)	1 (17)	0 (0)	1 (17)
Listeria monocytogenes	3 (2)	1 (0—1)	0 (0)	1 (33)	0 (0)	0 (0)
Enterococcus spp.	2 (1)	211 (159—262)	0 (0)	0 (0)	0 (0)	0 (0)
Gram-negative	89 (64)					
Escherichia coli	42 (30)	66.5 (0—363)	22 (52)	5 (12)	4 (10)	1 (2)
Salmonella spp.	25 (18)	271 (137—361)	2 (8)	1 (4)	13 (52)	0 (0)
Klebsiella spp.	7 (5)	53 (4—298)	3 (43)	0 (0)	1 (14)	1 (14)
Pseudomonas spp.	3 (2)	195 (176—313)	0 (0)	0 (0)	0 (0)	1 (33)

AGE = acute gastroenteritis; GBS = group B streptococcus; UTI = urinary tract infection.

gentamicin-resistant strains (83%) were also ampicillin resistant, and two isolates were resistant to cefotaxime, one of which had extended-spectrum beta-lactamase. If we divided the antibiotic resistance data into two parts, 2002—2006 and 2007—2012, and compared the change in the resistant rate of each antibiotic agent, there was no significant difference in the rate of resistance to ampicillin, cefazoline, cefmetazole, and cefotaxime. However, a significantly decreased rate of resistance to gentamicin was noted, from 45% to 3% ($p = 0.003$).

In 30 GBS strains, only one strain (4%) was recorded as penicillin resistant. Five strains (20%) of *Salmonella* species were ampicillin-resistant strains, whereas none were resistant to the third-generation cephalosporins. The rates of resistance to ampicillin, ciprofloxacin, and trimethoprim-sulfamethoxazole did not show significant difference between 2002—2006 and 2007—2012.

All three isolates of *L. monocytogenes* were susceptible to ampicillin. One isolate (14%) of *Klebsiella pneumoniae* was resistant to gentamicin. Four isolates of *S. aureus* were recovered after 2006, of which 3 (75%) were methicillin resistant.

Discussion

As the incidence of antimicrobial resistance increases, updated data on species distribution and resistance patterns of community-acquired pathogens become important to provide the basis for appropriate empirical therapy.[12] Our study showed that community-acquired bacteremia in infants happened mainly in the 0—90-days age group. 0—6-days and 7—90-days age groups consisted of similar case numbers. GBS and *E. coli* remained the two leading causative pathogens in these two age groups, whereas *Salmonella* species predominated in the 7—12-month group.

For all the Gram-negative pathogens with available data, 49 (62%) of 70 isolates were ampicillin resistant and 7 (12%) of 58 isolates were gentamicin resistant. In *E. coli* strains, the susceptibility rates of cefazolin, ampicillin plus gentamicin, and ampicillin plus cefotaxime were 73%, 88%, and 95%, respectively (Fig. 2). However, 97% of GBS strains were susceptible to ampicillin plus gentamicin. There was no cefotaxime or ceftriaxone-resistant *Salmonella* species in our data. Three of 4 strains *S. pneumoniae* (75%) were penicillin resistant. Half of the *S. aureus* strains were methicillin resistant. The only *Neisseria meningitides* strain was penicillin-intermediate but cefotaxime susceptible. *H. influenzae* type B was susceptible to ampicillin. For all pathogens, the susceptible rates of ampicillin, gentamicin, and cefotaxime/ceftriaxone were 50%, 40%, and 84%, respectively. The coverage rate of combination therapy with ampicillin plus gentamicin was similar to that with ampicillin plus cefotaxime (81% vs. 86%, respectively). The antimicrobial susceptibility of some isolates was incomplete and unavailable for repeated checkup. Thus, the rate of drug resistance could be higher. Therefore, this finding emphasized the need to revise the use of ampicillin as initial antibiotics in infants with suspected bacteremia in Taiwan because the common pathogens (such as GBS, *E. coli*, *Salmonella* species) of infant bacteremia were frequently resistant to ampicillin. Because 84% of all pathogens are susceptible to third-generation cephalosporin, it may be considered as the initial antibiotic for infant sepsis or bacteremia to cover the most common pathogens.

GBS had been considered the most common pathogen in young infants, especially in those with early-onset neonatal sepsis. *E. coli*, instead, was the leading cause of late-onset bacteremia. In our data, a decreasing trend of GBS bacteremia in neonates age 6 days or younger was observed. There was no apparently yearly decrease in our total case number. Gram-negative organisms accounted for a high percentage of all bacteremia episodes. The yearly decrease in the total number of newborns born in Taiwan could not explain the phenomenon of "pathogen-switching". Since the adoption of the 1996 consensus guidelines for intrapartum antibiotic prophylaxis, the incidence of GBS early-onset sepsis has declined by 65% (from 1.7 per 1000 to 0.6 per 1000) in the United States.[13] According to a previous study, the incidences of GBS infection during 1980 and 2000 had no obvious change and varied from 0.25 cases per 1000 live births to 0.9 cases per 1000 live births.[14] In our data, there were a total of 26 cases of GBS infection in young

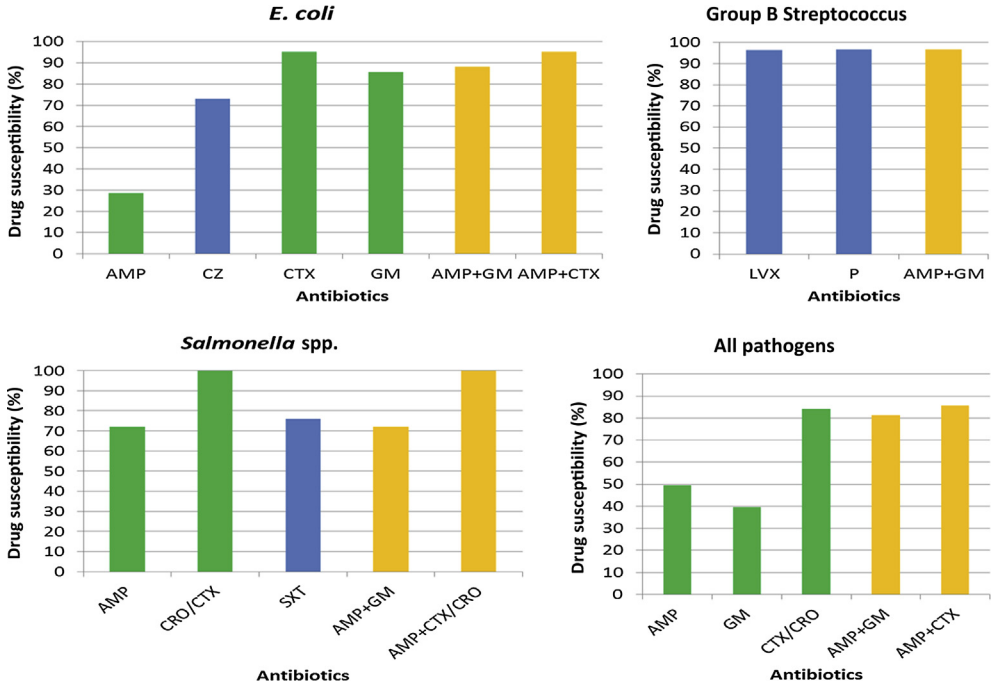

Figure 2. Drug susceptibility of *Escherichia coli*, group B streptococcus, *Salmonella* species, and all pathogens. AMP = ampicillin; CZ = cefazolin; CRO = ceftriaxone; CTX = cefotaxime; GM = gentamicin; LVX = levofloxacin; P = penicillin; SXT = sulfamethoxazole.

infants aged 3 months or younger. The incidences of GBS infection in young infants ranged from 0 cases per 1000 live births to 2.2 cases per 1000 live births during the 10-year study period. Early-onset infection accounted for 58% of these GBS infections. The promotion of GBS screening during pregnancy started in 1996 but this test had been self-paid until January 2012. Some studies have seen a correlation with intrapartum antibiotics and the risk for late-onset serious bacterial infections and ampicillin-resistant pathogens.[15,16] The effect of maternal screening for GBS and the resultant increased use of intrapartum prophylaxis on the epidemiology of infant bacteremia in Taiwan needs further investigation.

Our study had some limitations. This was a retrospective review of electronic medical records of all blood cultures obtained in infants aged 12 months or younger. First, some baseline data might be incomplete, such as the underlying diseases, presence of central catheter (e.g., Hickman catheter), date of previous admission at any hospital, or previous antibiotic usage. Without this information, we might overestimate or underestimate the incidence of community-acquired bacteremia. Second, acquisition of a blood culture was at the clinician's discretion. The numbers of blood cultures and the amount of blood sample taken in each patient were varied. A smaller blood sample could lower the positive rate of blood cultures. Third, some blood samples of patients with positive blood culture, not contaminants, were taken at our emergent department but these patients were neither admitted nor followed up at our outpatient department. We could not evaluate concomitant diseases and outcomes. Fourth, our study was not a multicenter study and may not be able to withstand all the resistant patterns nationwide.

In conclusion, GBS and *E. coli* remain the leading pathogens of community-acquired bacteremia in infants aged 6 months or younger and *Salmonella* species for those older than 6 months in northern Taiwan. Antibiotic resistance was common, so empirical antibiotics for infant bacteremia or sepsis may be revised in the future.

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