Pediatrics & Therapeutics

ISSN: 2161-0665

Kossiva et al., Pediat Therapeut 2014, 4:2
DOI: 10.4172/2161-0665.1000203

Research Article Open Access

Composite Bacterial Infection Index in the Evaluation of Bacterial versus Viral Infections in Children: A Single Centre Study

Kossiva L[1*], Gourgiotis Dl[2], Douna B[3], Marmarinos A[2], Sdogou T[1] and Tsentidis C[1]

[1]*Department of Pediatrics 'P&A Kyriakou' Children's Hospital, Medical School, Athens University, Greece*

[2]*Laboratory of Clinical Biochemistry-Molecular Diagnostics, Second Department of Pediatrics 'P&A Kyriakou' Children's Hospital, Medical School, Athens University, Greece*

[3]*Laboratory of Hematology, 'P&A Kyriakou' Children's Hospital, Athens, Greece*

[*]**Corresponding author:** Kossiva Lydia, Second Department of Pediatrics 'P&A Kyriakou' Children's Hospital, Thevon & Levadias Street, Goudi, Athens, 11527, Greece, Tel: +306977506306; E-mail: lydiakossiva@hotmail.com

Rec date: Mar 05, 2014, **Acc date:** Apr 24, 2014, **Pub date:** Apr 26, 2014

Abstract

Evaluation of febrile infants and children without source possess a great clinical concern as bacteremia is associated with morbidity and mortality in those ages. Differential diagnosis between bacterial and viral infections is of utmost importance for clinicians. Although several biochemical indices steer diagnosis towards bacterial agents, data are often indefinite. Haematological parameters were combined along with established infection indices in a low-cost and easily performed index that could confirm the presence of acute infection and we investigated whether that index could differentiate viral from bacterial infection in febrile infants and children.

We studied 69 children with infection and equal number of matched controls, during three years. Bacterial agents were demonstrated in 17 and viral pathogens in 52 patients. Complete blood count with differential, erythrocyte sedimentation rate and C-reactive protein were evaluated and combined into a single formula, constructing an index. Receiver Operating Characteristic curve analysis was performed to evaluate the index discriminating patients from controls as well as patients with bacterial from those with viral infection.

Therefore mentioned index value was significantly higher in febrile patients than controls. Bacterial infected patients had significantly higher values than those with viral infection. The composite index not only had high accuracy in discriminating patients from controls, but also in distinguishing bacterial from viral infections. If further and larger studies confirm these observations, the suggested index could be used as a low-cost, rapid and easily performed complementary index, discriminating bacterial from viral infection in the emergency department setting.

Keywords: Fever; Bacterial; Viral; Infection; Index; Diagnosis

Introduction

Infections in infants and children are very common. Differential diagnosis between viral and bacterial agents is important in order to avoid unnecessary antibiotic treatment. Classic infectious indices such as C - reactive protein (CRP), full blood count with differential and procalcitonin concentration are used in the evaluation of febrile episodes in children. The current bibliography demonstrates the superior performance of procalcitonin and CRP instead of the total white blood cell count and absolute neutrophil count [1-4].

The objective of our study was to evaluate whether the haematological leukocyte subpopulations in combination with the CRP and the Erythrocyte Sedimentation Rate (ESR) could reliably demonstrate the presence from the absence of acute infection. Additionally we questioned whether the application of the above composite formula could be helpful for the differential diagnosis between viral and bacterial infection in infants and young children who visit the emergency department due to fever without source.

Materials and Methods

Patients and study design

This case-control study was conducted during a three-year period between 2008 and 2011. Children of Greek origin and nationality participated voluntarily in the study. Informed consent from parents was obtained in advance. The Ethics Committee of our Hospital and the Athens University Medical School approved the research protocol. A total number of 138 children, admitted to the Athens' University 2nd Department of Pediatrics, were enrolled in the study. The study group consisted of children with fever and good clinical appearance, who visited the emergency department and admitted to the hospital for further evaluation. The subjects' parents filled in a detailed questionnaire. Children under antibiotic treatment and those with medical history of a chronic disease or other co-morbidities were excluded from the study.

According to the protocol, the study population was divided into two groups. Group A consisted of 69 infants and children (42 boys, mean age 28.28 ± 29.58 months, range 2 to 118 months) with acute febrile episode lasting 6 hours or less. The discrimination between bacterial and viral infection was based on the combination of positive blood/urine culture along with CRP >40 mg/dl and leukocytosis with

neutrophilia (white blood cell count >15.000/mm^3, neutrophils >60%). The viral infections were documented either by the presence of IgM antibodies or positive polymerase chain reaction tests (PCR). The most common infections were infections of the upper respiratory system due to inluenzae A or B, parainfluenzae, adenovirus or syncytial respiratory virus. The group B (control group) consisted of 69 children age and sex matched to study group. Those were otherwise healthy children without fever or infection which were admitted to the hospital for a routine surgical procedure (tonsilectomy, correction of strabismus). All children of the control group were afebrile with CRP <10mg/dl, leucocytes <10.000/mm^3, normal renal and liver function.

Methods

Full blood count with differential, ESR and CRP measurements as well as cultures of blood and urine and either IgM antibodies or PCR for viral agents were performed in all subjects using standard methods by the same laboratory within the first six hours from the onset of fever.

Statistical analysis

All statistical analyses and data management were performed using STATA for Windows v 8.5, (StataCorp, Texas, USA, 2006). Data are expressed as mean ± SD, median. Group data were compared using Mann-Whitney U test (independent samples) and $p<0.05$ was considered significant. Observing the data that were derived from study population we noted statistically significant marked differences between children with infection and control group and between children with viral and bacterial infection regarding neutrophils, lymphocytes, monocytes, ESR and CRP. We therefore used these parameters as discrimination markers between the mentioned above groups. Neutrophils were higher in children with bacterial infection compared to viral infected children. Respective changes were noted in lymphocyte and monocyte counts between groups. In order to maximize the effect of those differences we calculated the ratio of neutrophils (N) to the sum of lymphocytes (L) plus monocytes (M) and we further added the parameters of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). The new proposed formula (formula 1) was as follows:

$$\frac{N}{L+M} * CRP * ESR$$

We examined the optimal cutoff value of the Composite Bacterial Infection Index (CBII) in two distinct cases, using Receiver Operating Characteristic (ROC) curve analysis. First to discriminate between the absence and the presence of infection and secondly to discriminate between bacterial and viral infection. The area under the curve (AUC) is an index reflecting the overall accuracy of the diagnostic test. The AUC is actually the probability that the diagnostic test, which in our case is the composite index (CBII), correctly ranks a random pair of infected and noninfected children or a random pair of bacterial infected and viral infected children, based on their calculated Composite Bacterial Infection Index values.

Results

The first analysis was performed in the whole study population, consisting of 69 children with infection (group A) and 69 healthy children (group B). Neutrophils, Monocytes, ESR and CRP were significantly higher; whereas Lymphocytes were significantly lower in group A. Composite Bacterial Infection Index was also significantly higher in group A (Table 1). Most of the children were correctly classified between two groups without much loss (cost) in sensitivity and specificity. One typical Composite Bacterial Infection Index cutoff value of ≥ 32.45 can correctly classify 88.41% of study children with 85.51% sensitivity and 91.3% specificity. AUC value (± S.E.) of 0.9389 ± 0.02 can be considered highly accurate (Table 3).

The ROC scatterplot of Composite Bacterial Infection Index in diagnosis of infection in the whole study sample confirms a highly accurate test (Figure 1).

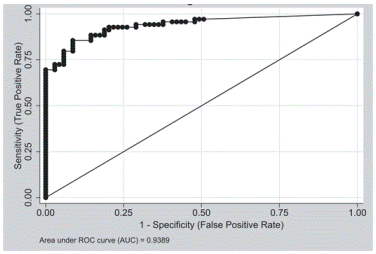

Figure 1: ROC curve of composite index in the diagnosis of infection in whole study sample

The second analysis was performed in the group of children with acute infection, consisting of 52 children with viral (group A1) and 17 children with bacterial infection (group A2). Neutrophils, ESR and CRP were significantly higher whereas Lymphocytes and Monocytes were significantly lower in children with bacterial infection (group A2). Composite Bacterial Infection Index was also significantly higher in children with bacterial infection (Table 2).

The second ROC analysis of Composite Bacterial Infection Index capability to discriminate between children with bacterial from those with viral infection also resulted in remarkable findings. To discriminate between viral or bacterial agent one typical Composite Bacterial Infection Index cutoff values of ≥ 2044 can correctly classify 86.96% of infected children with 82.35% sensitivity and 88.46% specificity.

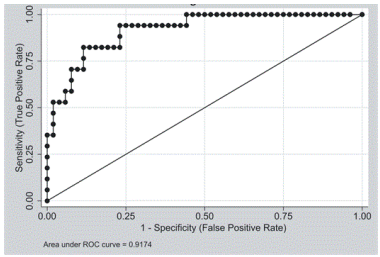

Figure 2: ROC curve of composite index in the diagnosis of bacterial infection

The AUC value (± S.E.) of 0.9174 ± 0.03 can similarly be considered highly accurate (Table 4). The ROC scatterplot of Composite Bacterial Infection Index in diagnosis of bacterial infection in the subgroup of children with infection indicates also a highly accurate test (Figure 2).

	A. Children with infection	B. Healthy children	p
N	69	69	
Gender male/female (%)	42(61%)/27(39%)	42(61%)/27(39%)	
Age in months	28.28(± 29.58), 18	29.60(± 29.99), 24	
Neutrophils (%)	57.16(± 19.6), 59	35.02(± 15.22), 33	<0.001
Lymphocytes (%)	29.23(± 17.47), 26	53.62(± 14.59), 55	<0.001
Monocytes (%)	11.4(± 5.39), 11	7.91(± 2.97), 7	<0.001
Erythrocyte Sedimentation Rate (mm/1h)	23.26(± 13.29), 20	6.34(± 3.13), 6	<0.001
C-Reactive Protein (mg/dl)	48.21(± 86.03), 23	2.26(± 4.62), 1	<0.001
Composite Bacterial Infection Index	7349.4(± 27715.3), 844.94	17.39(± 47.45), 0.845	<0.001

Table 1: Characteristics of the study population. Figures are expressed as mean (±SD), median

	A1. Children with viral infection	A2. Children with bacterial infection	p
N	52	17	
Gender male/female (%)	34(65.4%)/18(34.6%)	8(47%)/9(53%)	
Age in months	27.99(± 27.85), 21	29.17(± 35.31), 18	
Neutrophils (%)	52.4(± 18.68), 56.5	71.7(± 14.91), 66	<0.001
Lymphocytes (%)	32.92(± 17.99), 28	17.92(± 9.25), 16	0.0011
Monocytes (%)	12.26(± 5.25), 11	8.76(±5.1), 7	0.020
Erythrocyte Sedimentation Rate (mm/1h)	19.69(± 10.66), 17.5	34.11(± 14.88), 35	<0.001
C-Reactive Protein (mg/dl)	22.8(± 23.34), 16	125.9(± 145.62), 91	<0.001
Composite Bacterial Infection Index	933.7(± 1346.5), 496	26973.8(± 52113.8), 4725	<0.001

Table 2: Characteristics of the subgroups in children with infection. Figures are expressed as mean (± SD), median

Area Under the Curve (AUC) ± S.E. (95% C.I.)	
0.9389 ± 0.02 (0.899 – 0.978)	
Composite Bacterial Infection Index ≥	32.45
True-Positive Rate	85.51%
False-Positive Rate	8.7%
Correctly classified children	88.41%

Table 3: Cut off value of Composite Bacterial Infection Index in the diagnosis of infection

Area Under the Curve (AUC) ± S.E. (95% C.I.)	
0.9174 ± 0.03 (0.848-0.986)	
Composite Bacterial Infection Index ≥	2044
True-Positive Rate	82.35%
False-Positive Rate	11.54%
Correctly classified children	86.96%

Table 4: Cut off value of Composite Bacterial Infection Index in the diagnosis of Bacterial Infection

Discussion

Acute febrile infections are very common among infants and young children and a frequent reason for visits in primary care settings. Febrile children usually have viral self-limiting infections. Even though, many times they receive unnecessarily antibiotic treatment. Nowadays, the cost of antibiotics along with their over-the-count use is a common problem for every medical unit. In the emergency department the differentiation of viral from bacterial illness is based on the clinical appearance of the patient along with basic biochemical and hematological parameters. Many inflammatory indices have been studied in order to discriminate viral from bacterial infection in febrile infants and young children. This age group is considered highly

vulnerable to serious bacterial infections even though the vaccination against H. influenzae and S. pneumoniae had decreased the percentage of severe invasive disease.

The aim of our study was to evaluate the parameters from complete blood count in combination with CRP and ESR in order to find a low-cost, reliable and easily applicable formula to distinguish the presence from the absence of infection and to investigate whether the proposed formula might be used in differentiating bacterial from viral infection in the emergency department setting avoiding thus unnecessary antibiotic treatment.

Well established infection markers such as total white blood count, absolute neutrophil count, CRP and procalcitonin have been evaluated in different underlying pathologies [5-9]. Several studies had evaluated the total white blood count as a screening tool in children with serious bacterial infection with disappointing results. White blood cell count by itself was not an accurate predictor for bacterial infection as it has low sensitivity and specificity [10-16].

The most recent study by Hornik et al. evaluated the total white blood count, absolute neutrophil count, high immature – to – total neutrophil ratio and low platelet count in infants with late-onset sepsis and found that no complete blood count index possessed high sensitivity in anticipating late-onset sepsis reliably [10]. Gendrel et al. compared the concentration of CRP, procalcitonin, interleukin 6 (IL-6) and interferon – a in paediatric patients aiming at differentiation of viral from bacterial infection They concluded that the best parameter was procalcitonin (83% sensitivity and 93% specificity with a cutoff of 1.0 ng/ml) as the concentration of the CRP was above 10.0 in 47% and above 20.0 in 26.9% of children presenting with viral infection [8].

Pulliam et al. demonstrated that CRP performs better in predicting severe bacterial infection in febrile children less than 36 months of age compared to leukocyte and neutrophil count [14]. In a recent study performed by Andreola et al. on a group of patients under 36 months of age demonstrated that CRP and procalcitonin were the only factors that can predict severe bacterial infection [1]. The same results concerning the C-reactive protein and procalcitonin value in evaluating young children with bacterial or viral infection were demonstrated by the study of Olaciregui et al. [17]

In our study we evaluated the possible role of the combination of separate haematological parameters along with CRP and ESR (formula 1). Our goal was to evaluate the aforementioned formula as an indicator of the presence of acute infection and to examine whether the application of the Composite Bacterial Infection Index (CBII) in infants and young children could reliably discriminate the bacterial from viral agent. As showed, the ROC scatterplot of CBII in diagnosis of infection in the whole study sample yielded in a high accuracy of the proposed formula as far as the differentiation between the presence and the absence of infection is concerned. In the second analysis, which was performed in the group of children with acute infection, CBII was also significantly higher in children with bacterial infection. The second ROC analysis of CBII capability to discriminate bacterial from viral infection similarly yielded a highly accurate screening test. The application of CBII in the emergency department provides a cost-effective and easily performed solution in the evaluation of febrile children with good clinical appearance by without a source. Differential diagnosis between bacterial and viral infection may benefit further from the inclusion of CBII, Additionally the future use of the CBII in children with co-morbities (such as febrile neutropenic cancer children) might be useful in discriminating viral from bacterial infections in such a vulnerable group of patients.

Our study has several limitations due to the small number of patients of the study group. Additionally the CBII could not be applied in neutropenic cancer patients receiving chemotherapy or in neutropenic septic patients. In those cases the underlying pathology along with the deteriorated clinical condition are the basic criteria of the evaluation. Our goal was the detection of bacterial infection in a previously healthy and well-appearing febrile child.

In conclusion, we have shown, that CBII could be a reliable diagnostic tool to discriminate the presence from the absence of infection as well as differentiate viral from bacterial infection in infants and young children. The application of the CBII is superior to total white blood count or CRP alone for anticipating bacterial infection, especially in the emergency department where prompt decision making is of significant importance in order to avoid unnecessary antibiotic treatment. Before we can recommend BCII for more widespread use we recommend the formula to be used in larger studies that may aid in finding cutoffs with clinically useful predictive values.

References

1. Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, et al. (2007) Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. Peditar Infect Dis J 26: 672-677.
2. Manzano S, Bailey B, Gervaix A, Cousineau J, Delvin E, et al. (2011) Markers for bacterial infection in children with fever without source. Arch Dis Child 96: 440-446.
3. Galetto-Lacour A, Zamora SA, Gervaix A (2003) Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center. Pediatrics 112: 1054-1060.
4. Thayyil S, Shenoy M, Hamaluba M, Gupta A, Frater J, et al. (2005) Is procalcitonin useful in early diagnosis of serious bacterial infections in children? Acta Paediatrica 94: 155-158.
5. Arkader R, Troster EJ, Lopes MR, Junior RR, Carcillo JA, et al. (2006) Procalcitonin does discriminate between sepsis and systemic inflammatory response syndrome. Arch Dis Child 91: 117-120.
6. Enguix A, Rey C, Concha A, Medina A, Coto D, et al. (2001) 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 27: 211-215.
7. Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, et al. (2001) Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 164: 396-402.
8. Gendrel D, Raymond J, Assicot M, Avenel S, Lefèvre H, et al. (1998) Procalcitonin, C-reactive protein and interleukin 6 in bacterial and viral meningitis in children. Presse Med 27: 1135-1139.
9. Verbon-Maciolek MA, Thijsen SF, Hemels MA, Menses M, van Loon AM, et al. (2006) Inflammatory mediators for the diagnosis and treatment of sepsis in early infancy. Pediatr Res 59: 457-461.
10. Hornik CP, Benjamin DK, Becker KC, Daniel K Jr, Li J, et al. (2012) Use of the Complete Blood Cell Count in Late-Onset Neonatal Sepsis. Pediatr Infect Dis J 31: 803-807.
11. Bachur RG, Harper MB (2001) Predictive model for serious bacterial infections among infants younger than 3 months of age. Pediatrics 108: 311-316.
12. Ayoola OO, Adeyemo AA, Osinusi K (2002) Predictors of bacteraemia among febrile infants in Ibadan, Nigeria. J Health Popul Nutr 20: 223-229.

13. Bonsu BK, Harper MB (2003) Identifying febrile young infants with bacteremia: is the peripheral white blood cell count an accurate screen? Ann Emerg Med 42: 216-225.
14. Pulliam PN, Attia MW, Cronan KM (2001) C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. Pediatrics 108: 1275-1279.
15. Hsiao AL, Baker MD (2005) Fever in the new millennium: a review of recent studies of markers of serious bacterial infection in febrile children. Curr Opin Pediatr 17: 56-61.
16. Tugrul S, Esen F, Celebi S, Ozcan PE, Akinci O, et al. (2002) Reliability of procalcitonin as a severity marker in critically ill patients with inflammatory response. Anaesth Intensive Care 30: 747-754.
17. Olaciregui I, Hernandez U, Munoz JA, Emparanza JI, Landa JJ (2009) Markers that predict serious bacterial infection in infants under 3 months of age presenting with fever of unknown origin. Arch Dis Child 94: 501-505.