

## Etiology and laboratory abnormalities in bacterial meningitis in neonates and young infants

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### Abstract

We conducted a retrospective review of electronic medical records of all cases of bacterial meningitis in neonates and young infants at our institution from 2004 to 2014. Fifty-six cases were identified. The most common causative organism was group B streptococcus, followed by *Escherichia coli* and then *Listeria monocytogenes*. Forty-four of the 56 patients in the study had abnormalities of the blood white blood cell (WBC) count. The most common WBC count abnormalities were leukopenia and elevation of the immature to total (I:T) neutrophil ratio. Six patients in the case series lacked cerebrospinal fluid (CSF) pleocytosis. Overall, just 3 of the 56 patients had normal WBC count with differential, CSF WBC count, and urinalysis. Only 1 of the 56 patients was well appearing with all normal lab studies. Our study indicates that bacterial meningitis may occur without CSF pleocytosis but very infrequently occurs with all normal lab studies and well appearance.

### Introduction

Bacterial meningitis in neonates (0 to 28 days old) and young infants (29 to 90 days old) has an estimated incidence of 0.25 per 1000, and is known to have significant morbidity and mortality.<sup>1</sup> This infection is one type of serious bacterial infection (SBI) in neonates and young infants less than 90 days old. Due to the risk of SBI, current pediatric practice guidelines recommend that all febrile neonates have blood, urine, and cerebrospinal fluid (CSF) testing, be treated with intravenous (IV) ampicillin and a third generation cephalosporin or aminoglycoside, and be hospitalized.<sup>2</sup> For young infants who are well appearing and meet some defined low-risk lab criteria, several academic institutions have investigated the safety of using less conservative guidelines. These low-risk lab criteria have been some-

what variable for each study. As examples of this variation, Baskin et al used CSF white blood cell (WBC) count below 10 cells per microliter (uL) and blood WBC count below 20,000/uL, while Baker *et al.* utilized CSF WBC below 8/uL and blood WBC count below 15,000/uL, with an immature to total (I:T) neutrophil ratio in the blood below 0.2.<sup>3,4</sup> Furthermore, Jaskiewicz et al emphasized blood WBC count over 5000/uL and below 15,000/uL, and used blood absolute band count below 1500/uL rather than I:T ratio below 0.2, as important low-risk parameters.<sup>5</sup> Despite this variation in criteria, these studies all have shown that most febrile young infants can be safely and cost-effectively managed without hospitalization, antibiotics, and in some cases without lumbar puncture. The risk of missing an infection such as bacterial meningitis in these young infants who meet all low-risk criteria has been shown to be low.<sup>2,6</sup>

Because SBI such as bacterial meningitis can cause such significant morbidity and mortality, further research in this field has continued for the past 2 decades to further minimize the risk of a missing SBI.<sup>6</sup> One recent study showed that a *step by step* approach, incorporating C-reactive protein (CRP) <2 mg/dL and procalcitonin <0.5 ng/mL, may be superior to Rochester criteria.<sup>7</sup> Like the majority of past studies however, small numbers of patients with bacterial meningitis are included.<sup>3-7</sup>

In this study, we review all cases of bacterial meningitis in neonates and young infants at our institution over a ten-year time period. Our goal was to review the laboratory characteristics of this disease in a large case series, and to evaluate the performance of the previously studied low-risk lab criteria, to help determine the optimal criteria and further minimize the risk of missing the diagnosis of bacterial meningitis.

### Materials and Methods

We conducted a retrospective review of electronic medical records from 2004-2014 at 2 free standing children's hospitals that are part of a pediatric hospital system in the Southeast. The medical records were searched for all positive bacterial CSF cultures in patients 90 days old and younger. Our hospital system does not have a labor and delivery unit, and thus all patients were admitted through the emergency department or were transferred from other hospitals. To be included, patients must have had a positive CSF culture at our institution. Those patients with contaminated cultures,

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from the viewpoint of the treating clinicians, were excluded. In these excluded patients, the cultures showed rare growth from broth, or showed known common contaminants, such as coagulase-negative staphylococci, *Streptococcus viridans*, *Bacillus* species, and diphtheroids. These excluded patients were not treated with antibiotics for more than 3 days before being discharged. None of the excluded patients returned to the hospital after discharge. In addition, patients with ventricular drains or shunts in place prior to the development of infection were excluded from this study.

The previously referenced low-risk criteria were used as the normal limits for lab values.<sup>3-5</sup> Leukopenia was defined as blood WBC count below 5000 cells/uL. Leukocytosis was defined as WBC count above 15,000 cells/uL. An absolute band count above 1500 cells/uL was defined as elevated. An I:T ratio above 0.2 was defined as elevated. CSF pleocytosis, similar to the conservative criteria used by Baker *et al.*, was defined as CSF WBC >8 cells/uL.<sup>4</sup> Elevated CSF protein was defined as CSF protein >100 mg/dL. Pyuria was defined as urine WBC greater than 10 cells/uL.

All statistical analyses were performed using SAS Version 9.4 (Cary, NC, USA) with statistical significance assessed at P<0.05. Statistics were calculated for the overall cohort, and groups of patients of age 0 to 28 days old and 29 to 90 days old. Within these groups, confidence intervals for the proportion of patients with CBC abnormalities were calculated and frequen-

cies compared using two proportion z-tests. Specifically, the proportion of patients with elevated I:T ratio was compared with the proportion of patients with elevated absolute band count. Additionally, the proportion of patients with leukopenia was compared with the proportion of patients with leukocytosis. This study was approved by the institutional review board.

## Results

From 2004 to 2014, a total of 16,266 CSF samples were cultured in our microbiology laboratories for patients 0 to 90 days old. Of these samples, 725 were positive. The majority of these positives were contaminants or were repeat positives from patients with ventricular drains or shunts. These results were excluded from our study.

A total of 56 cases of bacterial meningitis met the criteria for our study. The age range was 4 to 82 days old. Thirty-seven cases (66%) occurred in neonates, while the other 19 cases (34%) occurred in young infants. Of these 19 cases in young infants, 14 occurred in 29 to 60 day-olds, and 5 occurred in 61 to 90 day-olds. Two (4%) of the 56 patients died, and in both of these deaths the causative organism was Group B *Streptococcus* (GBS).

The most common organism overall was GBS (30 cases), followed by *Escherichia coli* (7 cases) and then *Listeria monocytogenes* (5 cases). Other causative organisms are listed in Table 1.

Fever was found in 44 patients (79%) and was the most common presenting complaint. Twenty-two patients (39%) were described as ill appearing. Descriptive terms documented in the medical record for the ill appearance included lethargic, irritable, grunting, seizures, and/or apneic.

As per current pediatric practice guidelines, all patients had blood culture, urine culture, CBC, and urinalysis performed at the time of admission. Positive blood cultures were found in 32 cases (57%). CSF gram stain was positive in 26 cases (46%). One case of *E. coli* in a 37 day old, and one case of *Klebsiella pneumoniae* in a 30 day old, were associated with urinary tract infection (UTI). Both of these cases had pyuria and positive urine cultures.

Additional testing of the C-reactive protein (CRP), CSF enterovirus polymerase chain reaction (PCR), and viral respiratory PCR was performed in some, but not all, of the 56 meningitis cases. Enterovirus PCR was tested in 13 cases and was negative in all 13. Two patients tested positive for viruses on viral respiratory PCR panels. The CRP was elevated above 2.0 mg/dL in 22

patients, was below 2.0 mg/dL in 14 patients, and was not tested in 20 patients.

Of the 56 patients with positive CSF cultures, 5 had a large number of CSF red blood cells (RBC) and/or were noted to have traumatic lumbar punctures in the medical record. Of the remaining 51 patients, just 6 patients (11%) lacked CSF pleocytosis. Thirty-six of the remaining 51 patients had elevated CSF protein above 100 mg/dl. All patients with elevated CSF protein also had CSF pleocytosis. Four of the 45 patients with CSF pleocytosis had CSF WBC counts between 8 and 20 cells/uL. Two of these 4 patients were neonates, and the other 2 were young infants.

Figure 1 demonstrates the characteristics of the 6 patients without CSF pleocytosis.

As shown, just 3 of the 56 patients in this study had normal CSF WBC count, blood WBC count, and urinalysis. Only one patient, a 26 day old with *E. coli*, had a well-appearance and all normal blood WBC, urinalysis, and CSF WBC counts.

Table 2 shows important abnormalities of the blood WBC count. As shown, an elevated I:T ratio was significantly more common than an elevated band count in neonates (P=0.01). An elevated I:T ratio also occurred more commonly than an elevated band count in young infants, though this result was not statistically significant. Only 23% of patients had leukocytosis. Leukopenia was significantly more common than leukocytosis in neonates (P=0.03), but was not more common than leukocytosis in young infants.

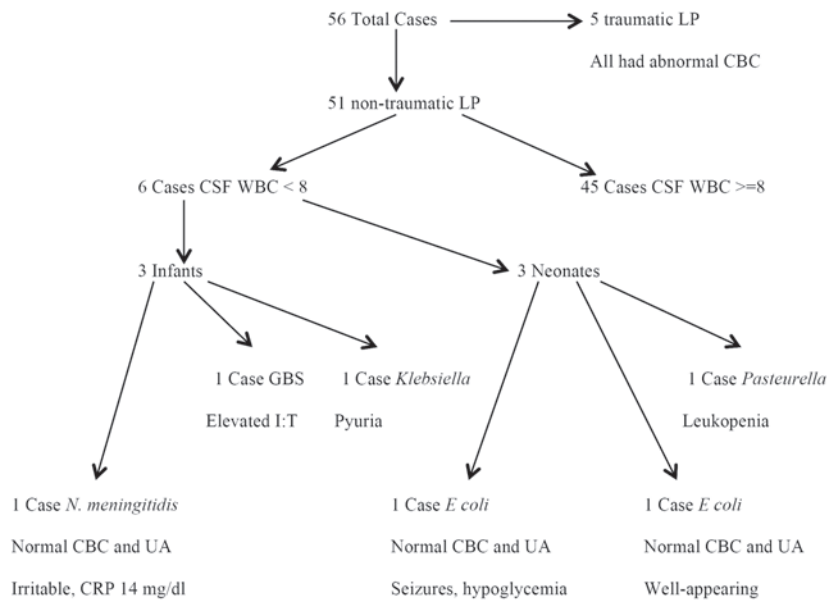


Figure 1. All Meningitis Cases.

Table 1. Bacteria summary.

Bacteria	0-29 Days Old (N=37)	30-90 Days Old (N=19)	Total (N=56)
Group B <i>streptococcus</i>	20 (54.1%)	10 (52.6%)	30 (53.6%)
<i>Escherichia coli</i>	6 (16.2%)	1 (5.3%)	7 (12.5%)
<i>Listeria monocytogenes</i>	4 (10.8%)	1 (5.3%)	5 (8.9%)
<i>Streptococcus pneumoniae</i>	0 (0.0%)	2 (10.5%)	2 (3.6%)
<i>Neisseria meningitidis</i>	1 (2.7%)	1 (5.3%)	2 (3.6%)
<i>Salmonella sp.</i>	1 (2.7%)	1 (5.3%)	2 (3.6%)
<i>Streptococcus bovis</i>	1 (2.7%)	1 (5.3%)	2 (3.6%)
<i>Enterococcus faecalis</i>	1 (2.7%)	1 (5.3%)	2 (3.6%)
<i>Klebsiella pneumoniae</i>	1 (2.7%)	1 (5.3%)	2 (3.6%)
<i>Enterobacter aerogenes</i>	1 (2.7%)	0 (0.0%)	1 (1.8%)
<i>Pasteurella multocida</i>	1 (2.7%)	0 (0.0%)	1 (1.8%)

Table 2. CBC abnormalities.

CBC abnormality	0-29 Days Old (N = 37)		P-value*	30-90 Days Old (N = 19)		P-value*	Overall (N = 56)		P-value*
	N	% (95% CI)		N	% (95% CI)		N	% (95% CI)	
I:T > 0.2	20	54.1% (38.0-70.2)	0.001	8	42.1% (19.9-64.3)	0.503	28	50.0% (36.9-63.1)	0.002
Bands > 1500/uL	6	16.2% (4.3-28.1)		6	31.6% (10.7-52.5)		12	21.4% (10.7-32.1)	
WBC < 5000/uL	17	46.0% (29.9-62.1)	0.027	4	21.1% (2.8-39.5)	0.704	21	37.5% (24.8-50.2)	0.101
WBC > 15,000/uL	8	21.6% (8.3-34.9)		5	26.3% (6.5-46.1)		13	23.2% (12.1-34.3)	

## Discussion

In this paper we describe our experience with bacterial meningitis in neonates and young infants. GBS was the most common bacterial pathogen, followed by *E coli* and then *Listeria*. It is important to note that at our institution, *E coli* and *Listeria* are less common causes of meningitis than herpes simplex virus (HSV). Our experience of 26 cases of HSV meningitis in neonates and young infants, over a slightly shorter time period, has been published.<sup>8</sup>

Previous studies have demonstrated the low risk of bacterial meningitis in neonates and young infants with UTI, and the low risk of SBI in patients with documented viral infections.<sup>9-11</sup> In this study, however, 2 young infants with meningitis had UTI, 1 young infant had a positive viral respiratory PCR test, and 1 neonate had a positive viral respiratory PCR test. None of our patients had a positive CSF enterovirus PCR test.

Recent studies have suggested that the incidence of *Listeria* infection in this patient population is likely decreasing.<sup>12,13</sup> However, in this case series *Listeria* was found to be the third most common cause of bacterial meningitis; therefore, ampicillin coverage is still likely necessary in neonates or young infants who are ill-appearing or have abnormal lab tests.

In their study of the management of febrile young infants referenced above, Baker *et al.* demonstrated the utility of the I:T ratio, a simple ratio calculation that adds no additional cost to the CBC with differential test.<sup>4</sup> In addition, leukopenia and elevation of the I:T ratio have previously been shown to be associated with sepsis in neonates and young infants.<sup>14,15</sup> In our case series, leukopenia was more common than leukocytosis, and leukocytosis occurred in less than a quarter of patients. Moreover, elevation of the I:T ratio was more common than elevation in the absolute band count. To minimize the risk of missing cases of bacterial meningitis, we believe that leukopenia and elevation of the I:T ratio should be included, together with leukocytosis and elevation of band count, in any clinical guidelines that are used to evaluate

febrile neonates and young infants.

Only one patient in our study, a 26-day-old neonate, was well appearing with all normal blood WBC, urinalysis, and CSF cell counts. Thus, we believe that the occurrence of bacterial meningitis in a well-appearing neonate or young infant with all normal lab results is very infrequent. Furthermore, many of our patients did not have CRP levels tested, and none were tested for procalcitonin. Other researchers have demonstrated that these two blood markers could help to further decrease the risk of missing SBI.<sup>7,16-19</sup>

## Conclusions

Our research shows that bacterial meningitis infrequently presents with all normal labs tests and well appearance in neonates and young infants. The majority of patients have abnormalities of the blood WBC count, with leukopenia and elevation of the I:T ratio being most common. A small number of patients lack CSF pleocytosis, and some have CSF WBC counts between 8 and 20 cells/uL. Though our research study is retrospective and involves just a single hospital system, and more research is needed, we believe our results could lead to fewer missed cases of bacterial meningitis, and contribute to the more cost-effective management of febrile neonates and young infants.

## References

- Hristeva L, Booy R, Bowler I, Wilkinson AR. Prospective surveillance of neonatal meningitis. *Arch Dis Child* 1993;69:14.
- Nield LS, Kamat D. Fever without a Focus. In: Kliegman RM, Stanton BF, Schor NF, St Geme JW, Behrman RE. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia, PA: Elsevier Inc.; 2016. pp 1280-1.
- Baskin MN, O'Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants

28 to 89 days of age with intramuscular administration of ceftriaxone. *J Pediatr* 1992;120:22-7.

- Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med* 1993;329:1437-41.
- McCarthy CA, Powell KR, Jaskiewicz JA, et al. Outpatient management of selected infants younger than two months of age evaluated for possible sepsis. *Pediatr Infect Dis J* 1990;9:385-9.
- Huppler AR, Eickhoff JC, Wald ER. Performance of low-risk criteria in the evaluation of young infants with fever: review of the literature. *Pediatrics* 2010;125:228-33.
- Gomez B, Mintegi S, Bressan S, et al. Validation of the "Step-by-Step" Approach in the Management of Young Febrile Infants. *Pediatrics* 2016;138:pii:e20154381.
- Kotzbauer D, Andresen D, Doelling N, Shore S. Clinical and laboratory characteristics of central nervous system herpes simplex virus infection in neonates and young infants. *Pediatr Infect Dis J* 2014;33:1187-9.
- Byington CL, Enriquez FR, Hoff C, et al. Serious bacterial infections in febrile infants 1 to 90 days old with and without viral infections. *Pediatrics* 2004;113:1662-66.
- Rittichier KR, Bryan PA, Bassett KE, et al. Diagnosis and outcomes of enterovirus infections in young infants. *Pediatr Infect Dis J* 2005;24:546-50.
- Greenes DS, Harper MB. Low risk of bacteremia in febrile children with recognizable viral syndromes. *Pediatr Infect Dis J* 1999;18:258-61.
- Biondi E, Evans R, Mischler M, et al. Epidemiology of bacteremia in febrile infants in the United States. *Pediatrics* 2013;132:990-6.
- Hassoun A, Stankovic C, Rogers A, et al. *Listeria* and enterococcal infections in neonates 28 days of age and younger: is empiric parenteral ampicillin still indicated? *Pediatr Emerg Care* 2014;30:240-3.

14. Philip AGS, Hewitt JR. Early diagnosis of neonatal sepsis. *Pediatrics* 1980;65:1036-41.
15. Hornik CP, Benjamin DK, Becker KC, et al. Use of the complete blood cell count in late-onset neonatal sepsis. *Pediatr Infect Dis J* 2012;31:803-7.
16. Chiu CH, Lin TY, Bullard MJ. Identification of febrile neonates unlikely to have bacterial infections. *Pediatr Infect Dis J* 1997;16:59-63.
17. Maniaci V, Dauber A, Weiss S, et al. Procalcitonin in young febrile infants for the detection of serious bacterial infections. *Pediatrics* 2008;122:701.
18. Vouloumanou EK, Plessa E, Karageorgopoulos DE, et al. Serum procalcitonin as a diagnostic marker for neonatal sepsis: a systematic review and meta-analysis. *Intensive Care Med* 2011;37:747.
19. Gomez B, Bressan S, Mintegi S, et al. Diagnostic value of procalcitonin in well-appearing young febrile infants.