Original Article

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Assessment of Febrile Neonates According to Low Risk Criteria for Serious Bacterial Infection

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Abstract

Objective: It is propounded that febrile neonates with low risk criteria (LRC) can be carefully observed without parenteral antimicrobial therapy; but yet, reliability of LRC to exclude serious bacterial infection (SBI) is uncertain.

Methods: The records of all febrile term neonates, seen in the emergency room and admitted in neonatal ward of 17 Shahrivar children's hospital of Rasht, Iran from January 2004 to January 2009 were reviewed. All of them underwent full sepsis workup. The prevalence of SBI in total population and LRC positive and negative neonates were calculated

Findings: A total of 202 records of previously healthy febrile neonates were evaluated. SBI was shown in 38 (18.8%). The most common type of SBI was urinary tract infection (UTI). Sixty-two (31%) neonates had LRC, and only one (1.6%) had SBI (UTI with E. coli). SBI was significantly more common in neonates without LRC (26.6% versus 1.6%, $P<0.001$). The negative predictive value (NPV) of LRC to exclude SBI was 98.4% (95%confidence interval: 96.7% to 100%).

Conclusion: These findings suggest that LRC may be relied upon to exclude SBI in febrile neonates. We propose that all febrile neonates be admitted, ill or LRC negative neonates should undergo a full sepsis work up and be administered systemic antibiotics immediately. LRC positive neonates should be under close observation.

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Key Words: Low-risk criteria; Neonate; Serious bacterial infection

Introduction

Serious bacterial infection (SBI) is prevalent in neonatal period. It is difficult to identify all newborns with SBI. As infection is frequently associated with fever in neonatal period, a cautious approach to the febrile neonate is needed. Meningitis and bacteremia as well as other serious bacterial infections are more common than any other time during life in neonatal period, but presenting signs of these infections are often subtle and nonspecific [1].

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Several studies have shown that a combination of patient's history, physical examination and laboratory findings can be used to predict febrile neonates who are at low risk for SBI [2] and infants with low risk criteria (LRC) can be carefully observed without parenteral antibiotic therapy as inpatients [3,4] or outpatients [1].

LRC are known as the Rochester criteria for the evaluation of febrile neonates (Table 1). There are several studies about the reliability of LRC in excluding SBI. Although the negative predictive value (NPV) of LRC for SBI has been reported as high as 95-100%, no protocol has been universally adopted [2].

The aim of this study was to assess the reliability of LRC to identify neonates unlikely to have SBI, and also report of some characteristics of febrile neonates with and without SBI.

Subjects and Methods

Retrospectively we reviewed the records of all febrile neonates (≤28 days of age), seen in the emergency room and admitted at 17 Shahrivar Children's Hospital in Rasht, Iran from January 2004 to January 2009. This study was approved by School of Medicine Ethics Committee, Guilan University of Medical Sciences.

Neonates with a rectal temperature of ≥38.5°C measured in emergency room were enrolled in our study. Exclusion criteria were prematurity, positive history of admission or receipt of antibiotics and chronic disease.

All febrile neonates underwent the same sepsis workup including blood, urine and cerebro-spinal fluid (CSF) cultures, complete blood cell count with differential evaluation, C-reactive protein (CRP), urine analysis with microscopic examination of urinary sediment, chest X-ray (when respiratory signs or symptoms were present), and stool examination and culture (only for infants with diarrhea). Urine culture was obtained by suprapubic bladder aspiration or by transient bladder catheterization.

All neonates were treated with systemic antibiotics after obtaining cultures. A questionnaire was designed for each neonate. SBI was defined by:

1) Growth of any bacterial pathogen in one or more of CSF, blood, urine, stool cultures.

2) Any disease commonly associated with bacterial pathogens including pneumonia or soft tissue infections (mastitis, cellulitis, omphalitis) [3]. Pneumonia was diagnosed according to clinical and radiological findings in chest X-ray. According to previous studies, otitis media was not considered as a SBI. Isolation of any bacteria from a bladder aspirate or counts of 10^3 or higher colony-forming units per milliliter of catheterized

Table1: The Rochester criteria

1) Infant appears generally well
2) Infant has been previously healthy
-born at term (≥37 weeks gestation)
- did not receive perinatal antibiotics therapy
-was not treated for unexplained hyperbilirubinemia
-has not received antimicrobial agents
-has not been previously hospitalized
-has no chronic illness
- was not hospitalized longer than mother
3) No evidence of skin, bone, joint or ear infection
4) Laboratory values
- peripheral blood WBC count 5-15×10³/mm³
- absolute band cells count <1500/mm³
- ≤10 WBC per high power field on microscopic examination of span urine sediment
- ≤5 WBC per high power field on microscopic examination of a stool smear (only for infants with diarrhea)

WBC: White blood cell

urine was considered as UTI [5].

We measured qualitative CRP, so positive CRP was considered as levels ≥12 mg/dl. LRC was defined according to all of the items in Rochester criteria (Table 1).

We applied the t-test, chi square test (Fisher exact where applicable); 95% confidence interval ($^{95\%}$CI) was calculated using the established mid-p method. *P*-value <0.05 was taken for significant. Sensitivity was the rate of a positive test in cases with disease and negative predictive value was the rate of no disease in infants with negative test.

Findings

A total of 253 previously healthy febrile neonates were presented to our emergency room during the period of study and all of them were admitted in neonatal ward. Fifty-one records containing incomplete data were excluded. Thus, the study was done on 202 newborns, of which 107 (52%) were males. SBI revealed in 38 (18.8%) neonates. Risk of SBI and some demographic and clinical parameters of neonates are shown in Table 2.

Mean age in SBI group was 15.8 days and 11.8 days in group without SBI (*P*=0.01).

Positive CRP was more sensitive than leukocytosis and leukopenia for predicting SBI (65.2% versus 21% and 7.9% respectively) but *P*-value was not significant. There were no cases with absolute neutrophil count >1500 in our study. UTI was diagnosed in 17 (44.7%) neonates with SBI. There were only 2 circumcised neonates, one in group with SBI and the other in group without SBI. Frequencies of different types of SBI and their causative agents are shown in Table 3. Sixty-three cases (31%) neonates had LRC (LRC+) and only one of them had SBI (UTI with E. coli). SBI was significantly more common in cases without LRC (LRC-) (26.6% versus 1.6% *P*<0.001). The NPV of LRC to exclude SBI was 98.4% ($^{95\%}$ CI: 96.7% to 100%).

Sensitivity, specificity and positive predictive value (PPV) of LRC to identify SBI was 2.63%, 62.2% and 1.6%, respectively.

Discussion

The findings of our study suggest that LRC with NPV of 98.4% may be relied upon to exclude SBI in febrile neonates. SBI was diagnosed in 1.6% of LRC+ neonates and 26.6% of neonates without LRC.

Table 2: Demographic, clinical and laboratory characteristics of neonates with and without SBI

Characteristics		SBI+ Frequency (%)	SBI- Frequency (%)	Total Frequency	*P*-value
Gender	Male	26 (24.3)	81 (75.7)	107	0.047
	Female	12 (12.6)	83 (87.4)	95	
Age (days)	≤7	7 (8.4)	76 (91.6)	83	0.002
	>7	31 (26.1)	88 (73.9)	119	
Fever (rectal)	38.5-39.4 c	29 (18.8)	125 (81.2)	154	0.99
	≥39.5 c	9 (18.8)	39 (81.2)	48	
C-Reactive Protein[1]	+ 1	15 (33.3)	30 (66.7)	45	0.008
	-	23 (14.6)	134 (85.4)	157	
Leukocyturia (/mm3)	<10	29 (15.3)	161 (84.7)	190	<0.001
	≥10	9 (75)	3 (25)	12	
Leukopenia[2]	+	3 (23.1)	10 (76.9)	13	0.7
	-	35 (18.5)	154 (81.5)	189	
Leukocytosis[3]	+	8 (38.1)	13 (61.9)	21	0.02
	-	30 (16.6)	151 (83.4)	181	

[1]Positive CRP: levels ≥12 mg/dl; [2]Leukopenia: WBC count less than 5000/mm_3 in peripheral blood; [3]Leukocytosis: WBC count more than 15000/mm_3 in peripheral blood

Table 3: Different types of SBI among 38 neonates*

Bacterial disease	Organism	Number of cases (%)
Sepsis		**6 (15.8)**
	Staph. epidermidis	**2**
	Staph. aureus	**1**
	Staph. hemolyticus	**1**
	Klebsiella	**1**
	Enterobacter	**1**
Sepsis + UTI		**1 (2.6)**
	Enterobacter	**1**
Sepsis + meningitis	Klebsiella	**1 (2.6)** **1**
Pneumonia		**10 (26.3)**
Omphalitis		**1(2.6)**
UTI		**17 (44.7)**
	E. coli	**9**
	Enterobacter	**5**
	Klebsiella	**3**
Mastitis		**2 (5.3)**
Total SBI cases		**38 (100)**

*Only one UTI with E. coli was LRC+ / Staph: Staphylococcus
UTI: Urinary Tract Infection / SBI: Serious bacterial infection

The overall incidence of SBI was 18.8%. UTI was the most common type of SBI and CRP was more sensitive than white blood cell (WBC) count to identify SBI. The reliability of LRC in febrile neonates has been previously evaluated in some investigations. The specific clinical criteria used are essentially like each other, with only minor differences. The findings of each study have led to different management recommendations.

Wu et al in their study on 112 febrile neonates with LRC found that the rate of SBI was 2.7% (UTI was the most common SBI). The NPV of LRC to exclude bacterial infections was 97.3%. The authors concluded that LRC can identify febrile outpatient neonates unlikely to have bacterial infections and selected febrile neonates can be managed as outpatients with careful observation at home and close follow-up, but further studies should be done [1]. Also Marom et al showed that NPV for SBI of the LRC was 99.4% and 0.6% of febrile neonates with LRC and 48.6% of LRC negative neonates had SBI. They suggested that febrile neonates with LRC might be observed without antibiotic therapy in the first instance in hospital but for verification, further studies are needed [2].

On the other hand, Schwartz et al in their study found that the NPV of LRC for SBI was 93.8%. The prevalence of SBI among LRC+ infants was 6.2%. UTI was the most common SBI. The higher rate of SBI in their study was due to the significant number of male infants who underwent ritual circumcision on the 8th day of life. This procedure may cause UTI to develop during the subsequent 1-12 days. So they concluded that LRC are not sufficiently reliable to exclude the presence of SBI. All febrile neonates should be hospitalized, undergo a full sepsis evaluation and receive empirical intravenous antibiotic therapy [6]. Kadish et al showed that 3.5% of febrile LRC+ neonates had SBI and NPV of LRC to exclude SBI was 97%. So all febrile neonates should be admitted [7].

The overall rate in previous reports of SBI is 6.5% to 28% of febrile neonates [2,6]. Enteroviral infection may be a major cause of febrile episodes in infants younger than 3 months[8]. Unfortunately, we had not access to viral culture facilities. UTI was the most common SBI in febrile neonates in our study in accordance with results of other investigators [2,6-9]. Furthermore, UTI is the most common missed SBI in febrile LRC+ neonates. So it is suggested that urine culture should be obtained in every febrile neonate [2]. As many as 50% of infants with UTI may have a normal urine analysis [3]. In our study 44% of neonates with UTI had <10 WBC in urine analysis. We had no positive nitrites in urine of neonates with UTI, because urinary nitrites are a poor indicator of UTI, with a sensitivity of 10% in infants under 2 years of age due to very frequent voiding [6].

According to our study and previous studies, it may be suggested that CRP is more sensitive to predict SBI than WBC or absolute neutrophil count in febrile neonates [9], also it is mentioned that CRP is superior to interlukin-8 and granulocyte colony stimulation factors level to predict SBI in febrile infants <3 months at initial survey [10].

Wu et al suggested that LRC+ neonates under observation who have a persistent fever >48 hours should receive systemic antibiotics after sepsis workup [1], but more studies are needed to

determine the exact necessary time for observing these neonates.

Conclusion

These findings suggest that LRC may be relied upon to exclude SBI in febrile neonates. We suggest that all febrile neonates should be admitted because we cannot provide careful observation for them at home. Ill or LRC- neonates should undergo a full sepsis workup and be administered systemic antibiotics. Not ill neonates should have CBC with differential evaluation, CRP, urine analysis and urine culture, LRC+ neonates should be under close observation during hospitalization, if their clinical status deteriorates or their urine culture shows bacterial growth, they should undergo full sepsis workup and be administered systemic antibiotics. But yet, we need further studies involving a large group of neonates to verify these recommendations, because delay in treatment of SBI may worsen the prognosis.

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Conflict of Interest: None

References

1. Wu W, Chen H, Chung P, et al. Ambulatory care of selected febrile outpatient neonates unlikely to have bacterial infections. *Int Pediatr* 2004; 19(1):52-6.
2. Marom R, Sakran W, Antonelli J, et al. Quick identification of febrile neonates with low risk for serious bacterial infection: an observational study. *Arch Dis Child Fetal Neonatal Ed* 2007; 92(1):15-8.
3. Jaskiewiez JA, McCarthy CA, Richardson AC, et al. Febrile Infant collaborative study groups. Febrile infants at low risk for serious bacterial infection - An appraisal of the Rochester critical and implications for management. *Pediatrics* 1994; 94(3):390-6.
4. Chiu CH, Lin TY, Bullard MJ. Identification of febrile neonates unlikely to have bacterial infections. *Pediatr Infect Dis J* 1997;16(1):59-63.
5. Edwards MS. Postnatal bacterial infections. In: Martin RJ, Fanaroff AA, Walsh MC (eds). Neonatal–Perinatal Medicine. 8th ed. Philadelphia: Mosby. 2006; P:815.
6. Schwartz S, Raveh D, Toker O, et al. A Week-by-week analysis of the low-risk criteria for serious bacterial infection in febrile neonates. *Arch Dis Child* 2009;94(4):287-92.
7. Kadish HA, Loveridget B, Tobeyt J, et al. Applying outpatient protocols in febrile infants 1-28 days of age: can the threshold be lowered? *Clinical Pediatr* 2000;39(2):81-8.
8. Shin SH, Choi CW, Lee JA, et al. Risk Factors for serious bacterial infection in febrile young infants in a community referral hospital. *J Kor Med Sci* 2009;24(5):844-8.
9. Bakes K. C-reactive protein level predicts SBI in febrile neonates. Available at: http://emergency–medicine.Jwatch.org/cgi/ content/full/2010/115/3. Access date: 3.1.2010
10. Chen HL, Hung CH, Tseng HI, et al. Circulating chemokine levels in febrile infants with serious bacterial infections. *Kaohsiung J Med Sci* 2009; 25(12):633-9.