ORIGINAL ARTICLE

YIELD OF BLOOD CULTURES IN CHILDREN PRESENTING WITH FEBRILE ILLNESS IN A TERTIARY CARE HOSPITAL

Bibi Aalia, Saima Gillani, Syed Sajid Hussain Shah, Nuzhat Raza*, Attia Iqbal, Sayeda Urooj Yadain

Department of Paediatrics, *Physiology, Ayub Medical College and Teaching Hospital, Abbottabad, Pakistan

Background: Blood stream infections (BSIs) leading to septicaemias and systemic inflammatory response syndrome (SIRS) are important causes of paediatric referrals, admissions and deaths. These have worse outcome in newborns, and infants especially if undernourished. In most of our hospitals blood cultures are carried out for selective number of patients. Low yields of blood cultures and sample contaminations are problems of concern. The objective of this study was to find out the yield of blood cultures in patients admitted with sepsis and fever without clear localizing signs. **Methods:** This one year cross-sectional prospective study was conducted at POF Hospital Wah Cantt. A total of 85 patients admitted in paediatric ward with complaints of febrile illness and diagnosis of sepsis or fever without localizing signs (FWLS), who had their blood sent for cultures and sensitivity at POF Hospital Wah Cantt, were included in the study. **Results:** Yield of blood cultures in our study was low as blood cultures yielded growth in only 8 out of 85 patients (95% confidence interval: 4.7–16.3%) .One sample was contaminated. The minimum age of patient was 1 month (0.08 years) and maximum age was 12 years (median 3.5 years). Majority of the patients, i.e., 62 (72.9%) were under age of 6 years as compared to the age group between 10 to 12 years that comprised 23 patients (27%) only. There was a male preponderance as from the total 85 patients 58 (68.24%) were males and 27 patients (31.76%) were females. Cross tabulation between gender and yield of blood culture showed a significant correlation ($p<0.05$). The correlation between total white cell counts and yield of blood cultures was not statistically significant ($p>0.05$). **Conclusion:** Male children are more likely to be affected by sepsis. A positive blood cultures yield is low in our setups. Total white cell counts are not a significant marker for sepsis in children.

Keywords: Neonatal and childhood sepsis, blood stream infections, blood culture and sensitivity, FWLS, SIRS

Pak J Physiol 2015;15(1):16–20

INTRODUCTION

Blood stream infections (BSIs) are an important cause of referrals, admissions and mortality among newborns and infants. Timely diagnosis and treatment of bacteraemia is essential. Indirect testing by measuring raised level white cell counts, CRP levels, are not so helpful.[1,2] Procalcitonin levels are not performed in our setup. The gold standard test is still considered the blood culture and sensitivity for detecting microorganism in blood stream infections and are usually requested for patients with fever associated with chills and rigors, fever without localizing signs (FWLS), septicaemia, pneumonias, osteomyelitis and SIRS.[3,4]

There is lack of clear cut indications for drawing blood cultures in paediatric emergency settings with the decision mainly resting on individual basis varying from patient to patient and judgment of the physician.[5,6] In spite of its importance blood cultures are not routinely sent in febrile patients even if septicaemia is suspected and most of the time the patient is started on empirical antibiotics combinations based on clinical judgment of consultant physician and indirect markers of blood stream infections (BSI) such as high total white cell counts (WCCs), D-dimers, procalcitonin (PCT) and C-reactive protein (CRP) levels in serum. Problems in children are many such as amount of blood drawn, multiple samples and strict observation of aseptic technique and use of multiple sites for sample collection, all of which affect yield of blood cultures. False positive results and contaminated samples are commonly encountered problems. Careful inoculation of sample, observing aseptic technique and appointing a phlebotomy team, timing of taking blood samples can all improve outcome of cultures.[7–9] Samples for cultures should preferably be taken before starting antibiotic treatment.[10]

The objective of this study was to find out the yield of blood cultures in patients admitted with sepsis and fever without clear localizing signs.

METHODOLOGY

It was a cross-sectional study carried over one year. A total of 85 children admitted in paediatric ward at POF Hospital Wah Cantt with complaints of a febrile illness and diagnosis of sepsis or FWLS were included in the study. Blood was sent for total WCCs, and 3 mL of blood was sent in standard paediatric blood culture bottle for aerobic and anaerobic culture and sensitivity

testing. Blood sample was collected from ante cubital fossa after cleaning area with pyodine and sent before start of antibiotics. Samples were incubated on blood agar culture media. Results of blood culture and sensitivity obtained between 2–5 days were recorded and data were analyzed. Pearson's Chi-square test was applied for correlation of gender and outcome of blood culture and sensitivity (C/S), and between total WCCs and C/S; $p \leq 0.05$ was considered statistically significant.

RESULTS

Total patients enrolled were 85. The minimum age of patient was I month (0.08 years) and maximum age was 12 years (median 3.5 years). Standard deviation was 3.40 and standard error of mean was 0.369. Minimum total WCCS was 6,000/µL and maximum was 22,000/µL, median being 11,000/µL (reference range: 4,000–11,000/µL). When divided into age groups the maximum number of patients (26, 30.6%) admitted fell in to age group of less than 2 years, followed by age group 2–4 years, (19, 22.4%), and up to 6 years (17, 20.0%). Majority of patients were under the age of 5 years (Table-1).

A male preponderance was noted in our study as majority (58, 68.24%) of patients included were males and only 27 (31.76%) were females. Cross tabulation between gender and yield of blood culture showed that a positive blood culture was obtained in all male patients ($p<0.05$) (Table-2).

Out of the 8 positive culture growths 2 (25%) yielded growth of *Staphylococcus aureus*, 2 (25%) showed growth of multi-drug-resistant *Staphylococci* (MRSA), 2 (25%) showed growth of *Kliebsiella*, 1 (12.5%) showed growth of *Salmonella* and 1 (12.5%) showed growth of gram-negative rods (Table-3).

The antibiotics to which these organisms were sensitive included cephalosporins, ciprofloxacin, vancomycin, gentamicin, tazocin and tiecoplanin. Resistant growths were only available for 4 patients out of which majority of cultures showed resistance to penicillins, and co-trimaxazole (Figure-1).

Yield of blood cultures in our study was low and blood cultures yielded growth in only 8 (9.4%) out of 85 patients. The correlation between total white cell counts and yield of blood cultures was not statistically significant ($p>0.05$) (Table-4).

Table-1: Cross tabulation of age groups and yield of blood cultures (n=85)

Age groups	No growth	Growth	Contaminated	Total	%
0 to <2 Years	24	1	1	26	30.6
2 to <4 Years	18	1	0	19	22.4
4 to <6 Years	15	2	0	17	20.0
6 to <8 Years	3	2	0	5	5.9
8 to <10 Years	8	1	0	9	10.6
10 to <12 Years	8	1	0	9	10.6
Total	76	8	1	85	100

Table-2: Cross-tabulation between gender and yield of blood cultures (n=85)

Yield	Males	Females	Total	%
No growth	49	27	76	89.4
Growth	8	0	8	9.4
Contaminated	1	0	1	1.2
Total	58	27	85	
Percentage	68.24	31.76	100	
p	0.038*			

*Significant correlation

Table-3: Frequency of microorganisms in the positive cultures (n=8)

Organisms in positive blood cultures	Number	%
Staphylococcus	2	25
MRSA	2	25
Salmonella	1	12.5
Gram negative rods	1	12.5
Kliebsiella	2	25
Total	8	100

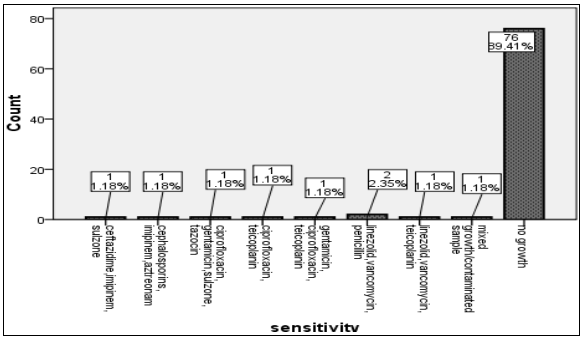

Figure-1: Antibiotic susceptibility of microorganisms in positive cultures

Table-4: Yield of blood cultures in febrile patients and confidence interval

Yield of Cultures	No	Percent	Bias	SE	95% CI	
					Lower	Upper
No growth	76	89.4	-0.4	3.1	82.6	94.1
Growth	8	9.4	0.3	3.0	4.7	16.3
Contaminated	1	1.2	0.1	1.1	0	3.5
Total	85	100	0	0	100	100

DISCUSSION

Blood stream infections (BSIs) are a serious problem in paediatric and adult populations. Sepsis in children is a public health problem causing burden in hospitals and considerable morbidity and mortality.[11] In the United States, more than 75,000 children are affected by severe sepsis each year causing death in 6,800 of the affectd.[12,13] Patients diagnosed having BSI are usually critically ill upon arrival and are immediately started on most suitable empirical antibiotic regimen and supportive treatment according to physicians best clinical judgments leaving little time to spare or wait for laboratory tests.[14] Worldwide emerging antibiotic resistance to some commonly used broad spectrum antibiotics is being recognized as an increasingly serious threat so we should think that targeting an identified microorganism with known susceptibilities and

resistance is perhaps the wiser choice. Blood cultures if positive are helpful but even a negative culture is also helpful in managing a febrile child with suspected BSI as saves needlessly prolonged and costly use of broad spectrum antibiotics.[15] There are very few clear-cut indications for sending a blood culture of a child, e.g., suspicion of immune-deficiencies in cases of repeated BSIs, suspicion of fungal infections if fever is not responding to antibiotics, HIV, febrile neutropenia, sub-acute bacterial endocarditis (SBE), and fever without localizing signs (FWLS).[16]

In spite of its diagnostic importance, blood cultures are not commonly sent even in established cases of infection in most hospitals. In children the blood volume to be collected for sampling in a sick child is a problem as mostly two samples need to be sent each time in two separate bottles, for anaerobic and aerobic organisms. In extremely wasted children repeated samples may be a problem as volumes of up to 10 ml are required to improve yield.[17] In our setup, 2–4 ml are sent for cultures as a single sample in paediatric patients. Mostly the first sample for cultures of blood is sent before starting antibiotics, and should preferably be sent during a temperature spike.[18] A second sample for repeat culture needs to be sent if fever isn't responding after 48 to 72 hours of antibiotic treatment.[14,15]

Sample collection technique is another factor that affects the yield of blood cultures and is an important cause of mixed growths or contaminated samples.[19] Most of our tertiary care units lack a proper facility for infection control in hospitals and ends of intravenous catheters, nasogastric tubes, and ends of Foley's catheters are rarely sent for cultures.

Conventional blood cultures are being replaced with rapid yield phenotypic testing abroad with a yield time ranging from a few hours to about a day, and by genetic testing by PCR. These newer techniques reduce the time for microorganism identification in blood, but their usefulness due to cost and comparable results to conventional methods in which enriched samples are used, is questionable. Though they quickly identify the microorganism in whole blood sample, susceptibility/ resistance report is not given, hence are not quite helpful in modifying course of antibiotics.[20]

In our study a male preponderance was noted. This gender predominance of childhood sepsis has also been reported in other studies. Female gender has been demonstrated to be protective in response to blood stream infections and males may have a relatively decreased cell-mediated immune response. Male sex hormones, have been shown to have suppressive effect on cell-mediated immune responses. In comparison, female sex hormones show protective effects which contribute to the natural advantages of females under septic conditions.[21] In another study[22], it was noted that not only septicaemia was a more common complication in males but males with sepsis also had a 70% more mortality rate compared to females with same diagnosis.

Serum markers for sepsis in children such as C-reactive protein (CRP) require repeated samples to check antibiotic response. PCT is not performed in our setups. Total WCCs are performed as part of routine blood counts for febrile patients but all of these inflammatory markers along with CRP level and PCT have variable sensitivity and specificity in childhood sepsis.[2,23,24] Correlation between total WCCs and positive blood cultures was not statistically significant in our study, so it was not a helpful marker in childhood sepsis. Galletto-Lacour *et al*[25] also confirmed limited usefulness of total and differential leukocyte counts as compared to CRP and PCT levels. In another study, Brown *et al*[2] focused on febrile neonates (aged ≤28 days) who visited the emergency department. They calculated the sensitivity and specificity of various WBCs for the detection of bacterial infection. They found modest discriminatory power of the WBC count and that a normal white blood cell count does not rule out bacteremia.

In our study from the 8 positive cultures, 4 (50%) yielded growth of *Staphylococci*. *Staphylococcus aureus* as the predominant microorganism in blood stream infections is a finding in other studies as well.[26,27] Strict hand washing and aseptic measures may reduce infections due to this organisms which is commonly isolated in blood cultutres.[28] Empirical treatment in our setups for sepsis usually is started with a combination of a third generation cephalosporin with either an aminoglycoside or vancomycin for MRSA. Majority of the organisms were susceptible to this empirical treatment.

In our study most patients were under age of 2 years. Overall sepsis mostly affects younger children especially under five year age and mortality is higher among infant and neonates who are victims of septicemia.[29] In another study it was stated that children under 12 months of age and elderly people have the highest incidence of severe sepsis.[30,31]

Low yield of blood, CSF, and urine cultures is a commonly faced problem in our hospitals and labs. There are multiple factors at multiple levels that affect the yield of blood cultures such as proper specimen collection, dispatching, inoculations, incubation, processing, culture techniques, result reporting, and result interpretation by the haematologists.[32] In our study of 85 patients with febrile illness admitted in a tertiary level hospital, only 8 patients yielded positive blood culture results. In one patient sample contamination was detected. Results of our study coincided with the results elsewhere where yields of blood cultures were low as well. In a retrospective study spanning over a two year period the aim of which was to find out the usefulness of blood cultures in children

diagnosed and admitted with community-acquired pneumonias, out of 215 patients included in that study, 177 blood samples were sent for cultures and only 7 yielded positive growth but final report of true positives were confirmed in only 2 out of 7 showing growth of *Streptococcus pneumoniae*. A conclusion was made that blood cultures had a low yield in children admitted to hospital with community-acquired pneumonia and had no significant effect on the initial treatment or its modification.[33] In another study on the yield of blood cultures and its impact on patient management it was noted that the effect of results of blood culture on modifying initial empiric antibiotic treatment were very small. A high contamination rate was noticed.[34]

In another study performed in Africa, out of 17,001 blood cultures included in the study over a period of 6 years from 935 cultures done 979 pathogens were isolated. There were high contamination rates.[35]

In a retrospective study done on 8,282 febrile children presenting to the emergency department in a Middle East hospital, positive yield occurred in only 20 (2.42%) patients and it was concluded that the incidence of positive blood culture in routine care of febrile patients presenting in ER is low.[36]

Regarding the usefulness of newer methods a comparison was done between yield of blood cultures by rapid identification method, i.e., BACTEC that gave 32% positive results to the conventional methods giving 19.88% positive yield. A conclusion was made that although BACTEC 9050 did have a significantly greater recovery of microorganisms from blood, but a conventional blood culture if performed appropriately can facilitate treatment.[37] In a comparison between the rapid and conventional methods it was noticed that isolating microorganisms from a conventional blood culture is less challenging as compared to direct detection from whole blood because their titres are enriched through inoculation and incubation in the samples used in conventional methods.[38]

CONCLUSION

Conventional blood cultures are an important aide in sepsis management. Most microorganisms in our study were susceptible to the empirical antibiotics used. Aseptic practices in handling patients helps limiting infection by *Staphylococci* and MRSA. Large scale studies will further improve our observations.

REFERENCES

1. Enguix A, Rey C, Concha A, Medina A, Coto D, Diéguez MA, *et al*. Comparison of procalcitonin with C-reactive protein and serum amyloid for the early diagnosis of bacterial sepsis in critically ill neonates and children. Intensive Care Med 2001;27(1):211–5.
2. Brown L, Shaw T, Wittlake WA. Does leucocyte count identify bacterial infections in febrile neonates presenting to the emergency department? Emerg Med J 2005;22(4):256–9.
3. Liesenfeld O, Lehman L, Hunfeld KP, Kost G. Molecular diagnosis of sepsis: New aspects and recent developments Eur J Microbiol Immunol (Bp) 2014;4(1):1–25.
4. Barenfanger J, Graham DR, Kolluri L, Sangwan G, Lawhorn J, Drake CA, *et al*. Decreased mortality associated with prompt Gram staining of blood cultures. Am J Clin Pathol 2008;130(6):870–6.
5. Davis T. NICE guideline: feverish illness in children –assessment and initial management in children younger than 5 years. Arch Dis Child Educ Pract Ed 2013;98:232–5.
6. Malone JR, Durica SR, Thompson DM, Bogie A, Naifeh M. Blood cultures in the evaluation of uncomplicated skin and soft tissue infections. Pediatrics 2013;132:454–9.
7. Self WH, Mickanin J, Grijalva CG, Grant FH, Henderson MC, Corley G, *et al*. Reducing blood culture contamination in community hospital emergency departments: a multicenter evaluation of a quality improvement intervention. Acad Emerg Med 2014(3):274–82.
8. Alahmadi YM, McElnay JC, Kearney MP, Aldeyab MA, Magee FA, Hanley J, *et al*. Tackling the problem of blood culture contamination in the intensive care unit using an educational intervention. Epidemiol Infect 2015;143(9):1964–71.
9. Snyder SR, Favoretto AM, Baetz RA, Derzon JH, Madison BM, Mass D, *et al*. Effectiveness of practices to reduce blood culture contamination: a laboratory medicine best practices systematic review and meta-analysis. Clin Biochem 2012;45(13–14):999–1011.
10. Jogenfors A, Stark L, Svefors JA, Löfgren S, Malmvall BE, Matussek A. Recommendation to perform a blood culture before the administration of intravenous antibiotics increased the detection of *Staphylococcus aureus* bacteremia. Eur J Clin Microbiol Infect Dis 2014;33(5):789–95.
11. Weiss S.L, Fitzgerald J.C, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, *et al*. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 2015;191:1147–57.
12. Sepsis and Children —Sepsis Alliance. Available from: https://www.sepsis.org/sepsis-and/children. [Cited: Nov 12, 2018]
13. Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of pediatric severe sepsis. Pediatr Crit Care Med 2013;14(7):686–93.
14. Shallcross LJ, Freemantle N, Nisar S, Ray D. A cross-sectional study of blood cultures and antibiotic use in patients admitted from the Emergency Department: missed opportunities for antimicrobial stewardship. BMC Infect Dis 2016;16:166.
15. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. Chochrane Database Syst Rev 2013;30(4):CD003543. Doi: 10.1002/14651858.CD003543.pub3.
16. Coburn B, Morris AM, Tomlinson G, Detsky AS. Does this adult patient with suspected bacteremia require blood cultures? JAMA 2012;308(5):502–11.
17. Buttery JP. Blood cultures in newborns and children: optimizing an everyday test. Arch Dis Child Fetal Neonatal Ed 2002;87(1):F25–8.
18. Riedel S, Bourbeau P, Swartz B, Brecher S, Carroll KC, Stamper PD, *et al*. Timing of specimen collection for blood cultures from febrile patients with bacteremia. J Clin Microbiol 2008;46:1381–5.
19. Madeo M, Jackson T, Williams C. Simple measures to reduce the rate of contamination of blood cultures in Accident and Emergency. Emerg Med J 2005;22:810–1.
20. Reier-Nilsen T, Farstad T, Nakstad B, Lauvrak V, Steinbakk M. Comparison of broad range 16S rDNA PCR and conventional blood culture for diagnosis of sepsis in the newborn: a case control study. BMC Pediatr 2009;9:5. Doi: 10.1186/1471-2431-9-5.
21. Angele MK, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis. Cardiovascular and immunological aspects. Virulence 2014;5(1):12–9.

22. Nasir N, Jamil B, Siddiqui S, Talat N, Khan FA, Hussain R. Mortality in sepsis and its relationship with gender. Pak J Med Sci 2015;31(5):1201–6.
23. Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. Crit Care 2004;8:R234–42.
24. Markic J. Biomarkers of sepsis in neonates and children. Signa Vitae 2015;10(2):1–19.
25. Lacour AG, Gervaix A, Zamora SA, Vadas L, Lombard PR, Dayer JM, *et al*. Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localising signs. Eur J Pediatr 2001;160(2):95–100.
26. Karam El-Din AA, Mohamed AM, Walaa HG, Lotfy GS. Prevalence of microbial pathogens in blood cultures: an etiological and histopathological study. J Taibah Univ Sci 2010;3(1):23–32.
27. Seigel TA, Cocchi MN, Salciccioli J, Shapiro NI, Howell M, Tang A, *et al*. Inadequacy of temperature and white blood cell count in predicting bacteremia in patients with suspected infection. J Emerg Med 2012;42(3):254–9.
28. Marimuthu K, Pittet D, Harbarth S. Effect of improved hand hygiene on nosocomial MRSA control. Antimicrob Resist Infect Control 2014;3:34. Doi: 10.1186/2047-2994-3-34.
29. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, *et al*. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet 2010;375(9730):1969–87.
30. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis 2005;41(Suppl 7):S504–12.
31. Plunkett A, Tong J. Sepsis in children. BMJ 2015;350:h3017. Doi: https://doi.org/10.1136/bmj.h3017.
32. Kirn TJ, Weinstein MP. Update on blood cultures: how to obtain, process, report, and interpret. Clin Microbiol Infect 2013;19:513–20.
33. Davis TR, Evans HR, Murtas J, Weisman A, Francis JL, Khan A. Utility of blood cultures in children admitted to hospital with community-acquired pneumonia. J Pediatrics Child Health 2017;53(3):232–6.
34. Lai EM, Nathan AM, de Bruyne JA, Chan LL. Should all children admitted with community acquired pneumonia have blood cultures taken? Indian J Pediatr 2015;82(5):439–44.
35. Dramowski A, Cotton MF, Rabie H, Whitelaw A. Trends in pediatric bloodstream infections at a South African referral hospital. BMC Pediatrics 2015;15:33. Available from: https://doi.org/10.1186/s12887-015-0354-3.
36. Salamah KM, Awean GZ, Alkume N, Abdussalam Shah AK. The outcome of blood cultures in febrile children presenting at the Emergency Department. Neonat Pediatr Med 2016;2(2):117.
37. Surase PV, Nataraj G, Pattamadai K, Mehta PR, Pazare AR, Agarwal MC, *et al*. An appropriately performed conventional blood culture can facilitate choice of therapy in resource-constrained settings-comparison with BACTEC 9050. J Postgrad Med 2016;62(4):228–34.
38. Kothari A, Morgan M, Haake DA. Emerging technologies for rapid identification of bloodstream pathogens. Clin Infect Dis 2014;59(2):272–8.

Address for Correspondence:

Dr Saima Gillani, Associate Professor of Paediatrics, Ayub Medical College, Abbottabad, Pakistan. **Cell:** +92-320-8512073
Email: drsaimagillani@gmail.com

Received: 16 Jan 2019 **Reviewed: 18 Feb 2019** **Accepted: 20 Feb 2019**