Community-acquired bacteremia in Paediatrics: Epidemiology, aetiology and patterns of antimicrobial resistance in a tertiary care centre, Malaysia

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ABSTRACT

Introduction: Bacteremia continues to be one of the major causes of morbidity and mortality despite the existence of numerous antimicrobial agents. This study aimed to provide a Malaysian perspective on paediatric community-acquired bacteraemia based on the documentation of epidemiology and antimicrobial profile of the isolated pathogens.

Method: A retrospective study was conducted by analysing clinical details, blood cultures and antimicrobial susceptibility testing results in children between the ages of 0 to 13 years old, who were admitted to Selayang Hospital over an 11-year period from 2001 until 2011. There were 222 bacteraemia cases and the median age was 11.7 months. The highest number (39%) of bacteraemia cases occurred between ages one month to one year. The three most commonly isolated aetiological agents were *Staphylococcus aureus* (17.1%), nontyphoidal *Salmonella* (16.2%), and *Streptococcus pneumoniae* (12.6%). Almost 8% of the *Staphylococcus aureus* isolates were methicillin resistant, while nontyphoidal *Salmonella* (NTS) isolates demonstrated 18.4%, 10.5% and 2.6% resistance towards ampicillin, trimethoprim-sulfamethoxazole and ciprofloxacin respectively. All NTS isolates were sensitive to ceftriaxone. *Streptococcus pneumoniae* isolates showed 17.9% resistance to penicillin. Skin and soft tissue infections as well as lower respiratory tract infections (63.2%) were the main foci of infections in *Staphylococcus aureus* bacteraemia. Acute gastroenteritis (80.0%) and pneumonia (60.8%) were the main presentations of NTS and *Streptococcus pneumoniae* bacteraemia respectively. Overall mortality rate was 8.1%.

Conclusion: Knowledge on the local epidemiology and antibiotic resistance pattern serves as a significant platform in improving the empiric antibiotic therapy for patients with community acquired bacteraemia.

KEY WORDS:
Community acquired bacteraemia, antimicrobial/antibiotic resistance, children

INTRODUCTION

The burden of disease attributable to bloodstream infections (BSIs) is inadequately studied in Malaysia. Despite being increasingly recognised as the major cause of morbidity and mortality in the region, there is relatively scarce information available on community acquired (CA) bacteraemia in Malaysia, particularly in children. The increasing antimicrobial resistance among bacteria and the existence of substantial variability between institutions have added into series of challenges to medical practitioners and institutions hence requiring individual analysis of the local trends of BSIs.

The CA and hospital acquired (HA) bacteraemia categories were first characterised to provide empiric treatment when the etiological agent and its antimicrobial susceptibility were unknown.[1] The peculiarity was based on both the timing of a positive sample taken from a patient in relation to hospital admission and the clinical presentation. In general, CA bacteraemia is primarily caused by organisms that are relatively virulent pathogens capable of infecting healthy people. In contrast, HA bacteraemia is caused mainly by organisms that thrive in the hosts who have a number of risk factors including underlying co-morbidities, compromised immunity or invasive procedures that breach the body's external defenses allowing pathogens entry.[1] Selection pressure from intensive antibiotic usage promotes the development of resistant strains in HA bacteraemia.

In industrialised nations, hospitalisations following onset of community associated BSIs are common, and case fatality rates are high at approximately 13–14%.[2,3] Mortality can be even greater for patients with antibiotic resistant CA bacteraemia due to delayed administration of effective antibiotics.[4] Antibiotic resistance patterns among HA bacteraemia have been well studied, however the patterns of antibiotic resistance among CA bacteraemia may be different. The determination of the type of aetiological agents involved in causing CA bacteraemia and the understanding of the local pattern of antibiotic resistance help to improve empiric antibiotic therapy and consequently, patient outcomes. Thus, the purpose of this study was to describe the distribution of the aetiological agents of CA

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bacteraemia, the clinical manifestations of common isolated pathogens, antibiotic resistance pattern of commonly used antibiotics, and patient outcomes due to CA bacteraemia in paediatric population in a tertiary care centre in Malaysia.

MATERIALS AND METHODS

Study setting, design, and population:
Selayang Hospital is a 960-bedded fully computerised government hospital located in Gombak District, Selangor, Malaysia. It consisted of 68 paediatric and 48 neonatal beds providing general paediatric and national tertiary care services for paediatric rheumatology, nephrology, gastroenterology, hepatology and neonatology. A comprehensive total hospital information system (THIS) is used in this hospital for effective integration and networking. A retrospective study was conducted by reviewing electronic records of children admitted to neonatal and paediatric wards in this hospital. We included all admissions and retrieved the patients' names and medical registration numbers (MRN) using selection criteria of positive blood culture, date of admission from 1st January 2001 until 31st December 2011 and age less than 13 years old. The electronic records of each patient were reviewed followed by gathering the demography, clinical diagnoses, blood cultures and antimicrobial susceptibility testing (AST) results of those who fulfilled the definition of community acquired bacteraemia.

Case definition:
The definition of community-acquired bacteraemia was based on the Centers for Disease Control and Prevention National Healthcare Safety Network (CDC's NHSN) guidelines.[5] Early onset neonatal infections which were defined as those presented in less than 7 days of life was an exclusion criteria as they were likely to be acquired from the mother. Bacteraemias that were caused by organisms such as coagulase-negative *Staphylococci, Bacillus spp, Corynebacterium spp,* and *Propionibacterium spp* were excluded from the study as they were considered as contaminants. Repeated isolates of the same organism from a patient during an admission were considered as one isolate.

Bacteriology:
Identification of the microorganisms was based on the API (bioMérieux, France) and VITEK identification system (bioMérieux, France). The antimicrobial susceptibility testings were performed via disc diffusion method in accordance to the Clinical Laboratory Standards Institute guideline (CLSI M100-S24 Performance Standards for Antimicrobial Testing). The extended spectrum beta-lactamase (ESBL) producing isolates were confirmed by the phenotypic confirmatory test. An increase of 5mm or more in zone diameter of ceftazidime or cefotaxime disc tested in combination with clavulanate vs the zone diameter of the agent when tested alone signified the presence of ESBL.

Ethical approval:
This study was registered with the National Medical Research Register of Malaysia (NMRR) and was approved by Ministry of Health Medical Research Ethics Committee (MREC).

Data collection and analysis:
All data were entered, cleaned and analysed using statistical software, IBM SPSS version 22. A descriptive and univariable analysis was done for different age groups, while Fisher's Exact Test was used to determine the patients' outcome (survival versus death) for all organisms. Level of significance was taken at 0.05 *($p < 0.05$).*

RESULTS

A total of 2134 blood cultures were found positive among patients between ages 0 and 13 years that were admitted to Selayang Hospital between 1st January 2001 and 31st December 2011. 222 patients met the case definition and were included in the study. The remaining were excluded as the organisms were regarded either as contaminants or HA bacteraemia.

The median age of the patients was 11.7 months with infants and children between 1 to 12 months (39%) made up the highest number of the population studied. (Table I)

There were 30 different organisms detected with gram-positive and gram-negative bacteria accounted for 46.4% and 53.6% respectively. The three most commonly isolated aetiological agents were *Staphylococcus aureus* (17.1%), nontyphoidal *Salmonella* (16.2%) and *Streptococcus pneumoniae* (12.6%). Nontyphoidal *Salmonella* (NTS) was the leading organism in infants beyond neonatal period until the age of 4 years, whereas *Streptococcus pneumoniae* predominated in children more than 4 years old. A different distribution of organisms was noted among the neonates, whereby the commonest organism was Staphylococcus aureus (32.3%), followed by Group B *Streptococcus* and *Escherichia coli* (each 19.4%) respectively. (Table II)

Nontyphoidal *Salmonella* isolates demonstrated 18.4%, 10.5% and 2.6% of resistance towards ampicillin, trimethoprim-sulfamethoxazole and ciprofloxacin respectively. There was no increase in resistance towards these antibiotics throughout the 11-year period. All NTS isolates were susceptible to ceftriaxone. All *Salmonella typhi* isolates (n = 5; 2.3%) were susceptible to the antibiotics tested. *Staphylococcus aureus* isolates exhibited 7.9% resistance to oxacillin/cefoxitin disc (MRSA), while the remaining isolates were susceptible. *Streptococcus pneumoniae* isolates revealed 17.9% resistance to penicillin and interestingly no increase in resistance was observed during the 11-year period. All Group B *Streptococcus* and *Streptococcus pyogenes* isolates were sensitive to penicillin. *Escherichia coli* were found in 6.3% of cases and none of the isolates were ESBL producer, in contrast to *Klebsiella pneumoniae* (n = 10; 4.5%) which was noted to be ESBL producer in one isolate. The patient was a 7 week-old baby who was admitted with first episode of urinary tract infection and had one previous hospitalisation due to neonatal jaundice which was treated with phototherapy. All *Haemophilus influenzae* isolates (n = 8; 3.6%) were sensitive to ampicillin and all *Pseudomonas aeruginosa* isolates (n = 6; 2.7%) were sensitive to ceftazidime.

Acute gastroenteritis (80.0%) was the main presentation in children with nontyphoidal *Salmonella* bacteraemia followed

Table I: Demographic characteristics of paediatric inpatients with community acquired bacteraemia at Selayang Hospital (2001-2011)

Characteristics		Frequency	Percentage (%)
Sex	Male	125	56.3
	Female	97	43.7
Race	Malay	154	69.4
	Chinese	24	10.8
	Indian	24	10.8
	Others	20	9.0
Age group	≤1 month	31	14.0
	>1 -1 2 months	87	39.2
	>12 - 48 months	67	30.2
	>48 months	37	16.7
Age	Median ± SD (months)	11.7 ± 32.8	
	Min-Max (months)	0-149	

Table II: Distribution of organisms isolated from blood cultures in paediatric inpatients with community acquired bacteraemia at Selayang Hospital (2001-2011)

Organisms		Age groups				
		≤1 month	>1-12 months	>12-48 months	>48 months	Total
Staphylococcus aureus	N (%)	10(26.3)	11(28.0)	13(34.2)	4(10.5)	38(17.1)
	% within age group	32.3	12.6	19.4	10.8	
Nontyphoidal *Salmonella*	N (%)	0(0.0)	18(50.0)	16(44.4)	2(5.6)	36(16.2)
	% within age group	0.0	20.6	23.9	5.4	
Streptococcus pneumoniae	N (%)	0(0.0)	12(42.9)	11(39.3)	5(17.9)	28(12.6)
	% within age group	0.0	13.8	16.4	13.5	
Escherichia coli	N (%)	6(42.9)	3(21.4)	3(21.4)	2(14.3)	14(6.3)
	% within age group	19.4	3.4	4.5	5.4	
Group B *Streptococcus*	N (%)	6(54.5)	3(27.3)	1(9.1)	1(9.1)	11(5.0)
	% within age group	19.4	3.4	1.5	2.7	
Klebsiella pneumoniae	N (%)	1(10.0)	2(20.0)	4(40.0)	3(30.0)	10(4.5)
	% within age group	3.2	2.3	6.0	8.1	
Streptococcus pyogenes	N (%)	1(12.5)	5(62.5)	1(12.5)	1(12.5)	8(3.6)
	% within age group	3.2	5.7	1.5	2.7	
Haemophilus influenzae	N (%)	1(12.5)	4(50.0)	2(25.0)	1(12.5)	8(3.6)
	% within age group	3.2	4.6	3.0	2.7	
Pseudomonas aeruginosa	N (%)	1(16.7)	4(66.7)	1(16.7)	0(0.0)	6(2.7)
	% within age group	3.2	4.6	1.5	0.0	
Salmonella typhi	N (%)	0(0.0)	1(20.0)	0(0.0)	4(80.0)	5(2.3)
	% within age group	0.0	1.1	0.0	10.8	
Other *Streptococcus* spp[1]	N (%)	2(11.8)	5(29.4)	6(35.3)	4(23.5)	17(7.7)
	% within age group	6.5	5.7	9.0	10.8	
Other *Pseudomonas* spp[2]	N (%)	0(0.0)	5(41.7)	6(50.0)	1(8.3)	12(5.4)
	% within age group	0	5.7	8.9	5.6	
Other organisms[3]	N (%)	1(3.4)	12(41.2)	9(31.0)	7(24.1)	29(13.1)
	% within age group	3.2	13.7	13.4.	18.9	
Total		29	85	73	35	222(100)

[1]Included *Streptococcus mitis*, group C *Streptococcus*, group G *Streptococcus*, *Streptococcus sanguis* and *Streptococcus sobrinus*
[2]Included *Pseudomonas stutzeri, Pseudomonas putida, Pseudomonas luteola* and *Pseudomonas fluorescens*
[3]Included *Acinetobacter* spp(6), *Sphingomonas*(3), *Neisseria meningitidis*(3), *Aeromonas* spp(3), *Enterococcus* spp(3), *Burkholderia* cepacia(2), *Actinobacillus*(2), *Enterobacter* spp(2), *Morganella morganii*(2), *Neisseria lactamica*(1), *Citrobacter diversus*(1), non-fermenting gram negative bacillus(1)

by bronchopneumonia (17.1%). Both skin and soft tissue infections (SSTIs; 31.6%) and lower respiratory tract infections (LRTIs; 31.6%) were common clinical manifestations for *Staphylococcus aureus* bacteraemia. In 8% of cases, there were no obvious foci of infection. Pneumonia (60.8%) was the main presentation in *Streptococcus pneumoniae* bacteraemia. 3 cases of peritonitis and 2 cases of meningitis were due to *Streptococcus pneumoniae* as well.

All patient outcomes were available, except for three patients who were transferred to other hospitals. Overall case fatality rate (CFR) was 8.2%, with the highest due to bacteraemia caused by *Pseudomonas aeruginosa* (60%), followed by Group B *Streptococcus* (27.3%). The mortality rate due to *Staphylococcus aureus* and *Streptococcus pneumoniae* were relatively lower at 2.6% and 3.6% respectively. All patients with nontyphoidal *Salmonella* bacteraemia survived. (Table III)

Table III: Case fatality rate (CFR) of paediatric inpatients with community acquired bacteraemia according to bacterial isolates at the Selayang Hospital (2001-2011)

Organisms	Total(N)	Died(n)	CFR(n/N%)	Fisher's Exact Test
Staphylococcus aureus	38	1	2.6	0.325
Nontyphoidal *Salmonella*	34	0	0.0	1.000
Streptococcus pneumoniae	28	1	3.6	0.481
Escherichia coli	14	0	0.0	1.000
Group B *Streptococcus*	11	3	27.3	0.051
Klebsiella pneumoniae	10	2	20.0	0.194
Streptococcus pyogenes	8	0	0.0	1.000
Haemophilus influenzae	8	0	0.0	1.000
Pseudomonas aeruginosa	5	3	60.0	0.004
Salmonella typhi	5	1	20.0	0.406
Other *Streptococcus* spp	17	1	5.9	1.000
Other *Pseudomonas* spp	12	2	16.7	0.258
Other organisms	29	4	13.1	0.270
Total	219	18	8.2	

DISCUSSION

According to our study, infants and children between one month and one year of age were found to be the main paediatric age group that developed CA bacteraemia. In general, this would possibly be explained by the physiological phenomenon of maturation of the immune system that is initiated during the foetal period. The immune system is dynamic in its character and is expanding in time through the first months and in the first few years of a child's life. Hence within the neonatal period, infancy and early childhood, dysfunctions of numerous components of the immune system were observed.[6]

Based on the physiological dysfunctions phenomenon in paediatric population, although the neonates have higher risk of developing CA bacteraemia, they are protected by the maternal IgG antibodies which persist for approximately six months duration.[6, 7] On the other hand, children between one month and less than one year are newly exposed to the environment and have yet to develop their own antibodies to various pathogens and thus are more susceptible to infections. The occurrence of CA bacteraemia is lower in the other groups of children, as they have most probably built up a more active acquired immunity which occurs after exposures to the infective agents. Thus, the antibodies will have been developed and these protect the child against specific antigens.[8]

Staphylococcus aureus was the predominant organism isolated from blood cultures among the paediatric inpatients presented with CA bacteraemia in Selayang Hospital, Malaysia. This observation was consistent with the findings from other institutions worldwide.[3,9-14] *S. aureus* is also known as a part of the normal skin flora, hence our finding of a high prevalence of *S. aureus* bacteraemia needs to be interpreted with caution. The detection of Panton-Valentine Leukocidin (PVL)-producing *S. aureus* especially in isolates recovered from SSTIs cases would provide a more definitive diagnosis of community associated *S. aureus* bacteraemia.[15] However, the presence of PVL gene was not performed by the laboratory.

Staphylococcus aureus, group B *Streptococcus* and *Escherichia coli* were the three commonest isolated aetiological agents in neonates and these corresponded to other published reports.[13, 16, 17] The consistent finding of *S. aureus* as a pathogen in neonates might be secondary to horizontal transmission in facility-based deliveries resulting in colonisation and infection. A considerable maternal colonisation rate with group B *Streptococcus* and *E. coli* may contribute to the frequent finding of the organisms in neonates, and prolonged labour may add up the risk to develop bacteraemia due to both organisms.[18-20] The finding of NTS as the main aetiological agent causing CA bacteraemia in infants beyond neonatal period until the age of 4 years was interesting, and this result was consistent with report from Tsai MH *et al*,[21] and from several other countries.[10,22-24] Most of the reports suggested that NTS had contributed more significant public health issue as compared to *Salmonella typhi*, and there were efforts towards developing vaccines for NTS.[11] It is noteworthy, that children more than four years old had higher proportion of being infected with *Streptococcus pneumonia* compared to other organisms, and this finding was consistent with report from Betuel Sigauque *et al*.[25] However there were other international studies which found *S. aureus* as the most prevalent pathogen in the similar age group.[26,27]

Nontyphoidal *Salmonella* isolates exhibited moderate antibiotic resistance rate towards ampicillin (18.4%) and trimethoprim-sulfamethoxazole (10.5%) in contrast to Thailand, Taiwan, Malawi, United Kingdom and Spain that showed 30% to 80 % of resistance rate for both antibiotics.[14, 28, 29] The resistance rate of ciprofloxacin is considered low (2.6%) and was consistent with reports from Thailand, Taiwan, and Spain.[28,29] The resistance rate for *Staphylococcus aureus* was low and corresponded well with report from David ZM *et al*, particularly in SSTIs.[30] *Streptococcus pneumoniae* demonstrated moderate resistance rate towards penicillin but this was lower compared to other local studies which showed resistance rate between 21.2 to 29.5%.[31,32] The rate of penicillin-resistant *Streptococcus pneumoniae* varied worldwide ranging from 1% in some African countries to 96% in western Pacific region.[33]

The highest case fatality rate (CFR) in this study was due to *Pseudomonas aeruginosa* bacteraemia (60%) even though all the isolates were susceptible to ceftazidime. This may partly be due to small number of cases. It can be also explained by the fact that ceftazidime was not the first line empirical antibiotic for community acquired infection in our institution. Nevertheless, few reports stated that the organism was associated with 40 to 60% mortality rate regardless of antibiotic susceptibility result.[34-36]

CONCLUSION

The data of this study imparts broad array of different aetiological agents that caused CA bacteraemia in the paediatric population in a tertiary care hospital in Malaysia. It also provides information regarding clinical diagnoses and mortality with CA bacteraemia based on aetiological agents, as well as antibiotic resistance rate towards commonly used antibiotics. Undoubtedly, these data would be an essential reference for the management of CA bacteraemia in children in Malaysia especially in choosing initial empirical antimicrobial therapy. Enhanced national and regional surveillance of antimicrobial resistance patterns indeed will help to improve the management of CA bacteraemia.

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