Bacteremia in febrile children under 3 years of age in an emergency department of a university hospital

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ABSTRACT

الهدف: دراسة نتائج زراعة الدم في الأطفال المصابين بالحمى دون سن الثالثة والذين تمت معاينتهم في قسم إسعاف الأطفال خلال فترة ثلاث سنوات.

الطريقة: أجريت دراسة إسترجاعية في قسم إسعاف الأطفال في مستشفى الملك عبد العزيز الجامعي على ٢٩٢٩ طفل مصاب بارتفاع شديد بدرجة الحرارة (≤ ٣٩٫٥ سيلسيس) وتراوحت أعمارهم بين ٢ إلى ٣٦ شهراً. وقد تم تقويم نتائج زراعة دمهم في قسم إسعاف الأطفال في مستشفى جامعي بين شهر يناير عام ٢٠٠١م وشهر ديسمبر ٢٠٠٣م. ولقد تم تحديد انتشار تجرثم الدم, ونتائج مزرعة الدم الإيجابية وتوزيع الكائنات الممرضة وتم إعادة تقويم كل المرضى الذين ظهر لديهم نمو بكتيريا ممرضة معروفه, وتم تقويم النتائج الخطرة.

النتائج: انطبقت الشروط على ٢٩٢٩ طفل وكان متوسط عمر المرضى ١٠٫٥٧شهراً وكان ٥٢٪ منهم ذكوراً, و ٤٨٪ إناثاً وكانت نسبة انتشار تجرثم الدم ١٫٥٧٪. تسببت البكتريا العقدية الرئوية في٣٦٫٩٪ من الحالات. وكان معدل التلوث ٢٫٢ ٪ وكان المتوسط الزمني للزراعة الإيجابية أقصر بصورة مهمة للكائنات الممرضة (١٨ ساعة ± ١٫٥ ساعة) منه للكائنات غير الممرضة (٢٤ ساعة ± ٤ ساعات).

خاتمة: أظهرت هذه الدراسة أن عوامل الخطورة في الأطفال المصابين بالحمى تشمل مجموعة الأعمار الأصغر تحت سن ٢٤ شهراً, وزيادة عدد كريات الدم البيضاء أكثر من ١٥,٠٠٠/ مم ٣ وإن كانت لا تطرد بالضرورة مع النتائج العكسية . كذلك أظهرت الدراسة أن هناك زيادة في نسبة مقاومة البكتيريا العقدية الرئوية للآمبسيلين والبنسلين مما يظهر الحاجة إلى وجود تطعيم مزدوج متعدد ضدها يضاف إلى برنامج التطعيم العادي (الروتيني) في المملكة.

Objective: To review the results of blood culture in febrile children seen in the pediatric emergency department over a 3 year period.

Methods: A retrospective cohort study was conducted in the Pediatric Emergency Department, King Abdul-Aziz University Hospital between January 2001 and December 2003 on 2929 highly febrile children (temperature ≥39.5°C), aged 2-36 months whose blood culture results were evaluated. Prevalence of bacteremia, positive blood culture, and distribution of pathogenic organisms were determined. All patients growing known pathogenic bacteria were reevaluated, and serious outcome was assessed.

Results: Two thousand nine hundred and twenty nine children met the inclusion criteria. The mean age of patients was 10.75 months, 52% of them were boys, and 48% were girls. The prevalence of bacteremia was 1.6%. *Streptococcus pneumoniae* was the causative agent in 37% of patients. The contamination rate was 2.2%. The mean time to positive culture was significantly shorter for pathogenic organisms (18±1.5 hours) than the non-pathogenic organism (24±4 hours).

Conclusion: The risk factors in highly febrile children included younger age group below 24 months of age, and increase in white blood cells of more than 15,000 cell/mm^3. The study also indicates that there is an increase in prevalence of *Streptococcus pneumoniae* resistance to ampicillin and penicillin, which necessitates the need for a polyvalent pneumococcal conjugate vaccine to be added to the routine immunization program in the Kingdom.

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Bacteremia has been increasingly encountered in children less than 3 years of age.[1-3] There are few data to show the incidence and prevalence of the invasive bacterial infection involving children in the Gulf area.[4,5] Septicemia is a pathological condition with mortality rate that varies between 30-70%.[4] The majority of bacteremia cases in children are caused by a number of pathogens including *Streptococcus pneumoniae (S.pneumoniae)*, *Haemophilus influenzae (H.influenzae)* type B, *Salmonella* species, and *Escherichia coli (E.coli)*.[3,4] Numbers of cases with bacteremia had declined substantially after introduction of conjugate *H.influenzae* B, and Pneumococcal vaccine. In such a life threatening condition, early isolation of the causative pathogen in the blood culture is crucial for proper anti-microbial treatment. The main objective of the study was to review the results of blood culture in febrile children under 3 years of age in a pediatric emergency department over a 3 year period. We also look for the risk factors for bacteremia, and to study the susceptibility of the main causative organisms. The scientific rational of the study was to identify the major causative organisms. Knowledge of the common microorganisms, and their susceptibility to antibiotics is important not only for the treating physicians, but also for the health service planners.

Methodology. This retrospective cohort study included all children from birth to 36 months old, with fever ≥39.5ºC in the Pediatric Emergency Department of the King Abdul-Aziz University Hospital (KAUH) between January 2001 and December 2003. Although KAUH (located in the center of Riyadh, which is the capital of Saudi Arabia), is a hospital specialized mainly in ear, nose and throat, and ophthalmology diseases, it serves a heavily populated area and receives an average of 40,000 children in the pediatric emergency department annually. Children with sickle cell, immunodeficiency, or oncological diseases were excluded from the study. The approval of the study was obtained from the Ethical Committee in the Research Center, College of Medicine, King Saud University. The standard practice during the period of study was to obtain complete blood count (CBC), blood culture, urine analysis, and culture from all febrile children. Lumbar puncture was performed depending on clinical assessment by the attending pediatrician. Stool analysis and cultures were carried out for patients with gastroenteritis, as well as serology in suspected cases of salmonellosis. For blood cultures, 1-3 mLs of blood were obtained aseptically by the pediatrician, and inoculated into pediatric blood culture bottle (Bactec Peds Plus/F medium, Becton Dickinson and Company, Sparks, Maryland, USA). The inoculated bottle was sent to the microbiology laboratory for incubation in the BACTEC 9050 system (Becton Dickinson, Maryland, USA) at 35ºC with a 5-day test protocol. The bottle that produced positive signal was removed, the specimen was then gram stained and subcultured. The gram stain result was conveyed immediately to the pediatrician on duty. At this stage, families of the children were called for reevaluation and repeated test. The organisms grown on subcultured plates were identified by the standard laboratory procedures. Microbial susceptibility testing was performed for all bacterial isolates by the disk diffusion method following the National Committee for Clinical Laboratory Standards.[6]

Antibiotics tested were amoxicillin, ampicillin, flucloxacillin, cefuroxime, ceftriaxone, gentamicin, vancomycin, imipenem, and meropenem. Resistant strains were identified by the conventional methods. Bacteria, which was considered pathogenic from the blood culture were: *S.pneumoniae*, *Staphylococcus aureus*, *Streptococcus* group A, *Neisseria meningitidis, Enterobacteriaceae, Salmonella species, Moraxella catarrhalis, H.influenzae,* and *E.coli*. Bacteria that were considered contaminants were: coagulase-negative *Staphylococcus* species, nonpathogenic *Streptococcus,* diphtheroids, *bacillus* species, and nonpathogenic *Neisseria* species. Time to positive culture was measured in hours. Serious outcome was defined as meningitis, or death within 2 weeks from the date that the blood culture was obtained.

The results of all blood cultures carried out for febrile patients during the study period were obtained from computer database. That data included the patient's name, medical record number, age, date of blood culture collection, disposition (admission or discharge), and blood culture final result classified into positive or negative according to the identification of bacteria (including time in hours to positive culture and identification of bacteria). The charts of these patients were then abstracted for medical history, previous antibiotic use, and emergency department discharge diagnoses, maximum fever documented in the emergency department, and antibiotic treatment or prescription. Charts of patients with positive blood cultures were abstracted for additional data including: follow-up visit site, date, and time; diagnosis and disposition at follow-up visit; maximum temperature documented at follow-up visit; result of repeat blood culture, CBC, chest radiograph, spinal fluid assessment, urinalysis, and urine culture and antibiotic treatment, or other therapy as indicated.

Results. The 2929 children who met the inclusion criteria had a mean age of 10.75 months, and 52% were males (**Table 1**). The mean maximum presenting

temperature was 39.9±0.5ºC. The prevalence of bacteremia in the cohort study was 1.6%. The majority (37%) of pathogens were *S.pneumoniae,* 15% were *H.influenzae*. **Table 2** presents the distribution of all pathogenic bacteria recovered from the study while the rate of contamination was 2.2%. Total number of the cohort study who had positive blood culture were 120 patients, 46 (38.3%) with pathogenic organism, and 74 (62%) without pathogenic organism on repeat (62%), 65 (88%) out of the 74 cases with transient bacteremia were due to contaminant organism. The focal bacterial infection that was identified on reevaluation of patients were bacteremia pneumonia 14 (30.4%), acute otitis media 13 (28%), meningitis 5 (11%), urinary tract infection 2 (4.3%), and one each (2.1%) for enteric fever and epiglottitis. None of the patients died. The data of 5 patients with meningitis are shown in **Table 3**. Occult bacteremia due to *H.influenzae* type B was found in 2 patients (0.1%), both of them had negative cerebrospinal fluid (CSF) culture. True occult bacteremia without focus was found in 10 patients (0.3%). None of those patients with positive blood culture with pathogens were found to have sickle cell anemia, immunodeficiency disorder, or oncological disease. The 3 children who had febrile convulsion had negative CSF culture result, 45% of the febrile children with pathogenic organisms had WBC >15,000 cell/mm^3.

Susceptibility testing. A total of 65% *S.pneumoniae* strains were moderately resistant to penicillin and ampicillin, and 43% *H.influenzae* type B to ampicillin; 11% *S.pneumoniae* to cefuroxime, while all the pathogens were sensitive to ceftriaxone.

Table 1 - Age and gender distribution of patients with bacteremia.

Age groups (in months)	Total (%)
1 - 6	7 (15.2)
7 - 12	13 (28.2)
13 - 18	18 (39.1)
19 - 24	5 (11.0)
25 - 36	3 (6.0)
Gender	
Male	24 (52)
Female	22 (48)

Discussion. This study highlights the prevalence of bacteremia, the changing epidemiology of causative organisms, and the ability of continuous monitored blood culture systems, to quickly identify bacteremia. It also shows the low incidence of adverse outcomes in children at risk. During the 3-year period, 2929 febrile children were investigated, 46 of them had positive blood culture with pathogenic organisms. Thirty-six patients

Table 2 - Distribution of pathogenic bacteria in children, 2-36 months of age, with fever ≥39ºC. (N=46)

Age group (months)	Organisms								
	Streptococcus Pneumoniae	*Streptococcus Viridins*	*Haemophilus Influenzae*	*Salmonella* species	*Streptococcus Group A*	*Moraxella catarrhalis*	*Neisseria meningitidis*	*Escherichia coli*	*Staphylococcus aureus*
1 - 12	6	4	3	--	3	2	1	--	1
13 - 24	9	6	4	4	--	--	--	1	--
25 - 36	2	--	--	--	--	--	--	--	--
Total n (%)	**17 (37%)**	**10 (22%)**	**7 (15%)**	**4 (9%)**	**3 (7%)**	**2 (4%)**	**1 (2%)**	**1 (2%)**	**1 (2%)**

Table 3 - Characteristics of the meningitis cases.

Year	Case	Age (Months)	Gender	Organism	WBC in blood (NR = 6-17)	WBC in CSF (NR = 0-7)
2001	1	11	Male	*Neisseria meningitidis*	14.5	300
2001	2	3	Female	*Haemophilus influenzae*	10.5	1340
2002	3	6	Male	*Streptococcus pneumoniae*	15.0	600
2003	4	8	Female	*Haemophilus influenzae*	24.5	1050
2003	5	24	Male	*Streptococcus pneumoniae*	24.8	550

WBC - white blood cells, NR - normal range, CSF - cerebrospinal fluid

had identified focal infections, of these 14 (30.4%) pneumonia, 13 (28%) otitis media, while 5 (11%) had meningitis. Of those children (37%) had illnesses due to *S.pneumoniae,* which is similar to previously reported results.[4,7,8] As noted by Nimri,[4] who reported 23.3% of the 94 patients in his study to have *S.pneumoniae*. McGowan et al[1] noted 61%, and McCarthy et al[2] noted 66% with bacteremia due to *S.pneumoniae*. The prevalence of bacteremia in this study was 1.6%, which is comparable to that reported by Alpern et al.[9] Before introduction of *H. influenzae* type B vaccine, McGowan et al[1] reported a rate of 4%, Dershewitz and colleague[10] found a rate of 2-6% in 3 different groups of children, while McCarthy et al[2] found a rate of 7%. The decline in the incidence was due to the introduction of *H.influenzae* type B vaccine nationwide in the Expanded Program on Immunization.

The mean age of children with bacteremia in this study was 10.75 months. Blood culture was positive in 7 out of 46 (15%) below 6 months, in 13 (28%) 7-12 months, in 18 (39%) 13-18 months, in 5 (10.8%) 19-24 months, and in 3 (6%) in more than 24 months of age, as noted in our series 78% were from 6-24 months. McGowan and colleagues[1] recorded pathogens in 22 of 521 out-patients children with elevated temperature. In that series, the number of children below 6 months was 1%; 9.5% were from age group 7-12 months, and 3.8% from 13-24 months. Only 2.2% were above 24 months of age. In his series, McCarthy et al[2] showed the highest incidence to be between 6 and 24 months. Similar results were noted by Abddulla et al,[7] and Kambal and Abdullah[8] in 2 different studies over a 5-year period, where 61% and 62% of the patients were below 2 years of age.

In this study, risk factors in children with elevated temperature included younger age group below 24 months of age, which means prematurity of immune response, and increase in WBC, which is generally increased in case of infection, however, went up to more than 15,000 cell/mm^3. In our series, 44.7% of children had WBC of 15,000 cell/mm^3, which does not correlate with adverse outcome, although 2 of our patients with meningitis had WBC below 15,000 cell/mm^3. However, 15% of the patients with WBC >15,000 cell/mm^3 had the risk of getting meningitis.[11] Coagulase negative staphylococci mainly *Staphylococcus epidermidis* accounted for 52 (1.1%) of febrile patients. Abdullah et al,[7] and Kambal and Abdullah[8] reported an increase in prevalence of *S.pneumoniae* resistant to penicillin in the range of 22% of their cases, while Almuneef et al[12] had 43% of their patients with moderately resistant strains. Nasrin and asociates[13] in Australia, found 14% of children in their study had penicillin-non-susceptible (PNS) *S.pneumoniae*, while Perez et al[14] in Barcelona, found 49% overall rates of PNS in their study. In our study, 65% of isolated strains of *S.pneumoniae* were resistant to ampicillin and penicillin. No mortality was reported in our series, compared with Almuneef et al[12] who reported 6% mortality due to meningitis, while Abdullah et al[7] and Al-Mazrou et al[11] reported complete recovery in all their patients.

The emergence of these resistant strains of *S.pneumoniae*[15-17] will highlight the need for a polyvalent pneumococcal conjugate vaccine to be added to the routine immunization program in the Kingdom. Previous trials have shown that conjugate pneumococcal vaccines are safe, and effective in normal healthy patients even those under the age of 2 years. The controlled trials have demonstrated immunogenicity (the body's response, without which there is no protection) of these vaccines.[16] The limitation of the study is that it represents the experience of one center in the Kingdom.

We conclude that conjugate pneumococcal vaccine proves to be protective, and there is the potential to prevent up to 85% of invasive pneumococcal disease occurring in American children.[17] Ispahani et al's[18] study indicated that inclusion of a pneumococcal conjugate vaccine in the primary immunization programme in the United Kingdom would have a considerable effect on the mortality and morbidity associated with the invasive pneumococcal disease. This study illustrates well that pneumococcal infection is a major cause of bacteremia in young children and the emergence of resistant strains is increasing necessitating an introduction of conjugate pneumococcal vaccine. Further prospective studies nationwide are needed.

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Statistics

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