DOI: 10.4274/jarem.galenos.2018.2577
J Acad Res Med 2020; 10(1): 70-4

The Comparison of the Management Models for Identifying the Risk of Serious Bacterial Infection in Newborn Infants with a Newly Developed Scale

Ateşli Yenidoğan Bebeklerde Ciddi Bakteriyel Enfeksiyon Riskini Tanımlamada Kullanılan Yönetim Modellerinin Yeni Geliştirilmiş Bir Ölçek ile Karşılaştırılması

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Cite this article as: Bülbül A, Bülbül L, Zübarioğlu U, Ocak S, Uslu S. The Comparison of the Management Models for Identifying the Risk of Serious Bacterial Infection in Newborn Infants with a Newly Developed Scale. JAREM 2020;10(1): 70-4

ABSTRACT

Objective: We aimed to evaluate the major approach protocols of fever in febrile newborn and to define the incidence of serious bacterial infections (SBI) in febrile newborns.

Methods: This study was designed as a prospective observational cohort study and directed between January 2011 and December 2015. All newborns with a rectal temperature of ≥38 °C and admitted to the neonatal intensive care unit were eligible for participation in the study. Infants were evaluated and classified as low-risk using the Boston criteria, the Philadelphia criteria, and the Rochester criteria, and our newly developed İstanbul criteria. The protocol results were compared regarding calculations of sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and likelihood ratio (LR).

Results: During the study period, 328 infants were enrolled and the frequency of SBI was found as 38.4%. The leading etiology was fever of unknown origin with 43.6%, followed by urinary tract infection, dehydration, and bacteremia, accounting for 15.5%, 14%, and 5.8%, respectively. The highest sensitivity and NPV and the lowest negative LR were noted with the İstanbul protocol. The highest PPV was found in the Philadelphia and Boston protocols.

Conclusion: The low-risk criteria of febrile infant protocols are not sufficiently reliable to exclude the presence of SBI in febrile neonates. The low-risk criteria in our new protocol were detected to be more reliable and may be useful in excluding SBI in the neonatal period.

Keywords: Fever, newborn, management, serious bacterial infections, dehydration, bacteremia

ÖZ

Amaç: Ateşli yenidoğan bebeklerde ciddi bakteriyel enfeksiyon (CBE) sıklığının tanımlanması ve ateşli bebeğe yaklaşım protokollerinin ateşli yenidoğanlarda değerlendirilmesi amaçlandı.

Yöntemler: Prospektif, gözlemsel kohort çalışmamız Ocak 2011-Aralık 2015 yılları arasında planlandı. Çalışmaya yenidoğan ünitesine yatan ve rektal ateşi ≥38 °C olan tüm bebekler alındı. Bebekler Boston, Philadelphia, Rochester ve yeni geliştirdiğimiz İstanbul kriterlerine göre düşük risk sınıflandırmasına göre değerlendirildi. Protokol sonuçları sensitivite, spesifite, negatif prediktif değer, pozitif prediktif değer ve olasılık oranları olarak karşılaştırıldı.

Bulgular: Çalışma süresince 328 bebek dahil edildi ve CBE sıklığı %38,4 olarak saptandı. Etiyolojik tanılar arasında ilk sırada nedeni bilinmeyen ateş (%43,4) gelirken, bunu sırasıyla idrar yolu enfeksiyonu (%15,5), dehidratasyon (%14) ve bakteriyemi (%5,8) takip etmekteydi. En yüksek sensitivite, negatif prediktif değer ve en düşük olasılık oranı İstanbul protokolündeydi. En yüksek pozitif prediktif değer Philadelphia ve Boston protokollerinde saptandı.

Sonuç: Ateşli yenidoğan bebeklerde CBE'yi dışlamada protokollerdeki düşük risk kriterleri güvenilir yeterlikte değildir. Yeni protokolümüzdeki düşük risk kriterlerinin daha kabul edilebilir olduğu saptanırken bu kriterler yenidoğan döneminde CBE'yi dışlamada faydalı olabilir.

Anahtar kelimeler: Ateş, yenidoğan, tedavi, ciddi bakteriyel enfeksiyon, dehidratasyon, bakteriyemi

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Received Date/Geliş Tarihi: 18.10.2018 **Accepted Date/Kabul Tarihi:** 25.03.2019

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INTRODUCTION

Febrile neonates are at higher risk of serious bacterial infections (SBI). They often need to undergo extensive laboratory investigations and to be hospitalized because if a SBI in a neonate is not diagnosed and treated promptly, it may lead to undesirable consequences. However, the origin of fever in some cases is not infection or other serious diseases, and routine hospitalization or antibiotic treatment are not essential in all neonates. Additionally, iatrogenic complications and emotional stress in parents may increase due to the hospitalization of the infants (1). The widely accepted approach is to determine babies at high risk for SBI and hospitalization, who need intravenous antibiotic treatment, and babies at low risk for SBI, who require treatment on an outpatient basis with or without antibiotics (2-4).

Different approaches for the determination of low-risk neonates for SBI have been compared (5,6). There are three studies addressing the efficacy and safety of outpatient management of febrile infants who are considered to be at low risk for SBI (3,6,7). The Philadelphia, Boston, and Rochester protocols can be used for infants aged less than 90 days and with fever, but they are not suitable during the neonatal period (6,8). The universally acknowledged approach is to use the Rochester criteria, which assess clinical and laboratory evidence to identify low-risk and high-risk groups (8). Even though the negative predictive value (NPV) of these criteria for SBI is as high as 95-100%, the protocol is not adopted generally for outpatient follow-up of a newborn with fever (1). It is suggested that low-risk criteria are not satisfactory in excluding the presence of SBI in febrile neonates and all febrile neonates aged ≤28 days should be hospitalized and undergo a complete sepsis evaluation, and empirical intravenous antibiotic therapy should be given (9).

We developed a new protocol for febrile neonates, which differs from other protocols for febrile infants. First, our protocol included only febrile newborn babies (gestational age ≥35 weeks and within 28 days of life). Secondly, we added C-reactive protein (CRP) levels in the laboratory examination. Lastly, we defined dehydration in febrile newborn. The aims of our study were to evaluate the usefulness of our new protocol and to compare it with major protocols used for evaluating febrile infants.

METHODS

This study was designed as a prospective observational cohort study, directed from January 2011 to December 2015 (5 years) at a tertiary care university-affiliated education and research hospital in İstanbul. The study protocol was approved by: Şişli Etfal Training and Research Hospital Ethic Committee (approval number: 745-2011). Written informed consent was obtained from the parents. This is a prospective observational cohort study registered at the NIH ClinicalTrials.gov (http://www.clinicaltrials.gov), with number NCT03183531.

The study consisted of two steps. The first step included the evaluation of the clinical and laboratory characteristics of febrile neonates and described the etiology and causative organisms in febrile neonates, which was published (10). The second step was formed by the data obtained in the first step. We have developed a new protocol that can be applied to febrile newborn babies. In the literature, protocols that evaluate febrile babies include infants in the first 90 days of life, there is not any protocol including only newborn babies. The aim of the second step (present study) was to evaluate the usefulness of our new protocol and major protocols of febrile infants in the assessment of only newborns with fever.

Study Population

All neonates (aged 1 to 28 days) who were admitted to our neonatal clinic with a rectal temperature ≥38 °C (documented at medical evaluation) were eligible for the study. Gestational age <35 weeks, refusal for participation by parents, chromosome anomaly, the presence of a chronic illness, congenital anomaly (e.g., anencephaly, truncus arteriosus), admission to pediatric surgery, antibiotic use before hospitalization, and insufficient records were accepted as exclusion criteria.

Patients Data

The following data were collected from all babies included in the study: The demographic features (birth weight, age and gender), general evaluation (appearing good and ill), medical history, physical examination signs, laboratory analysis results, and exact diagnosis. All patients underwent laboratory examinations containing: blood count, CRP, serum chemistry and blood culture, urine analysis and urine culture (obtained by bladder catheterization). Lumbar puncture and cerebrospinal fluid assessment were performed in the presence of neurological signs. If there was evidence of respiratory tract infection, X-Ray was performed.

Definition of Serious Bacterial Infections

The SBI acceptance criteria were as follows: Firstly, the growth of a known pathogenic bacteria in cultures [bacteremia, meningitis, pneumonia and urinary tract infection (UTI)] and secondly any disease that is often associated with bacterial pathogens such as abscess, mastitis, omphalitis, acute otitis media and cellulitis. The diagnosis of pneumonia was made according to the lung X-Ray findings presented by the radiologist.

All samples were assessed using standard microbiological methods to culture. The sample was not processed for viral cultures. If the organism is known to cause disease in neonate, blood culture isolates are accepted to be pathogenic. The isolation of a single pathogen by catheterization with $>10^4$ colony-forming units/mL in urine was considered UTI. Leukocyte ≥10 cells/mm^3 in uncentrifuged urine or with the dipstick stripe a positive result for nitrite or leucocyte esterase was defined as positive urine analysis.

Viral agent evaluation methods: Newborn with respiratory signs such as runny nose, sneezing or coughing were assessed from nasopharyngeal secretions by influenza-Ag (immunoassay test produced by Dalian Rongbang Medical Healthy Devices, Spain) and respiratory syncytial virus antigen: Rapid immunochromatographic test produced by Prima lab SA, Switzerland).

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Definition of dehydration: All neonates were weighed at admission and weight loss was assessed according to the birth weight. Dehydration is defined as the weight loss more than twelve percent with a serum sodium level ≥145 mEq/L.

Our newly proposed protocol (İstanbul) includes: (1) Unremarkable medical history (no perinatal antibiotic use, no chronic disease, no hospitalization longer than the mother); (2) good appearance (unremarkable physical examination); (3) no focal physical signs of infection; (4) CRP level <1 mg/dL; (5) white blood cell count 5000-15.000/mm^3 and immature/total neutrophil ratio (I/T) <0.2; and (6) normal urine analysis.

Infants who met these criteria were considered to be at low risk for SBI. All infants were classified as low risk using the criteria of the Rochester, Boston, Philadelphia and İstanbul protocols. The criteria of the four protocols are presented in Table 1. Our newly created protocol is different because of its inclusion of only febrile newborns, the addition of CRP levels in the laboratory examination, and with defined dehydration in febrile newborn features (Table 1).

Statistical Analysis

Statistical analysis was performed with SPSS version 16.0 (SPSS, Chicago, IL, USA). Categorical variables are given in percentages with mean ± standard deviation. The positive predictive value (PPV), NPV, and likelihood ratio (LR) for SBI of the low-risk criteria were calculated using the standard statistical formula. All patients were evaluated according to the Boston, Philadelphia, Rochester, and İstanbul protocols, and the results were compared for sensitivity, specificity, NPV, PPV, and accuracy values for predicting SBI. Statistical significance was accepted as p<0.05.

RESULTS

In the study period, 412 febrile newborns aged ≤28 days, who were hospitalized due to fever, were evaluated. The flow diagram of study is presented in Figure 1. A total of 328 infants fulfilled the inclusion criteria of the study. Of 328 infants in the study, 184 (56.1%) were boys. The mean birth weight was 3214±492 gram, gestational age was 39.2±1.4 weeks, mean rectal temperature was 38.3±0.4 °C (lower and upper limit: 38-40 °C), and the mean age during admission to the hospital was 12.5±8.0 days (lower and upper limit 1-28 days). The ratio of SBI was found to be 38.4% during the study period.

Febrile illness with no detectable cause was the most common diagnosis which accounted for 43.6% of all cases. UTI (15.5%), dehydration (14%), bacteremia (5.8%) pneumonia (5.5%), viral

Table 1. Evaluation criteria and differences of Boston, Philadelphia, Rochester and İstanbul protocols

	Boston[6]	Philadelphia[11]	Rochester[8]	İstanbul
Study design	Prospective	Prospective	Prospective	Prospective
Study period	3 years (1987-1990)	5 years (1987-1992)	8 years (1984-1992)	5 years (2011-2015)
Patient group	**28-89 days**	**29-60 days**	**≤60 days**	**≤28 days**
Criteria				
Temperature, rectal, °C	≥38.0	≥38.2	≥38.0	≥38.0
History	No immunization within last 48 hours, No antimicrobial given within 48 hours	Not defined	No perinatal antibiotics, No underlying disease, Not hospitalized longer than the mother	No perinatal antibiotics, No underlying disease, Not hospitalized longer than the mother
Well appearance with unremarkable physical examination and absence of any local infection	**+**	**+**	**+**	**+**
Gestational age	**–**	–	≥37 weeks	**≥35 weeks**
Healthy before	**+**	Not defined	**+**	**+**
Absence of dehydration	**+**	Not defined	Not defined	**+**
Leucocyte count, cells/mm^3	**<20.000**	**<15.000**	**5.000-15.000**	**5.000-15.000**
Band/neutrophil ratio (I/T)	Not defined	**<0.2**	**ABC ≤1.500**	**<0.2**
Urine analysis, WBC/hpf	**<10**	**<10**	**≤10**	**<10**
CSF, leucocyte, cells/mm^3	**<10**	**<8**	**Not defined**	**<10**
Chest radiography	**No infiltration (if obtained)**	**No infiltration**	**No focal infiltration (if clinically indicated)**	**No infiltration (if clinically indicated)**
Stool examination	Not defined	No blood or leucocyte (if indicated)	≤5 leucocyte (if indicated)	<5 leucocyte (if indicated)
CRP	--	--	--	<1 mg/dL

ABC: Absolute band form, WBC: white blood cells, CSF: cerebrospinal fluid, CRP: C-reactive protein

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respiratory tract infection (4.0%), and meningitis (3.7%) were the next most common diagnoses.

The comparison of sensitivity, specificity, PPV, NPV, and LR for the four protocols is presented in Table 2. The highest sensitivity and NPV and the lowest LR (-) were observed in İstanbul protocol, whereas high specificity and the highest LR (+) were detected in the Boston protocol. The highest PPV was found in the Philadelphia and Boston protocols (Table 2).

DISCUSSION

In current protocols for the evaluation of fever in infants aged ≤3 months, if no risk of severe bacterial infection is determined, infants can be observed without admission with close examination and monitoring. However, this approach is widely deemed as unacceptable in the neonatal period. The main purpose of our study was to investigate whether these protocols were suitable for monitoring febrile newborn infants.

The management of febrile illnesses in babies aged <90 days vary considerably among physicians. The reason for this variation is associated with the wide range of management protocols suggested during the last few decades (6-8,11). The current suggestions for the assessment and management of young febrile infants are based on studies conducted in the late 1980s and early 1990s (12). The globally accepted approach is to determine infants at high risk for SBI and in need of hospitalization for intravenous antibiotic treatment, and also to determine infants at low risk, who can safely go through outpatient care with or without antibiotics therapy (4). Three main studies reported the efficacy and safety of outpatient management of febrile infants considered at low risk for SBI (6,8,11). The rate of newborn infants in these three studies was 10-15% of all infants, which is very low. In a comprehensive review on SBI identification in infants younger than 90 days, it was stated that the Boston and Philadelphia protocols were more accurate when applied to older infants rather than neonates. The Rochester protocol, on the other hand, was more accurate for neonates than older infants (12).

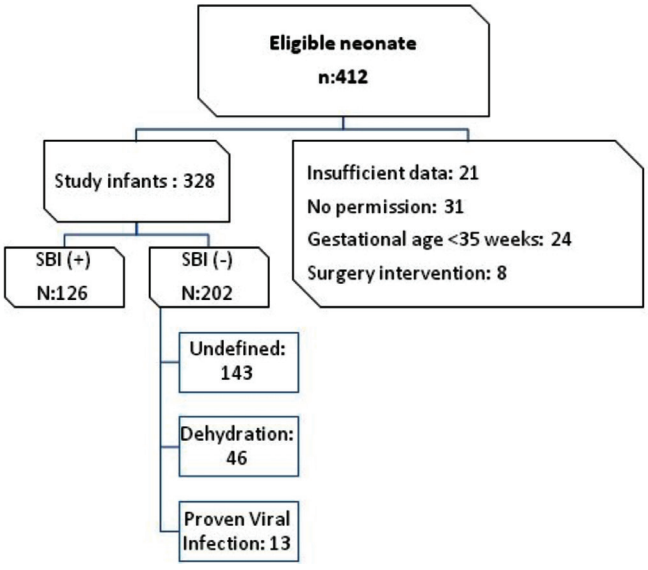

Figure 1. Flow diagram of the study
SBI: Serious bacterial infections

The management and treatment of newborns with fever vary widely among centers (13). These differences indicate the need of national or international guidelines for the evaluation of fever in neonatal period. Accordingly, given that the prevalence of SBI is higher in neonatal period, generally accepted practice in most centers is a full sepsis evaluation and hospitalization (14).

The prevalence of SBI in infants less than 3 months with fever is about 7.1-19.7%. The prevalence of SBI is higher in neonatal period (9-28%) than in infants aged 2-3 months (7.1%) (15-21). Garcia et al. (17) reported SBI prevalence as 31.9%, 33.3%, and 18.3% in infants aged 7-14 days, 15-21 days, and >21 days, respectively. In our study the incidence of SBI was high and our findings supported that SBI was seen more frequently in the newborn babies.

Several protocols that bring clinical and laboratory criteria together to diagnose young infants (<90 days of life) at low risk for SBI, who can be safely managed as outpatients, have been published. The use of these protocols are advised for different age groups of infants (Philadelphia: 29-60 days; Rochester: 60 days or younger; Boston: 28-89 days) (6,8,11). Our protocol was designed to be used only in newborn (0-28 days) babies. The main aim of our study was to evaluate febrile newborns in their first month of life according to these protocols. When evaluated separately, the neonates did not show similar test characteristics with older children or the whole group aged <3 months. The combined

Table 2. The effectiveness of the protocols in identifying serious bacterial infections in febrile neonates

Protocols	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	LR (+)	LR (–)
Boston	61.6% (54-68.7)	81.7% (75.1-86.9)	77.1% (69.2-83.5)	68% (61.2-74.1)	71.7% (66.5-76.3)	3.37	0.47
Rochester	47.6% (40.1-55.2)	72% (64.6-78.3)	62.9% (54.1-70.9)	57.8% (51-64.4)	59.8% (54.4-64.9)	1.70	0.73
Philadelphia	67.7% (60.2-74.4)	79.9% (73.1-85.3)	77.1% (69.6-83.2)	71.2% (64.3-77.3)	73.8% (68.8-78.2)	3.36	0.41
İstanbul	81.7% (75.1-86.9)	56.1% (48.4-63.5)	65% (58.3-71.2)	75.4% (67.1-82.2)	68.9% (63.7-73.7)	1.87	0.33

CI: Confidence interval, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio

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laboratory and clinical parameters demonstrated lower sensitivity in neonates as compared to older groups. Likewise, the false-positive rate for SBI tended to be higher in neonates compared to older infants (12). The comparison of different diagnostic tests across the age groups (≤28 days vs >29 days) was possible only for a few selected criteria reported in 14 studies. The Boston criteria and Philadelphia protocol have shown higher sensitivity, lower specificity, smaller PPV, and similar NPV when applied to older infants (age >28 days) compared to newborn babies for overall SBI or bacteremia. Contrarily, the Rochester criteria were more accurate (higher sensitivity, specificity, and PPV) in neonates than in older infants for SBI or bacteremia. The false positive ratio for SBI (i.e., the percentage of infants with SBI classified as low risk) tended to be higher for neonates (1.0% to 6.25%) versus older infants (0% to 5.4%) (12).

Study Limitations

This study has some limitations. The study included only febrile neonates but many more neonates presented with or developed SBI without fever. Neonates with non-febrile sepsis were not included in the study. Further studies with larger patient series are needed to validate our new protocol.

CONCLUSION

In this prospective observational study, we performed a comparison of the results of four protocols (Rochester, Philadelphia, Boston and İstanbul) in 328 febrile neonates. Our study demonstrated that the incidence of SBI in febrile newborns was encountered with higher rates. The most common etiology was UTI in neonates with SBI. The low-risk criteria of the Rochester, Philadelphia, and Boston protocols are not sufficiently reliable to exclude the presence of SBI in febrile neonates. In our study, with the inclusion of CRP, NPV was found at the highest level. The low-risk criteria in our newly created protocol were detected as more reliable and may be useful for excluding SBI in the neonatal period.

Ethics Committee Approval: The study protocol was approved by : Şişli Etfal Training and Research Hospital Ethics Committee (approval number: 745-2011).

Informed Consent: Written informed consent was obtained from the parents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.B., L.B., U.Z., S.O., S.U.; Design - A.B., L.B., U.Z., S.O., S.U.; Supervision - A.B., L.B., U.Z., S.O., S.U.; Resource - A.B.; Materials - S.O., U.Z.; Data Collection and/or Processing - L.B., U.Z.; Analysis and/ or Interpretation - L.B., A.B.; Literature Search - S.O., L.B.; Writing Manuscript - L.B.; A.B., S.O.; Critical Reviews - L.B.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Çalışma protokolü Şişli Etfal Eğitim ve Araştırma Hastanesi Etik Komitesi tarafından onaylandı (onay numarası: 745-2011).

Hasta Onamı: Yazılı bilgilendirilmiş onam velilerden alınmıştır.

Hakem Değerlendirmesi: Editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazarlık Katkıları: Fikir - A.B., L.B., U.Z., S.O., S.U.; Tasarım - A.B., L.B., U.Z., S.O., S.U.; Denetleme - A.B., L.B., U.Z., S.O., S.U.; Kaynaklar - A.B.; Malzemeler - S.O., U.Z.; Veri Toplanması ve/veya İşlemesi - L.B., U.Z.; Analiz ve/veya Yorum - L.B., A.B.; Literatür Taraması - S.O., L.B.; Yazıyı Yazan - L.B.; A.B., S.O.; Eleştirel İnceleme - L.B.

Çıkar Çatışması: Yazarların beyan edecek çıkar çatışması yoktur.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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