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Original Research Article

Evaluation of predictive value of total leukocyte count in acute serious bacterial infections in children 1 month to 5 years

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ABSTRACT

Background: Fever in a young child is a frequently encountered clinical problem with various causes. Most of them run a benign self-limiting course that requires only symptomatic treatment. However, in a few children the underlying etiology can be a life threatening serious bacterial infection (SBI). Early identification of SBI is warranted because of the need to start antibiotic therapy, often empirical, as soon as possible to prevent morbid sequela. Total leukocyte count (TLC) is with neutrophil predominance is considered to be a surrogate marker of a bacterial infection and facilitating decision - making regarding further evaluation and empiric antibiotic therapy. The purpose of this study was to determine the utility of leukocyte in predicting SBI in a young febrile child and to correlate the leukocyte count with non-serious infection.
Methods: One fifty children, age of 1 month to 60 months with fever > 38°c are included and were analyzed for demographic details, presenting symptoms, physical examination findings, clinical diagnosis, total leukocyte count, peripheral smear study, blood culture, stool culture, CSF analysis, x-ray chest, abdominal ultrasound, CT-brain.
Results: Out of 150 children included in the study, the mean age was 26.7±14.54 months and the average duration of fever was 4.3±1.02 days. The mean leukocyte count was 15016.43±5801.98 cells/cu.mm. 74 children had proven serious bacterial infection (49.3%) and were categorized in Group I and remaining non-serious infection were 50.66% are belonged to Group 2. Urinary tract infection and pneumonia were the most common SBI encountered (31/20/68.91%). The highest TLC counts were seen in children with UTI. Analysis of variance (ANNOVA) did not reveal significant differences in TLC between children with different diagnosis. In Group 2, majority of the etiology was lower respiratory tract infection/inflammation and short febrile illness.
Conclusions: SBI comprise only half of the febrile children with leukocytosis. The predictive accuracy of leukocytosis in diagnosing SBI is poor. Vomiting and seizures probably incite stress mediated leukocytosis and are commonly encountered in febrile child with a high TLC without SBI. Further models with addition of clinical data and other surrogates of infection need to be developed to improve prediction of SBI in a febrile child.

Keywords: Antibiotic therapy**,** Febrile illness, Serious bacterial infection, Total leukocyte count

INTRODUCTION

A young child, on an average, experiences three to six febrile illnesses per year.[1] About 20-40% of parents seek medical attention when their child develops fever.[1] Febrile illness is the single most common reason for a young child to visit the general pediatrician.[2] Among these children, 5-10% have serious bacterial infection like pneumonia, meningitis, urinary tract infection, bacteremia or bone/joint infection, children with SBI are

sometimes difficult to distinguish from those with a self-limiting viral illness and benefit from early antibiotic therapy.[3-5] Very often the decision to commence antibiotics is based on clinical evaluation supplemented by rapid available tests like urine routine examination and leukocyte counts. The results of microbiological cultures, the reference standard for SBI, can take up to 48 hours to arrive and cannot be used to guide management in the acute setting. A delay in diagnosis of SBI or initiation of treatment can have serious, or occasionally fatal consequences.[6]

Recent updates have stated that independent predictors of SBI from history and examination were, duration of fever, vomiting, ill clinical appearance, chest wall retractions1 and poor peripheral circulation (ROC area (95%CI): 0.69 (0.63-0.75). Additional independent predictors from laboratory were serum white blood cell count and C-reactive protein, and in urinalysis >70 white blood cells (ROC area (95% CI): 0.83 (0.78-0.88).[7] These findings have not been confirmed in larger studies or systematic analysis.[8,9]

The 1993 practice guideline for the management of fever recommends a white blood cell count of 15,000 per cu.mm as the threshold, or cutoff value, for deciding to obtain blood for culture and initiate empirical antibiotic therapy.[10] Much of the controversy relating to the practice guideline involves the selection of this cutoff value. In overwhelming sepsis, the total counts can in fact be low. One set of investigators has advocated 18,000 white blood cells per mm^3 (18x109 per L) as the cutoff value, arguing that use of this higher count is justified by the post-vaccination disappearance of H. influenza infection and a lower overall prevalence of bacteremia than previously reported.[11] However all later investigators have used the cut-off of 15000 to establish the usefulness of TLC to predict SBI. In fact, there is a positive correlation between the administration of antibiotics with the TLC and WBC > 15,000, regardless of cause, almost uniformly resulted in treatment.[2,12] Irrespective of the threshold, TLC remains one of the constant parameters in algorithms evaluating a febrile child.

Evidence points to the fact that though an elevated TLC might be worrisome, its specificity and sensitivity as a marker of SBI is fairly low to be used as a sole marker. These studies, however, have been performed in countries where the incidence of SBI is low. There is paucity of data from our own patient population where infectious disease stills a major burden. This study is an attempt to throw light on the clinical utility of leukocyte in identifying SBI in the patient subset unique to this part of the world.

Therefore, the objective of the study is to evaluate the predictive value of total leukocyte count in identifying serious bacterial infection (SBI) in children between the age of one month to sixty months belong to Group 1 and to study the correlation of total leukocyte count in children with non-serious infection (NSI) were categorized in Group 2.

METHODS

The study was conducted at Aarupadai Veedu Medical College and Hospital (AVMC and H) and it is a cross sectional study. Conducted during December 2013 - August 2015. Total 150 children were included of which 74 in Group 1 and 76 Group 2.

Inclusion criteria

All children between the age of one to 60 months with fever more than 38°C with symptoms suggestive of pneumonia / empyema, septicemia, meningitis/cerebral abscess, UTI/ Pyelonephritis, Osteomyelitis, and bacterial enteritis or colitis.

Exclusion criteria

- Those who had already received antibiotics prior to investigations.
- Children who were on steroids or colony stimulating factors or on immunosuppressive medications.

Those children admitted in AVMC and H pediatric ward and fulfills the inclusion criteria and got consent from their parents were included in this study and will be evaluated for SBI based on the clinical symptoms, findings on physical examination and appropriate laboratory investigations ordered on the discretion of the primary treating physician.

Investigation mandatory were total leukocyte count and if required peripheral smear study, blood culture, stool culture, CSF analysis, x-ray chest, abdominal ultrasound, CT-brain.

Group 1 (SBI) serious bacterial infection

- Pneumonia/empyema
- Septicemia
- Meningitis/cerebral abscess
- UTI/ pyelonephritis
- Osteomylitis
- Suppurative arthritis
- Bacterial enteritis or colitis was considered SBI

Group 2 (NSI) non-serious infection

Children not falling into any of the afore-mentioned categories were given an alternative diagnosis that was grouped separately (Group 2). Short febrile illness and appropriate cultures negative, LRTI that included wheeze associated lower respiratory infection, bronchiolitis and pneumonitis other than pneumonia, skin and soft tissue infections, cervical lymphadenitis, infective diarrhea (enteritis of non-bacterial etiology) and miscellaneous

conditions are all grouped into NSI - Group 2. Data was collected prospectively and included the demographic details, presenting symptoms, physical examination findings, clinical diagnosis, total leukocyte count, results of appropriate investigation to rule out SBI, final diagnosis and clinical outcome. Data was entered into a proforma.

Children with a clinical suspicion of SBI whose work up was incomplete and those who received antibiotic therapy before appropriate investigations were done to confirm/rule out SBI were further excluded from the study. All children were followed up till resolution of fever and those who were lost to follow up were also excluded from final analysis.

Essential criteria for each of the diagnosis was standardized as follows

Pneumonia

Chest radiograph evidence of lobar infiltrates or consolidation. All chest radiograph was interpreted by an experienced radiologist.

Empyema

Pleural fluid culture positive for non-tuberculous bacteria in a child with or without co-existing pneumonia.

Urinary tract infection

Positive culture with greater than 10^5 colonies forming units of a single pathogenic bacteria from a clean catch urine specimen.

Pyelonephritis

Ultrasound evidence of enlarged kidney or perinephric collection or nuclear scintigraphic hot spots.

Septicemia

At least one positive blood culture growing non-pathogenic bacteria in a child with a clinical suspicion of septicemia.

Meningitis

Cerebrospinal fluid (CSF) pleocytosis (usually WBC count more than 100/cu.mm) with neutrophil predominance, elevated protein levels and decreased protein levels and decreased sugar level or gram's stain positive CSF or culture positive CSF.

Cerebral abscess

Imaging evidence of cerebral abscess and culture from the abscess growing pathogenic bacteria.

Bacterial enteritis/colitis

Characteristic gastrointestinal symptoms and stool culture positive for pathogenic bacteria.

RESULTS

Totally150 children were included of which 74 in Group 1 and 76 Group 2. The mean age of the children was 26.7±14.54 months. The average duration of fever was 4.3±1.02 days. The mean leukocyte count was15016.43±5801.98 cells/cu.mm. 74 children had proven serious bacterial infection (49.3%) and were categorized in Group 1.

The remaining 76 children had non-serious infection (50.66%) are belonged to Group 2. The mean age, sex ratio, duration of fever and TLC did not differ significantly between both the Groups 2 (Table 1).

Table 1: Demographics.

N = 150	Group 1 (n = 74)	Group 2 (n = 76)	P
Age in months (standard deviation)	29.229 (14.475)	24.171 (14.623)	0.89
Sex (M:F)	42:32	53:23	0.16
Duration of fever in days (standard deviation)	5.472 (1.125)	3.302 (0.924)	0.81
Total leukocyte counts (standard deviation)	15598.65 (5915.165)	14434.21 (5688.806)	0.13

Table 2: Group 1 distribution of diagnosis.

Diagnosis (n, Percentage)	Sex ratio (Male/Female)	Age in months	Duration of fever in days	TLC in cells/cu.mm
UTI (31, 41.89%)	18/13	27.06	5.38	15100
Pneumonia (20, 27.02%)	10/10	30.95	5.7	14100
Empyema (4, 5.4%)	1/3	26.5	6.5	15750
Meningitis (7, 9.45%)	3/4	28.85	5.42	19057
Osteomyelitis (1, 1.35%)	1/0	33	5	23000
Pyelonephritis (7, 9.45%)	5/2	35.57	5	16371
Septicemia (4, 5.4%)	4/0	28.75	5	17550

Table 3: Group II distribution of diagnosis.

Diagnosis (n, Percentage)	Sex ratio (Male/Female)	Age in months	Duration of fever in days	TLC in cells/cu.mm
LRTI (36, 47.36%)	21/16	24.22	3.33	14702
Infective diarrhea (5, 6.57%)	5/0	12	2.8	14980
Left cervical lymphadenitis (2, 2.63%)	0/2	30	3	11900
Rickettsial infection (1, 1.31%)	1/0	26	4	20000
Short febrile illness (28, 36.84%)	23/5	25.32	3.35	13760
Skin and soft tissue infection (3, 3.94%)	3/0	26	3.33	14233

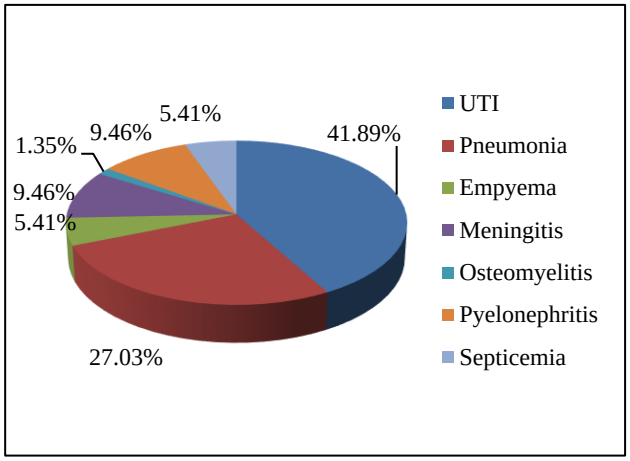

Figure 1: SBI distribution of diagnosis.

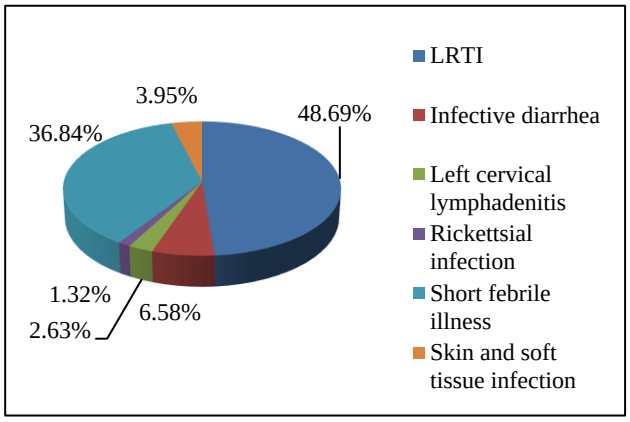

Figure 2: NSI distribution of diagnosis.

Urinary tract infection and pneumonia were the most common SBI encountered (31/20/68.91%). The remaining 23 (31.08%) children had meningitis, sepsis, empyema, pyelonephritis, osteomyelitis (Table 2). The highest TLC counts were seen in children with UTI (Figure 1). Analysis of variance (ANNOVA) did not reveal significant differences in TLC between children with different diagnosis.

In Group 2, majority of the etiology was distributed between lower respiratory tract infection/inflammation and short febrile illness (Figure 2, 3). Apart from infective diarrhea, the miscellaneous diagnosis in this was Ricketsial infection, cervical lymphadenitis and skin/soft tissue infection.

Although the highest TLC in Group 2 was seen in LRTI. Both short febrile illness and LRTI, which constituted the majority of diagnosis in Group 2, has similar TLC. 36 children in LRTI have leukocytosis (47.36%) At a threshold of 19,592.85 cells/cu.mm in Group 1 and 18,795.12 cells/cu.mm in Group 2, there was maximum tradeoff between sensitivity and specificity. Neither ROC curve nor likelihood ratios was able to determine a readily available TLC cutoff that proved to be an accurate predictor of SBI.

DISCUSSION

SBI was diagnosed with certainty in 49% of subjects in this study (48.6% in those with TLC between 15000 and 24900 cells / cu.mm and 8% when counts were >25000 cells / cu.mm). Shah and colleagues performed a retrospective case control study to evaluate febrile children with leukocytosis.[13] In their study, 25% of children with TLC > 25,000 cells/cu.mm (extreme leukocytosis) and 17% of children with TLC>15,000 cells/cu.mm (moderate leukocytosis) had proven bacterial infection. However, their patient population consisted of children between 2 to 24 months of age.

Brauner's study which included children between 3 to 36 months of age presenting with fever and leukocytosis revealed 39% of children with extreme leukocytosis and 15.4% of children with moderate leukocytosis had SBI.[14] The higher proportion of SBI in our series can be explained by inclusion of children as young as one month of age and an inherent bias in selecting the patients for the study as only 49% of the patients initially enrolled were finally included for analysis.

While UTI was the most common SBI that we encountered, pneumonia has been reported to be more common in literature.[13-16] In very large prospective cohort study including 15,781 subjects, pneumonia and UTI constituted 48% and 47% of diagnosis respectively in children with SBI.[15] Rudinsky and colleagues reported a 63.5% incidence of pneumonia as compared to 34.8% of

children with UTI.[16] They included only children with fever more than 102.3°F and that might have led to an increased representation of kids with pneumonia. In younger infants, UTI is the most common SBI.[17,18] Children with pneumonia are often initiated on early antibiotic therapy based on clinical picture alone and hence had lesser chance of inclusion in this study. In contrast children with UTI most often present with non-specific symptoms and even if a clinical diagnosis is made, antibiotic therapy is not started till at least urine routine examination results are available. The poor predictive value of leukocytosis in diagnosing SBI confirms the findings of existing evidence.

Rudinsky's study also used the ROC curve and AUC to determine the discriminatory power of TLC and did not find leukocytosis at any cutoff value to be helpful in predicting SBI.[16] Using similar study design, Shah and colleagues concluded that leukocytosis had poor discriminatory ability.[13] The prevalence of bacteremia has been shown to correlate with increase in TLC with an increase from 0.5% for white blood cell counts <15000 per cu. mm to as high as 18% for white blood cell counts < 30000 per cu.mm.[11] The incidence of bacteremia in our study is under estimated because of the restricted use of blood culture in our study group. The other predictive variable was the duration of fever. Greater duration of fever did not translate into an increased risk of SBI. There exists conflicting and inconclusive data to determine the association between duration of fever and SBI.[19] Only two studies have shown the duration of fever to be a predictor of SBI.[3,20] Other studies showed no significant association either in univariate or multivariate analysis.[21-24] Another systematic review of different studies by Bruel VD and colleagues also came to the conclusion that duration of fever was not a strong predictor of SBI.[8]

Transient hypoxia probably incites leukocytosis as a response to the stress. Mohebbi and colleagues, based on their analysis of 238 febrile children with seizures, state that the change in leukocyte count appeared more likely to be related to the underlying etiology of fever than to seizure itself.[25] Another group led by van Stuijvenberg studied 203 children with febrile seizures and recommended that leukocyte counts should be used to evaluate the underlying cause of fever because of misinterpretation of high leukocytes counts because of fever duration.[26]

Vomiting was also a common non-specific symptom in children with leukocytosis without SBI. The association is purely conjectural and there is no literature available pertaining to this observation. There are a few limitations in this study. We have taken a single but a commonly ordered test and attempted to find out its discriminatory power in predicting a group of conditions with wide variations in clinical manifestations, laboratory manifestations and diagnostic criteria. Even for individual infections standardization of diagnosis is extremely difficult.

We realize that leukocyte count alone is a very poor predictor of SBI, the next logical step will be to add more variables and develop a robust model that can be used in the clinical setting. One such diagnostic decision tool has been developed by Craig et al but has not been widely evaluated.[15] A multi factorial scoring system or computational model adapted to suit local conditions will be the best way to move forward in this regard.

To conclude, serious bacterial infections comprise only half of the febrile children with leukocytosis. The predictive accuracy of leukocytosis in diagnosing SBI is poor. Using different TLC cutoff points did not distinguish between patient with proven SBI and those without evidence of SBI. Neither the duration of fever nor the degree of leukocytosis could reveal underlying SBI. Vomiting and seizures probably incite stress mediated leukocytosis and are commonly encountered in febrile child with a high TLC without SBI. Further models with addition of clinical data and other surrogates of infection need to be developed to improve prediction of SBI in a febrile child.

Recommendations

- Clinical diagnosis of serious bacterial infection should be made with caution in a febrile child with leukocytosis
- Empirical antibiotics are not warranted based only on leukocytosis even in children with alarming symptoms like seizures
- Extremes of leukocytosis should prompt aggressive evaluation to rule out serious bacterial infections
- The value of additional markers like C-Reactive Protein and Pro- Calcitonin along with TLC needs to be evaluated further to predict serious bacterial infections with greater accuracy
- Computational models might also help in making a faster and more accurate prediction of underlying serious bacterial infection and this area needs to be studied in Indian children.

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