American Journal of Emergency Medicine 37 (2019) 1139–1143

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Brief Report

Factors associated with serious bacterial infections in infants ≤60 days with hypothermia in the emergency department

Sriram Ramgopal, MD [a,*], Lorne W. Walker, MD PhD [b], Melissa A. Vitale, MD [a], Andrew J. Nowalk, MD PhD [b]

[a] Division of Pediatric Emergency Medicine, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States of America
[b] Division of Infectious Disease, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States of America

ARTICLE INFO

Article history:
Received 4 April 2019
Received in revised form 9 April 2019
Accepted 10 April 2019

Keywords:
Serious infections
Cold injury
Neonates
SBI
IBI
Invasive infections

ABSTRACT

Background: We sought to investigate risk factors for serious bacterial infection (SBI: bacterial meningitis, bacteremia, and urinary tract infection [UTI]) among infants ≤60 days of age presenting to the emergency department (ED) with hypothermia (temperature < 36 °C).
Methods: We performed a single center study over a 12-year period including all patients ≤60 days old with hypothermia, excluding patients who did not receive a blood culture and patients who received antibiotics prior to culture acquisition. The primary outcome was SBI. Secondary outcomes were mortality and herpes simplex infection. We performed multivariable logistic regression to identify risk factors for primary outcomes reporting adjusted odds ratios with 95% confidence intervals (aOR, 95% CI).
Results: 360 infants were identified. 10/360 (2.8%) had an SBI. All episodes of SBI occurred in infants ≤28 days of age. Two patients had meningitis, two had meningitis with bacteremia, one had isolated bacteremia, and five had UTI. Associated diagnoses included prematurity (46.9%), hyperbilirubinemia (28.3%) and dehydration (14.7%). In multivariable analysis, presentation at 15–28 days (7.60, 1.81–31.86; $p = 0.005$) compared to 0–14 days, higher absolute neutrophil count (1.25, 1.04–1.50; $p = 0.015$) and lower platelet count (0.99, 0.99–1.00; $p = 0.046$) were associated with SBI. Three patients without SBI died during or soon after their hospitalization. One patient had positive testing for herpes simplex.
Conclusion: In this cohort of hypothermic infants, 2.8% had a SBI. Age of presentation, ANC, and lower platelet count were associated with serious infections. Hypothermic infants presenting to the ED carry significant morbidity and require prospective study to better risk-stratify this population.

1. Introduction

Serious bacterial infections (SBI) in infants carry significant morbidity if untreated [1]. Unlike febrile infants, for whom rigorous decision rules have been published [2,3], the management of hypothermic infants presenting to the emergency department (ED) is poorly established. The etiology of hypothermia may be related to an overwhelming immunosuppressed state [4-6] or altered levels of inflammatory cytokines [7].

Older studies have suggested a high rate of infections and mortality in infants with hypothermia, though these studies evaluated infants that were critically ill [8-11] or were performed in resource-limited regions [10]. More recent studies evaluating infants with hypothermia have been limited by small sample size and potential confounding [12-14]. One challenge throughout the literature lies in a varying definition of hypothermia, with investigators using cutoff temperatures for hypothermia as high as 36.5 degrees Celsius (°C) [12] and as low as 34.0 °C [8]. In the absence of rigorous evidence, many practitioners evaluate young infants with hypothermia for SBIs due to the proposed association between depressed temperature and severe infection. Better understanding of risk factors for SBI in this population may facilitate future prospective study with the goal of identifying a cohort of patients at low-risk of SBI.

In this study, we aim to identify rates of and risk factors for SBI among infants presenting to the ED with reported or documented hypothermia. In addition, we aim to identify rates of mortality and herpes simplex infections in this population.

2. Methods

2.1. Setting

We performed a single center retrospective study of infants ≤60 days of age who received testing for SBI. Eligible patients were identified by performing an electronic medical record (EMR) search of all patients ≤60 days of age presenting to the ED between January 1, 2006 to

* Corresponding author at: Division of Emergency Medicine, Children's Hospital of Pittsburgh, AOB 2400, 4401 Penn Avenue, Pittsburgh, PA 15224, United States of America.
E-mail address: sriram.ramgopal2@chp.edu (S. Ramgopal).

https://doi.org/10.1016/j.ajem.2019.04.015
0735-6757/

December 31, 2017 who received any culture of blood, CSF or urine. Prior to data collection, institutional board review approval was obtained with a waiver of informed consent.

2.2. Patient inclusion

Patients were considered eligible for inclusion if they had a history of hypothermia, defined as a reported temperature below 36.0 °C prior to arrival, or if they had documented hypothermia below 36.0 °C within the first 4 h of hospital stay. This cutoff has been recommended by the International Pediatric Sepsis Consensus Conference [15] and is often used in research among infants evaluated in neonatal intensive care units [16,17]. Only rectal temperatures were included. Patients were excluded if they could not be assessed for SBI due to lack of a blood culture, received antibiotics prior to blood culture acquisition, or if they presented as following known trauma or cardiac arrest.

2.3. Data acquisition

We abstracted clinical and laboratory data from the EMR. Clinical data included patient age classified into 2-week categories (0–14 days, 15–28 days, 29–42 days, and 43–60 days), sex, race (in categories of black, white, other and unknown), gestational age, minimum temperature in the first 4 h of hospitalization, and whether hypothermia was historical only (i.e. no measured temperature < 36.0 °C in the first 4 h of hospitalization), and season of presentation. We reviewed laboratory results of blood, urine and cerebrospinal fluid cultures, total white blood cell count (WBC, 10^9/L), absolute neutrophil count (ANC, 10^9/L), absolute band count (ABC, 10^9/L), and platelet count (10^9/L). We defined hyperbilirubinemia as any bilirubin level > 205.2 μmol/L (12 mg/dL).

2.4. Study outcomes

Our primary outcome was SBI. Our secondary outcomes were final diagnosis of herpes simplex viral infection and death. SBI was defined as bacteremia, bacterial meningitis or urinary tract infection (UTI). Bacteremia and bacterial meningitis were defined as growth of a single organism from blood culture or CSF culture, respectively. We used a standard definition of UTI based on colony counts and urinalysis [18]. In ambiguous cases, an infectious disease specialist (L.W. or A.N.) blinded to the clinical context reviewed the results.

2.5. Analysis

Summary statistics of clinical and laboratory parameters are reported. We aimed to identify factors associated with SBIs using multivariable logistic regression. For analysis, temperature data was multiplied by 10 to provide effect sizes for each tenth of degree change. We performed univariate logistic regression for each variable. Predictors with $p < 0.1$ in univariate analysis were used in bidirectional stepwise multivariable regression in order to achieve the minimum Akaike Information Criterion. Results were presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). $p < 0.05$ in multivariable analysis were considered statistically significant. For secondary outcomes, descriptions of patients are provided as proportions. Analysis was performed using the MASS package [19] (version 7.3–51.1) in R, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria https://www.R-project.org/).

3. Results

3.1. Patient inclusion

Of 5508 infants ≤60 days screened for inclusion, 447 had documented or reported hypothermia. 360 (50% male, median age 6.8 days, IQR 4.8–16.0) were included (Table 1). Reasons for exclusion were: no blood culture (n = 12), antibiotics given prior to blood culture (n = 72), history of trauma (n = 2), and cardiac arrest (n = 1). 354 (98.1%) had a urine culture, 328 (90.9%) had a CSF culture, and 140 (38.8%) had HSV testing. Additional diagnoses (n, %) included hyperbilirubinemia (102, 28.3%), dehydration (53, 14.7%), weight loss (49, 13.6%), respiratory disease (31, 8.6%), apnea or cyanosis (23, 6.4%), hypoglycemia (10, 2.8%), pneumonia (9, 2.5%) and apparent life-threatening event (8, 2.2%).

Table 1
Patient demographics, laboratory values, and outcomes.

	All patients	No SBI	With SBI
Demographics			
Number	360	350	10
Age (%)[a]			
0–14 days	263 (73.1)	257 (73.4)	6 (60.0)
15–28 days	43 (11.9)	39 (11.1)	4 (40.0)
29–42 days	35 (9.7)	35 (10.0)	0 (0.0)
43–60 days	19 (5.3)	19 (5.4)	0 (0.0)
Male sex (%)[a]	180 (50)	175 (50.0)	5 (50.0)
Race (%)[a]			
White	279 (77.5)	272 (77.7)	7 (70.0)
Black	53 (14.7)	50 (14.3)	3 (30.0)
Other/unknown	28 (7.8)	28 (8.0)	0 (0.0)
Season (%)[a]			
Winter	104 (28.9)	101 (28.9)	3 (30.0)
Summer	85 (23.6)	81 (23.1)	4 (40.0)
Spring	74 (20.6)	71 (20.3)	3 (30.0)
Fall	97 (26.9)	97 (27.7)	0 (0.0)
Gestational age (%)[a]			
≥36 weeks	191 (53.1)	184 (52.6)	7 (70.0)
<36 weeks	169 (46.9)	166 (47.4)	3 (30.0)
Initial temperature, median (IQR)	35.8 (35.0–36.0)	35.8 (35.3–36.3)	35.8 (35.0–36.0)
Minimum temperature, median (IQR)	35.6 (34.9–35.9)	35.6 (35.1–35.9)	35.6 (35.1–35.9)
Historical hypothermia only (%)[a]	85 (23.6)	83 (23.7)	2 (20.0)
Laboratory parameters			
Hyperbilirubinemia (%)[a]	117 (32.5)	116 (33.1)	1 (10.0)
White blood cell count (10^9/L), median (IQR)	9.0 (7.0–11.1)	9.1 (7.1–10.9)	9.85 (6.8–13.1)
Absolute neutrophil count (10^9/L), median (IQR)	2.84 (1.82–4.01)	2.90 (1.97–4.00)	2.96 (2.37–8.01)
Absolute band count (10^9/L), median (IQR)	0.02 (0.00–0.18)	0 (0.00–0.13)	0.35 (0.08–0.84)
Platelet count (10^9/L), median (IQR)	302 (239–370)	298 (238–358)	213 (111–359)

SD, standard deviation; IQR, interquartile range.
[a] Figures in parenthesis represent column percent (denominator listed in top row).

3.2. Primary outcome (Table 2)

10/360 patients (2.8%) had a SBI. Bacteremia was present in 3 (0.8%), meningitis in 4 (1.1%), and UTI in 5 (1.4%). Some had concurrent infections. No SBIs occurred in infants >28 days of age.

3.3. Factors associated with SBI

In univariate analysis, SBI was associated with presentation at 15–28 compared to 0–14 days, greater WBC and ANC, and lower platelet count. Following multivariable analysis, presentation on days 15–28 compared to days 1–14, higher ANC and lower platelets were independently associated with SBI (Table 3).

3.4. Secondary outcomes

Three patients (0.8%) died, none of whom had an SBI. The first case was a 31-day old term infant who presented with an apneic episode and temperature of 33.5 °C. This infant was intubated and had neuroimaging which revealed severe hemorrhagic encephalitis, the etiology of

Table 2
Clinical and laboratory characteristics of 10 infants with serious bacterial infections

No.	Age (days), sex	History of prematurity	Initial temperature	Minimum temperature	WBC[a]	ANC[a]	ABC[a]	Platelets[a]	SBI
1	4, boy	No	35.7	35.7	6.5	1.6	0.0	381	*Enterobacter cloacae* UTI
2	4, girl	No	36.4	35.9	12.1	4.7	0.0	210	*Enterococcus faecalis* UTI
3	5, boy	Yes	35.9	35.9	7.1	2.3	0.1	216	*Staphylococcus lugdunensis* bacteremia
4	6, girl	No	35.6	35.6	11.1	3.0	0.9	77	*Enterococcus faecalis* meningitis
5	6, boy	No	33.2	33.2	4.8	1.2	0.58	109	Group B *Streptococcus* bacteremia and meningitis
6	7, girl	No	36.0	36.0	19.4	9.8	1.8	108	*Bacteroides fragilis* meningitis
7	16, girl	No	34.0	34.0	6.7	2.9	1.1	118	Group B *Streptococcus* UTI
8	21, boy	No	36.6	36.5	8.8	2.5	0.1	489	*Escherichia coli* UTI
9	22, boy	Yes	34.8	34.8	23.1	14.8	0.7	442	*Listeria monocytogenes* bacteremia and meningitis
10	27, girl	Yes	35.8	35.5	13.4	9.1	0.1	293	Group B *Streptococcus* UTI

SBI, serious bacterial infection; WBC, white blood cell count; ANC, absolute neutrophil count; ABC, absolute band cell count, UTI, urinary tract infection.
[a] Cells 10^9/L.

which was indeterminate despite extensive testing. The second infant was a 29-day old full term infant who presented with lethargy and a temperature of 35.0 °C. This infant was found to have extensive encephalomalacia, likely related to an undetected congenital infection. The third was a 16-day old full term infant who presented following an apneic episode. This infant was hypothermic to 33.7 °C and had recurrent episodes of apnea and bradycardia before the family ultimately transitioned to comfort-oriented care. This infant had positive testing for ketoglutaric aciduria and had multiple white matter lesions at autopsy. One patient (0.3%) had positive testing for HSV from a nasopharyngeal specimen.

4. Discussion

We performed a multivariable analysis to identify risk factors for SBI in infants ≤60 days old with hypothermia in the ED. 2.8% of infants with hypothermia had an SBI. Presentation during days 15–28 of life, higher ANC and lower platelets were independently associated with SBI. Findings from this study suggest that infants with hypothermia in the ED carry significant morbidity, although SBI was not associated with any of the three fatal outcomes in this group.

Overall, the rate of SBI in hypothermic infants ≤60 days of age in the ED appears to be lower than that in febrile infants of the same age, where rates are estimated to be 9–14% [20-23]. Kasmire et al. identified 3 SBIs in 116 hypothermic patients ≤60 days of age (2.6%; one with bacteremia and two with UTI) [13]. Wood et al. found 2 confirmed SBIs in 68 infants ≤28 days of age (2.9%; both UTIs) [14]. Perry et al. identified 8 SBIs out of 104 infants with hypothermia (7.6%; 2 with bacteremia, 1 with meningitis and bacteremia, and 5 with UTI) [12]. The rate of SBI in our study is 2.8%, similar to other reported studies. However, our cohort was larger than the previous cited studies combined, making it the largest experience to date. Some patients who were excluded from analysis, such as those given antibiotics prior to culture acquisition, may have resulted in a higher rate of SBI if they could have been reliably included. Conversely, if a large number of infants with hypothermia were not tested for SBI, this group may have resulted in a lower rate of SBI, though this is unlikely to have been the case.

A notable finding of our analysis is the variation of SBI rate by age. While the rate of SBI in febrile infants is inversely proportional to age [20,24], in our series of hypothermic infants the youngest age group had a lower rate of SBIs (2.2%) compared to those 15–28 days of age (9.3%). One explanation for this finding is that a large number of younger infants were admitted for hypothermia related to temperature

Table 3
Factors associated with SBI in univariate and multivariable analysis

Variable	Univariate OR (95% CI)	*p*	Multivariable aOR (95% CI)	*p*
Age				
0–14 days	Ref	–	Ref	–
15–28 days	4.39 (1.19–16.27)	**0.027**	7.60 (1.81–31.86)	**0.005**
29–42 days	0.00 (0.00–infinity)	0.993	0.00 (0.00–infinity)	0.993
43–60 days	0.00 (0.00–infinity)	0.995	0.00 (0.00–infinity)	0.995
Male sex	1.00 (0.28–3.51)	1.000		
Race				
White	Ref	–		
Black	2.33 (0.58–9.32)	0.231		
Other/unknown	0.00 (0.00–infinity)	0.990		
Season				
Winter	Ref	–		
Summer	1.66 (0.36–7.64)	0.514		
Spring	1.42 (0.28–7.25)	0.672		
Fall	0.00 (0.00–infinity)	0.992		
Gestational age				
Term	Ref	–		
<36 weeks	0.48 (0.12–1.87)	0.286		
Historical hypothermia only	0.80 (0.17–3.86)	0.785		
First temperature (0.1 °C temperature increment)	0.96 (0.90–1.02)	0.173		
Minimum temperature (0.1 °C temperature increment)	0.98 (0.91–1.05)	0.592		
Laboratory values				
White blood cell count	1.12 (0.98–1.28)	**0.093**		
Absolute neutrophil count	1.25 (1.05–1.49)	**0.014**	1.25 (1.04–1.50)	**0.015**
Absolute band count	1.40 (0.83–2.38)	0.210		
Platelet count	0.99 (0.99–1.00)	**0.063**	0.99 (0.99–1.00)	**0.046**
Hyperbilirubinemia	0.22 (0.03–1.79)	0.158		

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval. Bold text indicates significant values in univariate ($p < 0.10$) and multivariable ($p < 0.05$) analyses.

dysregulation in the setting of low birthweight and/or prematurity [25], diluting the risk of SBI in similarly-aged infants without these conditions. The 15–28 days of age cohort had an SBI incidence of 9.3%, suggesting that the true rate of SBI in hypothermic infants past the first two weeks approaches that of febrile infants, and that complete evaluation is warranted in these patients.

We identified that presentation between days 15–28 compared to 0–14 days, higher ANC and lower platelets were risk factors for SBI in multivariable analysis. We did not identify any instances of SBI in patients over 28 days of age, which may be partially due to the relative infrequency of hypothermia in older ages. A repeated analysis limited only to patients ≤28 days of age produced similar findings in multivariable regression (not shown). A higher neutrophil count is associated with invasive infections in febrile neonates [21,26]. Similarly, thrombocytopenia has been associated with serious infections in critically ill adult [27] and pediatric patients [24,28]. We did not identify an association between band counts [12] or gestational age [13] and SBI as found in other studies, which may relate to varying definitions of SBI. Wood et al. [14] suggested an association between lower temperatures and SBI, a finding which is also corroborated by older studies [8-10]. While we did not find direct correlation between lower temperatures and SBI, 2/3 patients with mortality had a presenting temperature below 34 °C. Though an association between jaundice and sepsis is typically described [29], we did not identify an association with hyperbilirubinemia and SBI. This may be due to the large number of young infants with physiologic jaundice of the newborn and/or dehydration with associated temperature-dysregulation.

Additional data are needed to better risk stratify patients with hypothermia, ideally using prospective data. Use of additional biomarkers may also yield significant results. For example, C-reactive protein [24] and procalcitonin [2,3] have improved accuracy over parameters of the complete blood in identifying young febrile infants at low risk for SBI. The utility of these parameters in hypothermic infants warrants further evaluation.

This study is subject to limitations from a retrospective chart review. Patients who did not receive any cultures would not have been screened for study inclusion. However, the majority of infants in our center who receive no testing for hypothermia generally have temperatures above 36.0, which is above the threshold for hypothermia used in this study [12]. Therefore, few patients would have been excluded on this basis. Aside from a blood culture, not all patients received cultures or tests including lumbar puncture, urinalysis, or herpes simplex virus testing. Despite these limitations, this study is the largest investigation to our knowledge identifying rates of SBI among young infants with hypothermia and is the first to identify potential risk factors for serious infections in this population.

5. Conclusion

In this 12-year review of infants ≤60 days old presenting to the ED with hypothermia, SBIs occurred in 2.8%. Presentation during days 15–28 of life, ANC and platelets were independently associated with SBI. 0.8% of infants in this population died, and important comorbid diagnoses included hyperbilirubinemia and dehydration. These findings suggest that infants with hypothermia presenting to the ED carry risk of significant morbidity. Additional prospective research is needed to better risk-stratify this vulnerable population.

Declarations of interest

None.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

None.

References

[1] de Jonge RC, van Furth AM, Wassenaar M, Gemke RJ, Terwee CB. Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. BMC Infect Dis 2010;10:232. https://doi.org/10.1186/1471-2334-10-232.
[2] Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L, et al. Validation of the "step-by-step" approach in the management of young febrile infants. Pediatrics 2016;138:e20154381. https://doi.org/10.1542/peds.2015-4381.
[3] Kuppermann N, Dayan PS, Levine DA, Vitale M, Tzimenatos L, Tunik MG, et al. A clinical prediction rule to identify febrile infants 60 days and younger at low risk for serious bacterial infections. JAMA Pediatr 2019. https://doi.org/10.1001/jamapediatrics.2018.5501.
[4] Drewry AM, Fuller BM, Skrupky LP, Hotchkiss RS. The presence of hypothermia within 24 hours of sepsis diagnosis predicts persistent lymphopenia. Crit Care Med 2015;43:1165–9. https://doi.org/10.1097/CCM.0000000000000940.
[5] Leon LR. Hypothermia in systemic inflammation: role of cytokines. Front Biosci 2004;9:1877–88.
[6] Azab A, Kobal S, Rubin M, Kaplanski J. Inhibition of prostaglandins does not reduce the cardiovascular changes during endotoxemia in rats. Prostaglandins Leukot Essent Fatty Acids 2006;74:135–42. https://doi.org/10.1016/j.plefa.2005.10.004.
[7] Marik PE, Zaloga GP. Hypothermia and cytokines in septic shock. Norasept II Study Investigators. North American study of the safety and efficacy of murine monoclonal antibody to tumor necrosis factor for the treatment of septic shock. Intensive Care Med 2000;26:716–21.
[8] Dagan R, Gorodischer R. Infections in hypothermic infants younger than 3 months old. Arch Pediatr Adolesc Med 1984;138:483. https://doi.org/10.1001/archpedi.1984.02140430059015.
[9] Bower B, Jones L, Weeks M. Cold injury in the newborn. A study of 70 cases. Br Med J 1960;1:303–9.
[10] El-Radhi AS, Jawad MH, Mansor N, Ibrahim M, Jamil II. Infection in neonatal hypothermia. Arch Dis Child 1983;58:143–5.
[11] Arneil G, Kerr M. Severe hypothermia in Glasgow infants in winter. Lancet (London, England) 1963;2:756–9.
[12] Perry MC, Yaeger SK, Noorbakhsh K, Cruz AT, Hickey RW. Hypothermia in young infants. Pediatr Emerg Care 2018:1. https://doi.org/10.1097/PEC.0000000000001674.
[13] Kasmire KE, Vega C, Bennett NJ, Laurich VM. Hypothermia: a sign of sepsis in young infants in the emergency department? Pediatr Emerg Care 2018:1. https://doi.org/10.1097/PEC.0000000000001539.
[14] Wood JK, Halvorson EE, Auriemma JR, Ervin SE, Thurtle DP, Keskinyan VS, et al. Clinical characteristics and health outcomes of neonates reporting to the emergency department with hypothermia. Hosp Pediatr 2018;8:458–64. https://doi.org/10.1542/hpeds.2017-0176.
[15] Goldstein B, Giroir B, Randolph A. International consensus conference on pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8. https://doi.org/10.1097/01.PCC.0000149131.72248.E6.
[16] Hofer N, Müller W, Resch B. Neonates presenting with temperature symptoms: role in the diagnosis of early onset sepsis. Pediatr Int 2012;54:486–90. https://doi.org/10.1111/j.1442-200X.2012.03570.x.
[17] de Almeida MFB, Guinsburg R, Sancho GA, Rosa IRM, Lamy ZC, Martinez FE, et al. Hypothermia and early neonatal mortality in preterm infants. J Pediatr 2014;164:271–275.e1. https://doi.org/10.1016/J.JPEDS.2013.09.049.
[18] Schnadower D, Kuppermann N, Macias CG, Freedman SB, Baskin MN, Ishimine P, et al. Febrile infants with urinary tract infections at very low risk for adverse events and bacteremia. Pediatrics 2010;126:1074–83. https://doi.org/10.1542/peds.2010-0479.
[19] Venebles WN, Ripley BD. Modern applied statistics with S. . 4th ed.New York: Springer; 2002.
[20] Aronson PL, Thurm C, Alpern ER, Alessandrini EA, Williams DJ, Shah SS, et al. Variation in care of the febrile young infant <90 days in US pediatric emergency departments. Pediatrics 2014;134:667–77. https://doi.org/10.1542/peds.2014-1382.
[21] Greenhow TL, Hung Y-Y, Herz AM, Losada E, Pantell RH. The changing epidemiology of serious bacterial infections in young infants. Pediatr Infect Dis J 2014;33:595–9. https://doi.org/10.1097/INF.0000000000000225.
[22] Kuppermann N, Dayan PS, Levine DA, Vitale M, Tzimenatos L, Tunik MG, et al. A clinical prediction rule for stratifying febrile infants 60 days and younger at risk for serious bacterial infections. JAMA Pediatr 2019;297:52–60.
[23] Ramgopal S, Janofsky S, Zuckerbraun NS, Ramilo O, Mahajan P, Kuppermann N, et al. Risk of serious bacterial infection in infants aged ≤60 days presenting to emergency departments with a history of fever only. J Pediatr 2018. https://doi.org/10.1016/j.jpeds.2018.08.043.
[24] Carmon L, Goldbart A, Greenberg D, Ben-Shimol S. Serious bacterial infections in hospitalized febrile infants in the first and second months of life. Pediatr Infect Dis J 2017;36:924–9. https://doi.org/10.1097/INF.0000000000001632.
[25] Miller SS, Lee HC, Gould JB. Hypothermia in very low birth weight infants: distribution, risk factors and outcomes. J Perinatol 2011;31:S49–56. https://doi.org/10.1038/jp.2010.177.

[26] Cruz AT, Mahajan P, Bonsu BK, Bennett JE, Levine DA, Alpern ER, et al. Accuracy of complete blood cell counts to identify febrile infants 60 days or younger with invasive bacterial infections. JAMA Pediatr 2017;171:e172927. https://doi.org/10.1001/jamapediatrics.2017.2927.
[27] Venkata C, Kashyap R, Farmer JC, Afessa B. Thrombocytopenia in adult patients with sepsis: incidence, risk factors, and its association with clinical outcome. J Intensive Care 2013;1:9. https://doi.org/10.1186/2052-0492-1-9.
[28] Ree IMC, Fustolo-Gunnink SF, Bekker V, Fijnvandraat KJ, Steggerda SJ, Lopriore E. Thrombocytopenia in neonatal sepsis: incidence, severity and risk factors. PLoS One 2017;12:e0185581. https://doi.org/10.1371/journal.pone.0185581.
[29] Stoll BJ. Infectious of the neonatal infant. In: Kliegman R, Stanton B, St. Geme III J, Schor N, Behrman R, editors. Nelson textbook of pediatrics. Philadelphia: Elsevier Saunders; 2011. p. 629–47 19th ed.