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Fever without Focus in Children Aged 1 to 36 Months- Aetiological Profile and Predictors of Specific Aetiology- A Prospective Observational Study

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Authors
Padmasani Venkat Ramanan, *MD*[1]
Thasma Santhanakrishnan Arunprasath, *MD*[2*]

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[1]Department of Paediatrics, Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai, Tamilnadu, India- 600116.
[2] Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai, Tamilnadu, India- 600116.

** Correspondence*
Address: Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai, Tamilnadu, India- 600116.
drtsarunprasath@yahoo.com

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ABSTRACT

Backgrounds: This study aimed to describe the aetiological profile of fever without focus (FWF) in children aged one to thirty-six months and to identify clinical and laboratory predictors of specific aetiologies, especially serious bacterial infection (SBI).

Materials & Methods: Children in the age range of one to thirty-six months, who were hospitalised due to FWF were included in this study. This prospective study was done over a period of 20 months in a medical college hospital in southern India. CBC (complete blood count) and CRP (c-reactive protein) tests, urine microscopic examination, blood and urine culture, Dengue antigen testing, and chest X-ray test were done for all feverish children. For those with fever beyond 5 days, additional tests including serological tests for Dengue, scrub typhus, and leptospirosis as well as Widal test were done. The final diagnosis was recorded, and clinical and laboratory parameters were analysed.

Findings: Among 141 children with FWF, 41 (29%) had SBI, and 21(14.9%) had Dengue fever (DF). Leucocytosis, neutrophilia, and raised CRP levels were good predictors of SBI. Thrombocytopenia was an excellent predictor of DF. High fever was significantly associated with SBI and Dengue (p=.004), and fever beyond 3 days at presentation was significantly associated with SBI (p=<.001). Pyuria had a high specificity (94.5%) for identifying urinary tract infection (UTI). About 50% of UTIs were caused by extended spectrum beta lactamase (ESBL) producing organisms.

Conclusion: SBI and DF were the most common causes of FWF. High fever, fever beyond 3 days at presentation, leucocytosis, neutrophilia, and a positive CRP test were predictors of SBI. Pyuria suggests UTI. Empirical antibiotic therapy should cover ESBL producing organisms. High fever and thrombocytopenia suggest Dengue fever.

Keywords: Bacterial infections, Dengue fever, Fever.

CITATION LINKS

[1] Kelly M, McCarthy S, O'Sullivan R, Shiely F, Larkin P, Brenner M, et al. Drivers for... [2] Dayal R, Agarwal D. Fever in... [3] Pulliam PN, Attia MW, Cronan KM. C-reactive protein in febrile children 1 to 36 months of ... [4] Goh PL, Lee SW, Wong EH. Predictors of serious bacterial... [5] Kumar R, Tripathi P, Tripathi S, Kanodia A, Pant S, Venkatesh V. Prevalence and clinical differentiation of dengue fever in... [6] Long SS. Diagnosis and management of undifferentiated fever in children. J Infect. 2016;72:S68-76.... [7] Akpede GO, Akenzua GI. Aetiology and management of children... [8] Watt K, Waddle E, Jhaveri R. Changing epidemiology... [9] Williams-Smith JA, Fougère Y, Pauchard JY, Asner S, Gehri M, Crisinel ... [10] Ministry of health & family welfare. Facility ... [11] Lo SF. Reference intervals for laboratory tests and procedures. In: Kliegman RM, Stanton BF, Schor NF, St Geme III JW, Behrman RE, editors. Nelson textbook of... [12] Kundu R, Ganguly N, Ghosh TK, Yewale VN, Shah RC, Shah NK, et al. IAP task... [13] Murphy CG, van de Pol AC, Harper MB, Bachur RG. Clinical... [14] Jamuna R, Srinivasan S, Harish BN. Factors... [15] Pathak A, Upadhayay R, Mathur A, Rathi S, Lundborg CS. Incidence, clinical... [16] Susilawati TN, McBride WJ. Acute undifferentiated... [17] Department of health and family... [18] Esposito S, Rinaldi VE, Argentiero A, Farinelli E, Cofini M, D'Alonzo R, et al. Approach to neonates and... [19] Byington CL, Rittichier KK, Bassett KE, Castillo H, Glasgow TS, Daly J, et al. Serious bacterial... [20] Mintegi S, Benito J, Pijoan JI, Marañon R, Peñalba A, Gonzalez A, et al. Occult pneumonia... [21] Yo CH, Hsieh PS, Lee SH, Wu JY, Chang SS, Tasi KC, et al. Comparison of the... [22] Brauner M, Goldman M, Kozer E. Extreme leucocytosis and the risk of serious bacterial... [23] Rosenfeld-Yehoshua N, Barkan S, Abu-Kishk I, Booch M, Suhami R, Kozer E. Hyperpyrexia and ... [24] Pratt A, Attia MW. Duration of fever and markers of... [25] Venkat Ramanan P, Sharma S, Krishna V. Changing profile of pediatric... [26] Lukac PJ, Bonomo RA, Logan LK. Extended-spectrum β-lactamase-producing Enterobacteriaceae in ... [27] Akram M, Shahid M, Khan AU. Etiology... [28] Balasubramanian S, Kuppuswamy D, Padmanabhan S, Chandramohan V, Amperayani S. Extended-spectrum... [29] Mørch K, Manoharan A, Chandy S, Chacko N, Alvarez-Uria G, Patil S, et al. Acute... [30] Ali N, Khan NU, Waheed S, Mustahsan S. Etiology of ... [31] Gupta V, Yadav TP, Pandey RM, Singh A, Gupta M, Kanaujiya P, et al. Risk factors... [32] Kularatnam GAM, Jasinge E, Gunasena S, Samaranayake...

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Introduction

Fever is a common symptom in children, causing significant anxiety among parents [1]. Fever as the only symptom, without any other localizing symptoms or signs is called "fever without focus" (FWF) [2]. For treating physicians, FWF presents both diagnostic and management dilemmas. Though most children with FWF have a benign course, neonates and children aged 1 to 36 months are at higher risk of developing a serious bacterial infection (SBI) [3, 4]. In endemic regions, Dengue fever (DF) could also be manifested as FWF [5]. The aetiological profile of FWF has changed over the last years [6]. But the pattern of clinical assessment, initial laboratory evaluation, and initiation of empirical antibiotic therapy has remained the same over the years [7]. There is a need for changes in laboratory evaluations and choice of antibiotic therapy in children presenting with FWF based on epidemiological changes in diseases and the emergence of antibiotic resistance among bacterial isolates [8]. Vaccination status of the child, vaccination schedule, and vaccination coverage affect the relative incidence of SBI in children with FWF [9]. Early identification of SBI and Dengue helps prevent morbidity and mortality. Considering all these factors, knowledge of the possible etiology of FWF, epidemiological changes, and antimicrobial resistance pattern allows the initiation of appropriate treatment and care.

Objectives: This study was done to describe the aetiological profile of FWF in children aged one to thirty six months and to identify clinical and laboratory predictors of specific aetiologies.

Materials and Methods

This cross sectional study was done in the paediatric ward of a medical college hospital in southern India after obtaining the approval of the institution Ethics Committee (CSP-MED/14/SEP/18/158) and informed consent of parents. Children in the age range of one to thirty six months, who were hospitalised with a fever of less than seven days with no identifiable focus based on clinical history and physical examination, were included in this study. Those already receiving antimicrobial therapy, immunocompromised children, and children discharged before fever defervescence were excluded.

At admission, the clinical details were recorded, and blood samples were collected for complete blood count (CBC), peripheral blood smear examination (PS), C-reactive protein (CRP) test, Dengue non-structural 1 antigen (NS1Ag) testing, and blood culture. Urine samples were collected for microscopic examination and culture (mid stream/catheterised sample). Chest X-ray was done and interpreted by the clinician. For children with a fever of more than five days, additional tests including serological tests for Dengue, scrub typhus, and leptospirosis as well as serum Widal test were done. Study subjects were followed up till discharge, and clinical and laboratory parameters were recorded.

CBC was done by automated technique using UniCel DxH 800 Coulter cellular analysis system. PS examination was done based on manual method by trained pathologists. CRP assay was done by nephelometric method. Serological tests were performed for Dengue, scrub typhus, and leptospirosis using ELISA (Enzyme linked immunosorbent assay). Widal test was done by tube agglutination method. Blood culture was done by automated BACTEC system with fluorescent technology. Microscopic analysis was done for pus cells in centrifuged urine and urine culture by agar plate method. Urine culture was done by semi-quantitative calibrated loop method, and ESBL producers were identified by disk diffusion method based on an inhibition zone diameter of < 27 mm (for 30-mcg cefotaxime disk).

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Study Definitions

Fever: Axillary temperature more than 99.5 °F [10] measured with a digital thermometer.

High fever: Axillary temperature more than 101.3 ^{0}F [10].

Leucopenia: Total leucocyte count (TLC) less than 4000 cells/mm^3 [11].

Leucocytosis: TLC more than 14000 cells/mm^3 [11].

Neutrophilia: Total neutrophil count (NC) more than 5800 cells/mm^3 [11].

Lymphopenia: Lymphocyte count less than 1500 cells/mm^3 [11].

Eosinopenia: Eosinophil count less than 50 cells/mm^3 [11].

Thrombocytopenia: Platelet count (PC) less than 1.5 lakh cells/mm^3 [11].

Positive CRP: CRP value more than 1.2 mg/dl [11].

Dengue fever: Positive NS1 antigen/IgM antibody test.

Enteric fever: Growth of *Salmonella typhi/ paratyphi* in blood culture or O and H antibody levels greater than 1:160 in Widal test by tube agglutination method [12].

Scrub typhus: Positive IgM ELISA test.

Leptospirosis: Positive IgM ELISA test.

Occult pneumonia (OP): Radiographic pneumonia in a child without clinical signs of pneumonia [13].

Pyuria: More than 5 white blood cells per high-power field (WBC/HPF) in centrifuged urine.

Urinary tract infection (UTI): Growth of single bacteria in urine culture with a colony count of > 10^5.

Occult bacteremia (OB): Growth of bacteria in blood without definitive localizing signs [14].

Serious bacterial infection: Occult pneumonia, occult bacteremia, UTI, enteric fever [15].

Acute undifferentiated fever (AUF): Temporary self-limiting febrile illness without specific positive laboratory results [16].

Statistical analysis: Data were entered into Microsoft Excel database, and statistical analysis was performed using IBM SPSS Statistics, Version 26. Categorical variables were expressed as frequency and percentage. Continuous variables were expressed as mean and standard deviation. Categorical variables were compared using Chi-square test. The normality of continuous variables was assessed by Shapiro-Wilk test. Continuous variables were compared using non-parametric tests. The discriminative ability of test parameters was assessed by analyzing the area under the receiver operating characteristic (ROC) curve (AUC). A *p* value of <.05 was taken as significant. The sensitivity and specificity of test parameters were calculated using the diagnostic test evaluation calculator of MedCalc software limited.

Findings

A total of 166 children presented with FWF during the study period. Of these, 25 cases were excluded according to the predefined exclusion criteria, and 141 children were enrolled. The subjects' median (interquartile range) age was 16 (11.5-24) months. All of these children were immunized according to the national immunization schedule of the Government of India [17], and none of them were vaccinated by pneumococcal, typhoid, or flu vaccine. The aetiological profile of FWF in the study subjects is shown in Table 1.

Out of 141 children, 41(29%) had SBI, 21 (14.9%) had DF, and 77 (54.6%) had acute undifferentiated fever. One child was diagnosed with scrub typhus and leptospirosis each.

The final diagnosis was culture-proven UTI in 14 (9.9%) children, which was caused by *Escherichia coli* in 9 (64.2%) and *Klebsiella* in 5 (35.8%) cases, respectively. Of these organisms, 7 (50%) isolates were extended-spectrum beta lactamase (ESBL) producers. Occult bacteremia (OB) was present in 3 (2.1%) children, caused by *Streptococcus pneumonia* and *Klebsiella* in two and one cases, respectively.

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Table 1) Aetiological profile of FWF in children (1 to 36 months)

Diagnosis	Number of Children (N=141)	Percentage of Total Children
Dengue	21	14.9
Occult pneumonia	20	14.2
Urinary tract infection	14	9.9
Enteric fever	4	2.8
Occult bacteremia	3	2.1
Scrub typhus	1	0.7
Leptospirosis	1	0.7
Acute Undifferentiated fever	77	54.6
Total	141	100

FWF: Fever without focus

No antibiotic resistance was observed in pneumococcal isolates, but *Klebsiella* was resistant to ampicillin and ciprofloxacin. None of these three OB cases were associated with occult pneumonia or UTI.

Occult pneumonia was diagnosed in 20 (14.2%) children. No bacterial growth was detected in the blood of these children. There were 4 (2.8%) children with enteric fever diagnosed by a positive Widal test but not confirmed by blood culture.

For further analysis, the diagnosed infections were categorised as SBI, Dengue, and other infections. Clinical and laboratory characteristics of these categories are shown in Table 2. The maximum temperature recorded, fever duration, CRP level, TLC, NC, PC, monocytes count, and basophils count were found to be significantly associated with specific etiologies.

Pairwise comparison test was done for maximum temperature (TMax) recorded during the illness. Tmax was significantly higher in SBI (p=.005) and Dengue (p=.024) compared with other infections. There was no difference in Tmax between SBI and Dengue. Duration of fever (fever beyond three days) at presentation was longer in SBI compared with other infections (p <.001). There was no significant difference in the duration of fever between other groups.

Areaundercurve(AUC)analysisoftestaccuracy is shown in Table 3. Thrombocytopenia had an excellent discriminatory ability to identify DF (AUC=0.99, p value <.001). Leucocytosis (AUC=0.714, p value <.001) and neutrophilia (AUC=0.713, p value <.001) had the best discriminatory ability to identify SBI, followed by CRP test (AUC=0.617, p value=.029).

Sensitivity and specificity of test parameters according to predefined cut offs are shown in Table 4. Thrombocytopenia had good sensitivity and specificity for predicting Dengue. Leucocytosis, neutrophilia, and positive CRP levels had high specificity for detecting SBI. Pyuria had high specificity for UTI detection.

Discussion

The prevalence of SBI in this study was 29%. High fever and fever duration of more than three days at presentation were clinical clues, and leucocytosis, neutrophilia, and positive CRP test were lab parameters significantly associated with SBI. Empirical antibiotic therapy after sending culture samples is suggested for these children. Conversely, in children without these clinical and laboratory signs, SBI is unlikely, and antibiotic therapy should be withheld till culture reports suggest otherwise. This approach could effectively reduce the morbidity of SBI while preventing antibiotic misuse, which is an essential strategy in combating antimicrobial resistance.

The reported prevalence rate of SBI in literature is in the range of 5 to 15% [18, 19].

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Table 2) Clinical and laboratory characteristics of SBI, Dengue, and other categories

Variable	SBI (n=41)	Dengue (n=21)	Others (n=79)	P Value
Male (n=77) N(%) Female (n=64) N(%)	18(43.9) 23 (56.1)	13(61.9) 8 (38.1)	46(58.2) 33 (41.8)	.251
Age in months Mean (SD)	15.88(10.20)	18.71(7.59)	19.70(9.87)	.109
Maximum temperature recorded in F Mean (SD)	100.98(0.54)	100.96(0.47)	100.69(0.40)	.001
High fever(Tmax > 101.3) (n=19) N(%)	10(24.4)	5(23.8)	4(5.1)	.004
Duration of fever at presentation Mean (SD)	4.12(0.781)	3.76(1.338)	3.34(0.861)	<.001
Hemoglobin Mean (SD)	11.40(0.71)	11.73(0.61)	11.35(1.04)	.436
Total leucocyte count Mean (SD)	11398(4032)	7485(1328)	9282(2883)	<.001
Neutrophil count Mean (SD)	6488(3986)	3110(867)	4453(2353)	<.001
Lymphocyte count Mean (SD)	4254(1766)	3977(839)	4183(1552)	.841
Eosinophil count Mean (SD)	72(65)	36(40)	83(113)	.008
Monocytes count Mean (SD)	866(401)	536(146)	675(273)	<.001
Basophil count Mean (SD)	52(29)	34(11)	41(20)	.031
Platelet count Mean (SD)	280487(58006)	110809(21544)	291772(73200)	<.001
CRP Mean (SD)	1.04(0.8)	0.6	0.62(0.2)	<.001
Leucocytosis (n=17, 12.1%) N(%)	10(24.4)	0	7(8.9%)	.009
Neutrophilia (n=27, 19.1%) N(%)	16(39)	0	11(13.9%)	<.001
Thrombocytopenia (n=21, 14.9%) N(%)	0	20(95.2)	1(1.3)	<.001
Raised CRP level (n=11, 7.8%) N(%)	10(24.4)	0	1(1.3)	<.001

SBI: Serious bacterial infection, CRP: C-reactive protein, SD: Standard deviation

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Table 3) Area under the receiver operating characteristic curve analysis of test parameters

Test Parameter	AUC	95% CI	P Value
Total leucocyte count for SBI	0.714	0.616-0.812	<.001
Neutrophil count for SBI	0.713	0.615 -0.811	<.001
CRP level for SBI	0.617	0.507-0.727	.029
Platelet count for Dengue	0.999	0.997-1.000	<.001

AUC: Area under curve, SBI: Serious bacterial infection, CRP: C-reactive protein, CI: Confidence interval

Table 4) Sensitivity and Specificity of test parameters

Factor	Sensitivity%(95% CI)	Specificity% (95% CI)
Leucocytosis for SBI	24.4(12.4-40.3)	93(86.1-97.1)
Neutrophilia for SBI	39(24.2-55.6)	89(81.2-94.3)
Positive CRP for SBI	24.4(12.4-40.3)	99(94.6-99.8)
Thrombocytopenia for Dengue	95.2(77.2-99.9)	99.2(95.4-99.9)
Pyuria for UTI	64.3(35.1-87.2)	94.5(89-97.8)

SBI: Serious bacterial infection, CRP: C-reactive protein, CI: Confidence interval, UTI: Urinary tract infection

The higher prevalence rate obtained in this study may be due to the higher incidence of pneumonia and enteric fever. At the time of this study, the pneumococcal and typhoid vaccines were not included in India's national immunisation schedule. It is well known that the incidence of pneumonia decreases with the introduction of the pneumococcal vaccine in the routine vaccination schedule [20]. The clinical and lab predictors of SBI identified in this study are similar to those previously reported [21-24].

In this study, pyuria as a simple point-of-care test had high specificity for predicting UTI, and 50% of UTIs were due to ESBL producing organisms. The profile of organisms causing UTI and their antibiotic sensitivity pattern exhibit temporal changes [25]. A significant rise in the prevalence of ESBL UTI among children, even CAI (community acquired infection), has been reported in earlier studies [26, 27]. Since there are no clinical clues to identify ESBL UTI as reported earlier [28], empirical choice of antibiotic for SBI should cover ESBL producers if pyuria is also present. The use of appropriate antibiotics for UTI is important to prevent renal scars, and the choice of antibiotic should always be guided by the prevalence of isolates in the local population.

In our study, 15% of children with FWF had DF, and this finding is consistent with those previously reported in other studies [29, 30]. High fever and thrombocytopenia had good sensitivity and specificity for predicting DF, which is consistent with the findings reported in previous studies as well [31, 32]. In endemic regions, DF should be considered in the differential diagnosis of FWF when there is thrombocytopenia.

The main limitation in our study was that OP was diagnosed by the clinician's interpretation of chest X-ray, and all pneumonia cases were presumed to be

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due to bacterial causes. Diagnostic tests for viral markers were not done due to logistics reasons. Also, the Widal test is not ideal for diagnosing enteric fever.

Conclusion

SBI and Dengue fever could be manifested as FWF. High fever, fever beyond 3 days, leucocytosis, neutrophilia, and raised CRP levels in a child with FWF suggest SBI. Pyuria suggests UTI. Empirical antibiotic therapy should cover ESBL organisms. High fever and thrombocytopenia suggest Dengue fever, and if markers of SBI are absent, empirical antibiotic therapy should be withheld.

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References

1. Kelly M, McCarthy S, O'Sullivan R, Shiely F, Larkin P, Brenner M, et al. Drivers for inappropriate fever management in children: A systematic review. Int J Clin Pharm. 2016;38(4):761-70.
2. Dayal R, Agarwal D. Fever in children and fever of unknown origin. Indian J Pediatr. 2016;83(1):38-43.
3. Pulliam PN, Attia MW, Cronan KM. C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. Pediatrics. 2001;108(6):1275-9.
4. Goh PL, Lee SW, Wong EH. Predictors of serious bacterial infection in children aged 3 to 36 months with fever without source. Singapore Med J. 2006;47(4):276-80.
5. Kumar R, Tripathi P, Tripathi S, Kanodia A, Pant S, Venkatesh V. Prevalence and clinical differentiation of dengue fever in children in northern India. Infection. 2008;36(5):444-9.
6. Long SS. Diagnosis and management of undifferentiated fever in children. J Infect. 2016;72:S68-76.
7. Akpede GO, Akenzua GI. Aetiology and management of children with acute fever of unknown origin. Paediatr Drugs. 2001;3(3):169-93.
8. Watt K, Waddle E, Jhaveri R. Changing epidemiology of serious bacterial infections in febrile infants without localizing signs. PLoS One. 2010;5(8):e12448.
9. Williams-Smith JA, Fougère Y, Pauchard JY, Asner S, Gehri M, Crisinel PA. Risk factors for urinary tract infections in children aged 0-36 months presenting with fever without source and evaluated for risk of serious bacterial infections. Arch Pediatr. 2020;27(7):372-9.
10. Ministry of health & family welfare. Facility based integrated management of neonatal and childhood illness (F-IMNCI): IMNCI chart booklet. India: Government of India, Ministry of health & family welfare; 2003.
11. Lo SF. Reference intervals for laboratory tests and procedures. In: Kliegman RM, Stanton BF, Schor NF, St Geme III JW, Behrman RE, editors. Nelson textbook of paediatrics. First south Asia edition. India, New Delhi: Reed Elsevier India; 2016, Vol. 3, p. 3466-8.
12. Kundu R, Ganguly N, Ghosh TK, Yewale VN, Shah RC, Shah NK, et al. IAP task force report: Diagnosis of enteric fever in children. Indian Pediatr. 2006;43(10):875-83.
13. Murphy CG, van de Pol AC, Harper MB, Bachur RG. Clinical predictors of occult pneumonia in the febrile child. Acad Emerg Med. 2007;14(3):243-9.

[DOI: 10.52547/iem.8.1.61]

14. Jamuna R, Srinivasan S, Harish BN. Factors predicting occult bacteremia in young children. Indian J Pediatr. 2000;67(10):709-11.
15. Pathak A, Upadhayay R, Mathur A, Rathi S, Lundborg CS. Incidence, clinical profile, and risk factors for serious bacterial infections in children hospitalized with fever in Ujjain, India. BMC Infect Dis. 2020;20(1):1-11.
16. Susilawati TN, McBride WJ. Acute undifferentiated fever in Asia: A review of the literature. Southeast Asian J Trop Med Public Health. 2014;45(3):719-26.
17. Department of health and family welfare. National immunisation schedule (NIS) for infants, children, and pregnant women. India: Government of India, Ministry of health and family welfare; 2021.
18. Esposito S, Rinaldi VE, Argentiero A, Farinelli E, Cofini M, D'Alonzo R, et al. Approach to neonates and young infants with fever without a source who are at risk for severe bacterial infection. Mediators Inflamm. 2018;2018.
19. Byington CL, Rittichier KK, Bassett KE, Castillo H, Glasgow TS, Daly J, et al. Serious bacterial infections in febrile infants younger than 90 days of age: The importance of ampicillin-resistant pathogens. Pediatrics. 2003;111(5):964-8.
20. Mintegi S, Benito J, Pijoan JI, Marañon R, Peñalba A, Gonzalez A, et al. Occult pneumonia in infants with high fever without source: A prospective multicenter study. Pediatr Emerg Care. 2010;26(7):470-4.
21. Yo CH, Hsieh PS, Lee SH, Wu JY, Chang SS, Tasi KC, et al. Comparison of the test characteristics of procalcitonin to C-reactive protein and leukocytosis for the detection of serious bacterial infections in children presenting with fever without source: A systematic review and meta-analysis. Ann Emerg Med. 2012;60(5):591-600.
22. Brauner M, Goldman M, Kozer E. Extreme leucocytosis and the risk of serious bacterial infections in febrile children. Arch Dis Child. 2010;95(3):209-12.
23. Rosenfeld-Yehoshua N, Barkan S, Abu-Kishk I, Booch M, Suhami R, Kozer E. Hyperpyrexia and high fever as a predictor for serious bacterial infection (SBI) in children-a systematic review. Eur J Pediatr. 2018;177(3):337-44.
24. Pratt A, Attia MW. Duration of fever and markers of serious bacterial infection in young febrile children. Pediatr Int. 2007;49(1):31-5.
25. Venkat Ramanan P, Sharma S, Krishna V. Changing profile of pediatric community-acquired UTI in a hospital in South India. J Trop Pediatr. 2014;60(6):483.
26. Lukac PJ, Bonomo RA, Logan LK. Extended-spectrum β-lactamase-producing Enterobacteriaceae in children: Old foe, emerging threat. Clin Infect Dis. 2015;60(9):1389-97.
27. Akram M, Shahid M, Khan AU. Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in JNMC Hospital Aligarh, India. Ann Clin Microbiol Antimicrob. 2007;6(1):1-7.
28. Balasubramanian S, Kuppuswamy D, Padmanabhan S, Chandramohan V, Amperayani S. Extended-spectrum beta-lactamase-producing community-acquired urinary tract infections in children: Chart review of risk factors. J Glob Infect Dis. 2018;10(4):222-5.
29. Mørch K, Manoharan A, Chandy S, Chacko N, Alvarez-Uria G, Patil S, et al. Acute undifferentiated fever in India: A multicentre study of aetiology and diagnostic accuracy. BMC Infect Dis. 2017;17(1):1-11.
30. Ali N, Khan NU, Waheed S, Mustahsan S. Etiology of acute undifferentiated fever in patients presenting to the emergency department of a tertiary care center in Karachi, Pakistan. Pak J Med Sci. 2020;36(6):1285-90.
31. Gupta V, Yadav TP, Pandey RM, Singh A, Gupta M, Kanaujiya P, et al. Risk factors of dengue shock syndrome in children. J Trop Pediatr. 2011;57(6):451-6.
32. Kularatnam GAM, Jasinge E, Gunasena S, Samaranayake D, Senanayake MP, Wickramasinghe VP. Evaluation of biochemical and haematological changes in dengue fever and dengue hemorrhagic fever in Sri Lankan children: A prospective follow up study. BMC Pediatr. 2019;19(1):1-9.

[DOI: 10.52547/iem.8.1.61]