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Performance of Low-Risk Criteria in the Evaluation of Young Infants With Fever: Review of the Literature

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WHAT'S KNOWN ON THIS SUBJECT: Fever in neonates is common. The rate of SBIs in young infants may be as high as 12%. Low-risk criteria have been developed to aid in management decisions for well-appearing, febrile young infants.

WHAT THIS STUDY ADDS: Although the total risk of SBI in febrile young infants in this review was 10.9%, low-risk criteria allowed 30% of these patients to be treated safely without empiric antibiotic therapy.

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KEY WORDS
fever, infant, bacteremia, meningitis, urinary tract infection

ABBREVIATIONS
SBI—serious bacterial illness
CI—confidence interval
RR—relative risk
UTI—urinary tract infection

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abstract

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OBJECTIVE: The goal was to determine the performance of low-risk criteria for serious bacterial illnesses (SBIs) in febrile infants in prospective studies in which empiric antibiotic treatment was withheld, compared with studies (prospective and retrospective) in which empiric antibiotic treatment was administered.

METHODS: A search of the English-language literature was undertaken by using a PubMed database and reference lists of relevant studies of fever, low-risk criteria, and SBIs. Studies of infants >90 days of age, infants with specific infections, or infants with additional risk factors for infection were excluded. Publications were categorized as retrospective, prospective with empiric antibiotic treatment for all patients, or prospective with antibiotics withheld. The relative risk of SBI in high-risk versus low-risk patients was determined for pooled data in each category. The rates of SBIs in low-risk patients in each category were compared.

RESULTS: Twenty-one studies met the inclusion criteria. In prospective studies in which patients were cared for without empiric antibiotic treatment, 6 patients assigned to the low-risk category had SBIs; all recovered uneventfully. The rate of SBIs in these low-risk patients was 0.67%. The relative risk of SBIs in high-risk versus low-risk patients in these studies was 30.56 (95% confidence interval: 7.0–68.13). The rate of SBIs in low-risk patients in all studies was 2.23%. The rate of SBIs in low-risk patients in the prospective studies without empiric antibiotic treatment was significantly different from the rate in all other studies (0.67% vs 2.71%; $P = .01$).

CONCLUSIONS: Low-risk criteria perform well in prospective studies in which empiric antibiotic treatment is withheld. These criteria allow ~30% of young febrile infants to be observed without antibiotic treatment, thus avoiding unnecessary hospitalization, nosocomial infection, injudicious use of antibiotics, and adverse effects of antibiotics. *Pediatrics* 2010;125:228–233

Fever in very young infants is a common and important problem. Neonates have unique vulnerabilities to infection because of their immature immune systems and incomplete barriers to invasion. The rate of serious bacterial illnesses (SBIs) in young febrile infants has been reported to be between 8.5% and 12%.[1–3]

Before 1985, it was recommended that all febrile infants (<60 days of age) be hospitalized and treated with parenteral antibiotic therapy after a full sepsis evaluation, because various criteria used to identify "high-risk" infants were insufficiently sensitive to identify all infants with SBIs.[4–6] However, the approach of hospitalizing and treating all febrile young infants with empiric antibiotic therapy had the disadvantages of unnecessary hospitalizations, nosocomial infections, injudicious use of antibiotics, emergence of resistant bacteria, and adverse effects of antibiotics.[7,8]

During the late 1980s and early 1990s, investigators changed strategies and attempted to identify febrile infants who were at low risk for SBIs and might be treated with close observation (inpatient or outpatient) without antibiotic treatment.[3,9–16] After the development of various low-risk criteria, several groups undertook studies to validate the criteria in their own populations.[17–27] The designs of those studies alternated between retrospective and prospective, with variable approaches to empiric use of ceftriaxone. We hypothesized that prospective studies that implemented a strategy of observation without antibiotic treatment for low-risk infants, thereby relying on meticulous evaluation and careful decision-making, would show significantly better performance of low-risk criteria than would studies that continued to treat all patients (prospectively or retrospectively), regardless of risk stratification.

METHODS

We searched the English-language literature for original articles studying low-risk criteria for SBIs in febrile infants between 0 and 90 days of age. A National Library of Medicine PubMed database search for articles was performed by using combinations of the following search terms: "low risk criteria," "criteria," or "risk"; "serious bacterial illness," "serious bacterial infection," "bacterial infection," or "bacteremia"; and "fever" or "fever without source".Studies were limited to humans, infants, and publication after 1985.

The search criteria identified 740 articles. Bibliographic references from the relevant studies (original research and review articles) were reviewed for additional citations. Articles were excluded on the basis of abstracts if they focused on infants >90 days of age, patients with underlying conditions (such as patients with sickle cell disease, neutropenia, malignancy, central vascular catheters, or other immunocompromised states), or patients with a single focus of bacterial infection (eg, urinary tract infection [UTI] or meningitis). Sixty-three publications were reviewed carefully for inclusion criteria, definition of SBIs, and evaluations performed for study patients. The components of the low-risk criteria used in each study were reviewed and compared with the original Rochester Criteria[9] (Tables 1 and 2). Studies with overlapping subjects were excluded.

Articles were grouped according to type of study, and total patients were aggregated. The categories of studies were prospective without antibiotic treatment of low-risk infants, prospective with antibiotic treatment of low-risk infants, and retrospective.

Portions of studies using different management plans for low-risk infants were classified accordingly. Data were extracted from the tables and text of each study and included the number of low-risk infants, the number of high-risk infants, the number of SBIs in each group, types of SBIs, and the outcomes of low-risk infants with SBIs. The random-effects method described by DerSimonian and Laird[28] was used to estimate overall relative risks (RRs) and corresponding 95% confidence intervals (CIs). This method accounts for the heterogeneity of studies through a statistical parameter representing interstudy variation.

Heterogeneity between studies was assessed by using the Q statistic, as well as graphic techniques. The β-binomial model for overdispersed data[29] was used to estimate pooled rates of SBIs for low- and high-risk patients. Comparison of pooled rates between groups was performed by using a likelihood ratio test. Linear regression analysis was used to evaluate the trend in the proportions of infants designated as being at low risk over time.

TABLE 1 Rochester Criteria for Infants at Low Risk of SBIs[9,27]

1. Previously healthy term infant without perinatal complications and with no previous antibiotic treatment
2. Normal physical examination findings (including no otitis media)
3. White blood cell count: 5000–15 000 cells per mm^3
4. Band count: <1500 cells per mm^3
5. Urinalysis: <10 white blood cells per high-power field in centrifuged catheterized specimen

No comment about stool

Reference 9 established the original Rochester criteria. Reference 27 used identical laboratory criteria and slightly different inclusion criteria.

RESULTS

Twenty-one studies met inclusion criteria; 14 were prospective studies (Tables 3 and 4) and 7 were retrospective (Table 5).[3,9–27,30] Among the prospective studies, 9 treated low-risk patients empirically with antibiotics, 4 monitored low-risk patients without antibiotic treatment, and 1 used both strategies.

TABLE 2 Variations of Rochester Criteria

Type of Low-Risk Criteria	Differences From Original Rochester Criteria	References
Rochester 2	If diarrhea, ≤5–10 WBCs per high-power field in stool	10, 17, 18, 20, 30
Modified Rochester	Normal inflammatory markers (C-reactive protein levels or ESR)	13, 19, 21
Milwaukee	CSF: <10 WBCs per mm^3; WBC count: <15 000 cells per mm^3 (no band criteria); urinalysis: ≤5–10 WBCs per high-power field, no bacteria; urine dipstick: negative LE/nitrite	14
Philadelphia	Infant observation score[33]: <10; WBC count: <15 000 cells per mm^3 (no band criteria); urinalysis: <10 WBCs per high-power field, few or no bacteria; CSF: <8 WBCs per mm^3, no bacteria, nonbloody	11
Philadelphia 2	WBC count: <15 000 cells per mm^3; band/neutrophil ratio: <0.2; CSF: <8 WBCs per mm^3, no bacteria, nonbloody	20, 22–25
Boston	WBC count: <20 000 cells per mm^3 (no band criteria); CSF: <10 WBCs per mm^3; urinalysis: <10 WBCs per high-power field, no LE	12, 24
Pittsburgh	Enhanced urinalysis: ≤9 WBCs per mm^3, negative Gram stain results; CSF: ≤5 WBCs per mm^3, negative Gram stain results (if <6 wk)	26
Impression of sepsis	"Not ill" or negative clinical impression of sepsis (history, physical examination, ESR of <30 mm/h, WBC count of <15 000 cells per mm^3)	3, 15, 16

WBC indicates white blood cell; ESR, erythrocyte sedimentation rate; CSF, cerebrospinal fluid; LE, leukocyte esterase. The infant observation score includes 5 observations, that is, quality of cry, reaction to parent stimulation and state variation, color, hydration, and response to social overtures, each scored on a scale of 1 to 5.[31]

The type of low-risk criteria was categorized, with 10 studies using variations of the Rochester criteria, 6 studies using Philadelphia criteria (2 comparing Rochester criteria with Philadelphia criteria), 2 studies using Boston criteria, 1 study using Pittsburgh criteria, 1 study using Milwaukee criteria, and 3 studies using "clinical impression of sepsis" or "not ill" descriptions (Tables 1 and 2). Studies were performed between 1979 and 1999. One study[12] included only children in the low-risk category, without a high-risk comparison group. Fever was defined as a temperature of >38.2°C in 1 study,[11] >38.1°C in 3 studies,[15,20,27] and >38.0°C in the rest of the studies.

SBIs included bacteremia, meningitis, bacterial diarrhea, pneumonia, and UTIs.[31] The defining characteristics for each type of infection varied slightly between the studies, most notably in the definition of UTI. Two studies accepted bagged urine specimens for culture, resulting in 8 diagnoses of UTIs in low-risk patients.[13,19] Ten studies diagnosed UTIs in patients with catheterized urine cultures with <50 000 colony-forming units of a single organism per milliliter.[11,12,14,17,18,20–23,25] Four studies provided no microbiologic definition of UTI or description of urine collection methods.[3,15,16,30] Another variation was the inclusion of pneumonia as a SBI without microbiologic documentation. All infants studied were between 0 and 90 days of age. Six studies included only infants in the first month of life, and 4 studies excluded infants in the first month of life. The majority of studies were limited to the first 2 months of life, with 6 studies extending to 3 months.

A summary of the prospective studies in which patients underwent observation alone is shown in Table 3.[10,11,18,19,22] A total of 1858 patients were included, and 870 were classified as being at low risk. Six patients with SBIs were missed, including 2 patients with bacteremia and 4 patients with UTIs. The first child with bacteremia received parenteral antibiotic treatment within 24 hours after presentation and recovered uneventfully.[11] The identity of the organism was not noted. The second child had a blood culture positive for *Yersinia enterocolitica* and fared well after treatment.[18] The authors noted that a confirmatory culture was not performed before initiation of treatment. Three urine specimens obtained with sterile technique yielded either group B streptococcus or *Escherichia coli*.[18] Those patients fared well with treatment. One urine specimen collected by bag yielded *E coli*.[19]

TABLE 3 Prospective Studies of Performance of Low-Risk Criteria for SBIs in Young Infants in Which Antibiotics Were Withheld From Low-Risk Patients

Year and Reference	Criteria Type	Age, d	No. of Patients	No. of High-Risk Patients	Cases of SBI in High-Risk Patients	Rate of SBIs in High-Risk Patients, %	No. of Low-Risk Patients	Cases of SBI in Low-Risk Patients	Rate of SBIs in Low-Risk Patients, %
1988[10]	Rochester 2	0–56	236	88	21	23.9	148	0	0.00
1993[11]	Philadelphia	29–56	747	460	64	13.9	287	1	0.35
1994[18]	Rochester 2	0–60	203				203	4	1.97
1997[19]	Modified Rochester	4–28	250	119	40	33.6	131	1	0.76
1999[22]	Philadelphia 2	29–60	422	321	43	13.4	101	0	0.00
Total			1858	988	168	20.6	870	6	0.67

TABLE 4 Prospective Studies of Performance of Low-Risk Criteria for SBIs in Young Infants With Empiric Use of Antibiotics for All Patients

Year and Reference	Criteria Type	Age, d	No. of Patients	No. of High-Risk Patients	Cases of SBI in High-Risk Patients	Rate of SBIs in High-Risk Patients, %	No. of Low-Risk Patients	Cases of SBI in Low-Risk Patients	Rate of SBIs in Low-Risk Patients, %
1985[9]	Rochester	0–90	233	89	22	24.7	144	1	0.69
1987[16]	Impression of sepsis	0–56	97	36	5	13.9	61	2	3.28
1988[15]	Impression of sepsis	0–14	35	11	4	36.4	24	2	8.33
1992[12]	Boston	28–89	503				503	27	5.37
1993[14]	Milwaukee	28–56	534	391	23	5.9	143	1	0.70
1994[18]	Rochester 2	0–60	802	494	61	12.3	308	1	0.32
1994[13]	Modified Rochester	0–31	254	120	37	30.8	134	8	5.97
2004[30]	Rochester 2	0–90	1378	922	118	12.8	456	12	2.63
2005[20]	Rochester 2 and Philadelphia 2	0–56	259	186	63	33.9	73	2	2.74
2007[21]	Modified Rochester	Neonate	386	220	107	48.6	166	1	0.60
Total			4481	2469	440	23.8	2012	57	2.71

TABLE 5 Retrospective Studies of Performance of Low-Risk Criteria for SBIs in Young Infants

Year and Reference	Criteria Type	Age, d	No. of Patients	No. of High-Risk Patients	Cases of SBI in High-Risk Patients	Rate of SBIs in High-Risk Patients, %	No. of Low-Risk Patients	Cases of SBI in Low-Risk Patients	Rate of SBIs in Low-Risk Patients, %
1986[27]	Rochester	0–90	117	47	4	8.5	70	3	4.29
1990[3]	Impression of sepsis	0–91	443	222	48	21.6	221	5	2.26
1997[17]	Rochester 2	0–29	119	71	19	26.8	48	3	6.25
1997[25]	Philadelphia 2	3–90	492	196	52	26.5	296	8	2.70
1999[23]	Philadelphia 2	3–28	254	145	27	18.6	109	5	4.59
2000[24]	Boston and Philadelphia 2	1–28	372	141	37	26.2	231	8	3.46
2001[26]	Pittsburgh	0–60	404	277	41	14.8	127	0	0.00
Total			2201	1099	228	19.8	1102	32	2.70

TABLE 6 Comparison of Performance of Low-Risk Criteria for SBIs in Young Infants, According to Study Design

Type of Study	Total No. of Patients	No. of Patients With SBIs	No. of High-Risk Patients	Pooled Rate of SBIs in High-Risk Patients, Estimate (95% CI), %[a]	No. of Low-Risk Patients	Pooled Rate of SBIs in Low-Risk Patients, Estimate (95% CI), %[a]	RR of SBI in High-Risk vs Low-Risk Patients (95% CI)
Prospective, no antibiotic treatment	1858	174	988	20.6 (9.4–31.8)	870	0.67 (−0.04–1.30)	30.56 (7.0–68.13)
Prospective, empiric antibiotic treatment	4481	497	2469	23.8 (13.4–34.1)	2012	2.71 (0.93–4.50)	8.75 (2.29–15.21)
Retrospective	2201	260	1099	19.8 (14.5–25.1)	1102	2.70 (0.40–5.02)	6.93 (3.10–10.75)
Retrospective and prospective, empiric antibiotic treatment	6682	757	3568	22.3 (15.8–28.3)	3114	2.71 (1.4–4.0)	7.74 (3.82–11.67)

[a] Estimated by using the β-binomial model for overdispersed data.[29]

In the rest of the studies summarized in Tables 4 and 5 (prospective studies in which patients received empiric antibiotic treatment and retrospective studies), 89 low-risk infants (2.71%) were diagnosed as having SBIs. This total included 2 cases of meningitis (1 with UTI and 1 with bacteremia), 22 cases of bacteremia (1 with gastroenteritis and 1 with osteomyelitis), 39 cases of UTI, and 14 cases of gastroenteritis. Twelve cases of SBI did not have a source identified.

Table 6 shows a comparison of the performance of the low-risk criteria for SBIs in young infants according to study design. The overall validity of the low-risk criteria in pooled studies was assessed by calculating the RR for SBI in high-risk versus low-risk infants. The RR reached statistical significance in all 3 categories of studies. In prospective studies with no empiric antibiotic treatment, the RR was 30.56 (95% CI: 7.0–68.13). In prospective studies with empiric antibiotic treatment, the RR was 8.75 (95% CI: 2.29–15.21). In retrospective studies, the RR was 6.93 (95% CI: 3.10–10.75). Of importance, there was a statistically significant difference in the rates of SBIs in low-risk patients in the prospective studies with no empiric antibiotic treatment, compared with all other studies (*P* for difference = .010). When prospective studies with no empiric antibiotic treatment were compared with all other studies, no significant difference in the rate of SBIs in high-

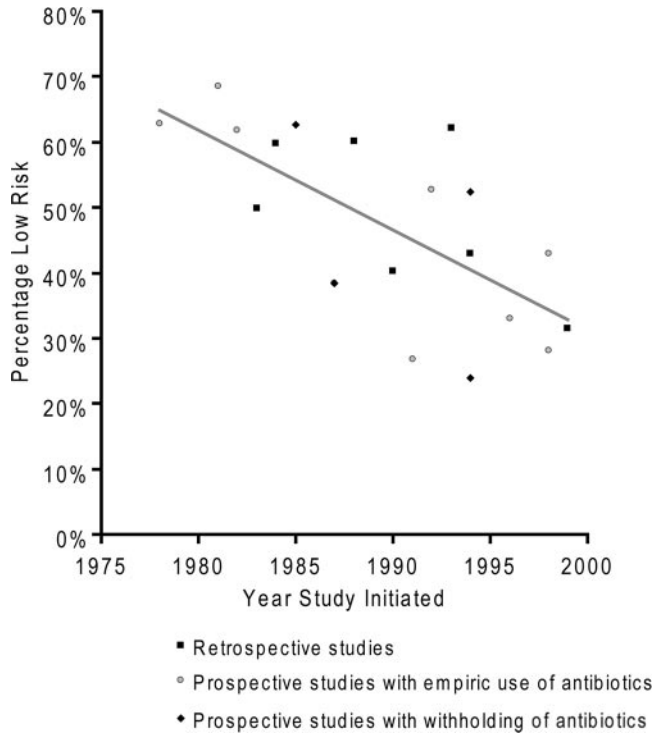

FIGURE 1
Proportions of infants assigned to the low-risk category according to year of study initiation, with a statistically significant trend toward assignment of fewer infants to the low-risk category over time ($P = .001$).

risk patients was found (RR: 1.10; $P = .75$).

An analysis examining the proportion of infants designated as low risk in all studies showed a significant trend toward assigning fewer infants to the low-risk category over time ($\rho = -0.67$; $P = .001$). The slope parameter of the linear regression model of the proportions of infants designated as low risk by time (year) was −0.015 ($P < .001$). Early studies placed ~60% of children in the low-risk category. By the middle 1990s, only 30% of children were considered at low risk, as illustrated in Fig 1.

DISCUSSION

The impetus for this study was the apparent discrepancy in the rate of SBIs among low-risk febrile infants reported in the literature. Previous studies reported a range of rates of SBIs in low-risk infants of 0% to 8.3%.[10,15,22,26] This can be explained, in part, by the different sets of criteria used by various investigators (Table 2).[3,9–26,30] We showed that the rates of SBIs in low-risk patients in both retrospective studies and prospective studies using empiric antibiotic treatment were the same (2.7%) and were significantly different from the rate of SBIs in low-risk patients in prospective studies in which antibiotics were withheld (0.67%). We hypothesized that the low-risk criteria would function best when used in prospective studies in which low-risk patients underwent observation alone. Without reliance on empiric antibiotic treatment, it would be essential to capture all infants at risk of early deterioration in the high-risk group. Careful sample collection, as well as meticulous physical examination, excluded infants with SBIs from the low-risk group.

For physicians to rely on clinical algorithms, they must be convinced that patients will not be placed in jeopardy. The clinical predictability provided by low-risk criteria will be deemed satisfactory if the children identified as being at low risk either do not have a SBI or remain in stable condition until the SBI is recognized. In prospective trials that treated low-risk infants with observation alone, the low-risk criteria "missed" SBIs in 6 patients (bacteremia in 2 patients and UTIs in 4 patients). One of the cases involved a positive urine culture from a bagged specimen, which may represent a contaminant. These patients were treated with appropriate antibiotics when the cultures yielded positive results, and all recovered uneventfully. Therefore, careful application of these low-risk criteria was very effective in identifying children from whom empiric antibiotic therapy could be withheld.

Overall, data from 8540 infants were analyzed in this study. The total number of SBIs was 931, that is, 10.9%, consistent with rates commonly reported in the literature. With the use of low-risk criteria, ~30% of febrile infants can be identified as being at low risk for SBIs and can be treated with observation alone. These patients can be spared the negative effects that may be associated with empiric use of antibiotics, including cost, adverse effects of medications, development of resistant organisms, and psychosocial stresses on family dynamics. The criteria must be applied carefully to avoid misassignment of infants. Special attention should be given to the physical examination and medical history.

This study represents a comprehensive review of the literature that has evaluated the effectiveness of low-risk criteria in the identification of infants unlikely to have SBIs over the previous

23 years. The major weakness of this analysis is that the studies demonstrated minor variations in the low-risk criteria used and the age groups included. Although these small differences in demographic characteristics prohibit a "clean" comparison of all of the studies, we conclude that the observed difference in the performance of low-risk criteria was a function of the study design. When low-risk criteria are applied prospectively after careful evaluation, clinicians should be confident in withholding empiric antibiotic treatment.

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