Prevalence of Serious Bacterial Infection in Young Infants with Hypothermia with Positive Respiratory Pathogen Testing

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Objectives We sought to compare the prevalence of serious bacterial infections (SBI; urinary tract infection, bacteremia, and/or meningitis) and invasive bacterial infections (IBI; bacteremia and/or meningitis) among infants with hypothermia with positive vs negative respiratory pathogen testing.

Study design We conducted a multicenter retrospective cohort study of infants ≤90 days presenting to an emergency department or directly admitted to a hospital from September 1, 2016, to May 5, 2021, with reported or documented hypothermia (≤36°C). Positive respiratory pathogen testing included positive single or multiplex nucleic acid amplification testing. The primary outcome was prevalence of SBI, defined as positive blood, urine, and/or cerebrospinal fluid culture and antibiotic treatment course; the prevalence of SBI and IBI was compared between infants with positive vs negative respiratory pathogen tests using the χ^2 test.

Results Respiratory pathogen testing was obtained in 40.6% (446/1098) of infants with hypothermia; of those, 24.9% (111/446) had a positive respiratory pathogen result. Infants with a positive respiratory pathogen result were more often older, ill-appearing at presentation, and evaluated during fall/winter months. The prevalence of SBI in our cohort was 7.4%, and the prevalence of IBI was 4.5%. There were no associations between respiratory pathogen test result and SBI or IBI.

Conclusions Most young infants with hypothermia evaluated did not have respiratory pathogen testing performed. The diagnosis of SBI or IBI was not associated with a positive respiratory pathogen test. Further research is needed to understand the utility of respiratory pathogen testing in risk stratification for infants with hypothermia.

Change in body temperature may be the only clinical symptom of an invasive bacterial infection (IBI; defined as bacteremia or meningitis) or serious bacterial infection (SBI; IBI and/or urinary tract infection [UTI]) in well-appearing young infants.[1] The prevalence of SBI in febrile infants <90 days of age is well characterized and ranges from 8% to 12.5%,[2-4] whereas the prevalence of IBI in febrile infants <60 days of age is approximately 2.5%.[5] Although less studied, infants with hypothermia have a similarly increased risk, with a 2.1%-8.0% prevalence of culture-positive IBI and/or SBI.[6-12] Several strategies exist to risk stratify febrile infants based on clinical and diagnostic testing factors to reduce unnecessary testing, treatment, and hospitalization of children at low risk for SBI; however, these strategies have not been studied in the population of infants with hypothermia.[13,14]

Among febrile infants, positive respiratory pathogen (RP) testing has been associated with decreased incidence of SBI compared with those with negative testing.[3,15-18] These findings are limited in that a positive test for any single pathogen is not associated with a uniform reduction in risk across all

AAP	American Academy of Pediatrics
CSF	Cerebrospinal fluid
ED	Emergency department
HRV	Human rhino/enterovirus
IBI	Invasive bacterial infection
PCR	Polymerase chain reaction
RP	Respiratory pathogen
RP+	Positive respiratory pathogen test result
RP–	Negative respiratory pathogen test result
SBI	Serious bacterial infection
UTI	Urinary tract infection

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https://doi.org/10.1016/j.jpedcp.2024.200095

young infant age groups or type of SBI.[16,19] For example, bacterial infections are more likely among febrile infants with human rhino/enterovirus (HRV) detection compared with non-HRV viruses.[16] Recognizing this, the American Academy of Pediatrics (AAP) febrile infant clinical practice guideline recommends positive testing results not preclude infants from undergoing evaluation for SBI but instead can be used by clinicians when making individual treatment decisions in the 29- to 60-day age group.[13] Infants with hypothermia may similarly benefit from incorporating RP testing results into risk stratification. However, existing studies investigating factors associated with SBI in young infants with hypothermia are limited by single-center study designs or varying definitions of hypothermia and have not included RP testing in the modeling of SBI outcomes. Recently, we demonstrated significant variation in the use of RP testing in evaluating well-appearing infants with hypothermia.[20]

The primary objective of this study was to compare the prevalence of SBI by RP testing results in young infants with hypothermia presenting to the emergency department (ED) or inpatient care. Our secondary objective was to compare the prevalence of IBI by RP testing. We hypothesized that the prevalence of SBI and IBI would differ between patients with positive and negative RP testing.

Methods

Study Design and Population

We conducted a secondary analysis of a multicenter retrospective cohort study across 9 sites participating in the Hypothermic Young Infant Collaborative (**Table I**) of young infants ≤90 days presenting to an ED or directly admitted to the hospital with hypothermia (≤36.0°C) from September 1, 2016, to May 5, 2021.[12] This definition of hypothermia was based on the International Pediatric Sepsis Consensus Conference statements regarding systemic inflammatory response syndrome[21] as well as previous studies investigating SBI in infants with hypothermia.[6,8,12] The study protocol was approved by the institutional review board at each participating site.

We undertook a thorough approach to identify eligible infants, using both diagnosis codes attributed to temperature disturbances and actual temperatures recorded in the electronic health records. Patients with *International Classification of Diseases*, *Ninth* and *Tenth Revision* diagnosis codes corresponding to hypothermia or other temperature disturbances (778.3, 778.4, 991.6, 780.65, R68, P80, P808, P818, P819, T68, T69.8XXA) were eligible for inclusion.[8,11,12,22] Because infants with SBI and other serious pathology are not accurately identified by temperature-related diagnosis codes, additional infants were identified by an electronic health record query of infants with a documented temperature of ≤36°C within 24 hours upon arrival to the ED or direct admission and included if reported hypothermia prior to arrival or hypothermic on initial vital signs.

Infants ≤90 days with documented or historical hypothermia who received RP testing were included in this study.

Table I. Participating sites

Site numbers	City	Institution
Site 1	Birmingham, AL	Children's Hospital of Alabama
Site 2	Columbus, OH	Nationwide Children's Hospital
Site 3	Greenville, SC	Prisma Health Children's Hospital-Upstate
Site 4	Los Angeles, CA	Children's Hospital of Los Angeles
Site 5	New York, NY	New York-Presbyterian Morgan Stanley Children's Hospital
Site 6	Portland, OR	Doernbecher Children's Hospital
Site 7	Richmond, VA	Children's Hospital of Richmond at VCU
Site 8	St. Petersburg, FL	Johns Hopkins All Children's Hospital
Site 9	Winston-Salem, NC	Brenner Children's Hospital at Atrium Health Wake Forest Baptist

Documented hypothermia was defined as a temperature ≤36°C measured at a health care facility (eg, primary care physician office or referral hospital), on initial vital signs in the ED, or upon admission to the hospital if directly admitted. For patients identified by *International Classification of Diseases*, *Ninth* and *Tenth Revision* codes but no documented hypothermia, historical hypothermia was defined as a recorded temperature ≤36°C measured at home by a caregiver as documented within the medical chart. RP testing included polymerase chain reaction (PCR) testing for single (eg, influenza-only) or multiple viruses (ie, "panel"). Infants with central venous lines, those transferred from a referring facility without documentation of final culture results or ability to see the treatment team's management, and those who presented with known cardiac arrest or trauma were excluded. Also, infants with documented fever (≥38.0°C) before or within 48 hours of initial encounter were excluded, as the presence of fever was likely to dictate care using febrile infant clinical decision support guidelines. Finally, infants who were hypothermic during a birth hospitalization (including neonatal intensive care unit) were excluded as a result of the differences in risk factors for infection.[23,24]

Data Collection and Definitions

Data extraction was performed via manual chart review by trained investigators at each site adhering to a standard operating procedure provided by primary site; all data were recorded in a central REDCap database.[25] Patient demographics included age, sex, insurance payor, known medical complexity (defined as a severe medical condition expected to last ≥12 months and requiring subspecialty care or involving multiple organ systems[26]), and gestational age. Clinical characteristics included lowest temperature recorded or reported, vital signs on presentation, presenting symptoms, physical examination findings, and discharge diagnosis. Diagnostic evaluation, including culture results, laboratory studies, and diagnostic imaging, was recorded.

IBI was defined as bacteremia or meningitis, whereas SBI was defined as an IBI and/or UTI. A complete SBI evaluation was defined as obtaining 3 cultures (urine, blood, and cerebrospinal fluid [CSF]), whereas a partial SBI evaluation was

defined as obtaining at least 1 but not all of these cultures. Infants with no SBI evaluation or partial SBI evaluation were considered negative for SBI if it was not subsequently diagnosed within 7 days of initial presentation as previously described.[12]

Repeated temperature instability was defined as more than 1 temperature ≤36.0°C within 24 hours of initial documented hypothermia. Ill appearance was defined as the following terms documented on physical examination: ill appearance, toxic, limp, unresponsive, gray, cyanotic, apnea, weak cry, poorly perfused, grunting, listless, lethargic, or irritable.[10,27]

Outcomes

The primary outcome was prevalence of SBI, and the secondary outcome was the prevalence of an IBI. Bacteremia was defined as growth of a bacterial organism from a blood culture treated by the medical team with a treatment course of antibiotics. Meningitis was similarly defined as growth of a bacterial organism from a CSF culture or positive PCR test result of CSF fluid from commercially available assays that was treated by the medical team with a treatment course of antibiotics. UTI was defined as ≥50 000 colony-forming units/mL of an organism from a catheterized sample obtained with an abnormal urinalysis (presence of leukocyte esterase, nitrite, or >5 white blood cells per high-power field)[28] or a positive urine culture treated by the medical team with a treatment course of antibiotics.

Statistical Analyses

Descriptive statistics were used to characterize patient demographic and clinical characteristics, clinical course, and prevalence of SBI. Continuous data were summarized using means (SDs), and categorical data were summarized with counts (percentages). We conducted comparisons of demographic and clinical characteristics between those with and without RP testing. We also compared demographics, clinical characteristics, and the prevalence of SBI and IBI between patients with positive RP testing with those with negative testing. The proportion of infants with an SBI or IBI are categorized by positive testing for human rhino/enterovirus (HRV), positive testing for non-HRV pathogen, and negative testing to allow for meaningful comparisons to existing literature that focused on similar groupings.[16,29,30] Continuous variables were analyzed using *t* tests or ANOVA. Discrete variables were analyzed using χ^2 and Fisher exact tests. Analyses were carried out using R statistical software (version 4.0.4; R Foundation for Statistical Computing).

Results

Study Population

Among the 1098 infants with hypothermia included in the parent study,[12] a total of 446 patients received RP testing; demographic and clinical characteristics of infants receiving and not receiving RP testing are summarized in **Table II**.[26] The prevalence of RP testing varied by age groups and season. Patients receiving RP testing were more often ill-appearing at presentation (48% vs 13%; $P < .001$) and more likely to undergo either partial or full evaluation for SBI (94% vs 61%; $P < .001$). SBI was more prevalent among infants receiving RP testing compared with those who did not receive RP testing (7% vs 2%; $P < .001$).

Approximately 25% (111/446) of infants with hypothermia who underwent RP testing had a positive respiratory pathogen result (RP+). Demographic and clinical characteristics of infants by RP testing result are shown in **Table II**. An RP+ result was associated with patient age, with fewer infants ≤28 days testing positive compared with infants 29-60 and 61-90 days of age (16.2% vs 52.8% vs 51.4%, $P < .001$; **Table III**). Infants with RP+ testing were more often ill-appearing at presentation (67% vs 41%, $P < .001$), and the extent of SBI workup (full, partial, or none) differed between RP+ and negative testing (RP–) groups, with patients who were RP+ receiving less-extensive workups. Positive RP test results also differed by season, with 79% ($P < .001$) of positive test results occurring during fall and winter.

Identification of Respiratory Viruses

Table III summarizes the RP testing results. The most frequently detected pathogen was HRV (12%; 52/446). The prevalence of HRV and non-HRV viruses differed significantly between age categories ($P < .01$ vs $P < .001$, respectively).

Serious and Invasive Bacterial Infections

Overall, SBI occurred in 7.4% (33/446) of infants with hypothermia who underwent RP testing. The prevalence of SBI did not significantly differ between RP+ (5.4%; 6/111) and RP– (8.1%; 27/335) groups (**Table II**; $P = .47$). IBI occurred in 4.5% (20/446) of infants with hypothermia with RP testing. Prevalence of IBI also did not significantly differ between RP+ (4.5%; 5/111) and RP– (4.5%; 15/335) groups ($P > .99$). Five patients with bacteremia and 1 patient with meningitis had a positive RP result. **Table IV** summarizes the overall frequencies of SBI and IBI stratified by RP test result and age category. The greatest proportion of infants with SBI occurred in the ≤28 days age group; among those infants, 12% (3/25) had a positive RP result.

Discussion

In this multicenter retrospective cohort study of infants with hypothermia undergoing testing for respiratory pathogens, the overall prevalence of SBI was 7.4%. SBI status did not differ between those with positive and negative respiratory pathogen testing. Among infants with and without SBI, the most frequently detected pathogen was HRV. Our study is among the first to investigate associations between RP testing status and prevalence of SBI in infants with hypothermia. The contribution of data from 9 tertiary-care pediatric centers supports the generalization of our findings to similar institutions and suggests that RP testing status should be used cautiously in the medical decision-making for this population.

Table II. Demographic and clinical characteristics of patients receiving RP testing

	RP	No RP		RP+	RP–	
Variables, No. (%)	n = 446	n = 652	*P* value	n = 111	n = 335	*P* value
Age, d			<.001			<.001
<7	196 (44.0)	346 (53.1)		7 (6.3)	189 (56.4)	
7-28	143 (32.1)	123 (18.9)		48 (43.2)	95 (28.4)	
>28	107 (24.0)	183 (28.1)		56 (50.5)	51 (15.2)	
Sex			>.99			.48
Female	214 (48.0)	317 (48.6)		57 (51.4)	157 (46.9)	
Race/ethnicity			.16			.17
White	264 (59.2)	346 (53.1)		63 (56.8)	201 (60.0)	
Black/African American	90 (20.2)	144 (22.1)		29 (26.1)	61 (18.2)	
Hispanic/Latinx	37 (8.3)	71 (10.9)		10 (9.0)	27 (8.1)	
Other	54 (12.3)	91 (14.0)		9 (8.1)	46 (13.7)	
Insurance			.5			.007
Private	158 (35.4)	240 (36.8)		26 (23.4)	132 (39.4)	
Public	262 (58.7)	381 (58.4)		79 (71.2)	183 (54.6)	
Uninsured	26 (5.8)	31 (4.8)		6 (5.4)	20. (6.0)	
Gestational age, wk			<.001			<.001
Preterm (<34)	55 (12.3)	26 (4.0)		34 (30.6)	21 (6.3)	
Late preterm (34-36)	145 (32.5)	151 (23.2)		29 (26.1)	116 (34.6)	
Term (≥37)	222 (50.0)	393 (60.3)		35 (31.5)	187 (55.8)	
Not documented	24 (5.4)	82 (12.6)		13 (11.7)	11 (3.3)	
Medical complexity*	44 (9.9)	56 (8.6)	.24	10 (9.0)	34 (10.2)	.87
Seasonality			.001			<.001
Winter	166 (37.2)	175 (26.8)		50 (45.1)	116 (34.6)	
Spring	101 (22.7)	162 (24.9)		20 (18.0)	81 (24.2)	
Summer	63 (14.1)	145 (22.2)		3 (2.7)	60 (17.9)	
Fall	116 (26.0)	170 (26.1)		38 (34.2)	78 (23.3)	
Ill-appearing†	212 (47.5)	88 (13.5)	<.001	76 (67.6)	137 (40.9)	<.001
Mode of temperature			.001			.82
Rectal	371 (83.2)	558 (85.6)		92 (82.9)	279 (83.3)	
Axillary	19 (4.3)	38 (5.8)		6 (5.4)	13 (3.9)	
Other	3 (0.7)	14 (2.2)		1 (0.9)	2 (0.6)	
Unknown	53 (11.9)	42 (6.4)		12 (10.8)	41 (12.2)	
Repeated temperature instability‡	298 (66.8)	279 (42.8)	<.001	68 (61.3)	230 (68.7)	.19
SBI workup			<.001			.03
None	27 (6.1)	257 (39.4)		12 (10.8)	15 (4.5)	
Partial§	311 (69.7)	249 (38.2)		78 (70.3)	233 (69.6)	
Full¶	108 (24.2)	146 (22.4)		21 (18.9)	87 (26.0)	
Full RP panel test	–	–	–	100 (90.1)	314 (93.7)	.28
SBI**						
Any SBI	33 (7.4)	15 (2.3)	<.001	6 (5.4)	27 (8.1)	.47
UTI	15 (3.4)	12 (1.8)	.072	1 (0.9)	14 (4.2)	.13
Bacteremia	18 (4.0)	2 (0.3)	<.001	5 (4.5)	13 (3.9)	.78
Meningitis	5 (1.1)	1 (0.2)	.042	1 (0.9)	4 (1.2)	>.99
Any IBI	20 (4.5)	3 (0.5)	<.001	5 (4.5)	15 (4.5)	>.99

Values are No. (%) unless otherwise indicated.
*Medical complexity defined as a severe medical condition expected to last 12 months and requiring subspecialty care or involving multiple organ systems.[26]
†Ill-appearing defined as the following terms documented on physical examination: ill appearance, toxic, limp, unresponsive, gray, cyanotic, apnea, weak cry, poorly perfused, grunting, listless, lethargic, or irritable.
‡Repeat temperature instability defined as >1 temperature of ≤36.0°C in a 24-hour time period.
§Partial SBI evaluation defined as having ≥1 but <3 cultures (urine, blood, CSF).
¶Full SBI evaluation defined as having all 3 culture sources obtained.
**Patients with >1 infection source only counted once as SBI and IBI.

The risk of SBI and IBI among febrile infants is well characterized, allowing for stratification of individual infants by clinical features and diagnostic results to guide value-driven testing and interventions.[13,14] In febrile infants, PCR-based respiratory pathogen testing has been used to aid in risk stratification for SBI, as febrile infants with positive respiratory viral testing have decreased risk for SBI compared with infants who have a negative test result.[15,31] However, the effect of positive RP results on the risk for meningitis, bacteremia, or UTI, or the composite of any SBI, varies across infant age groups and specific pathogen results. In a study of febrile infants aged 1-90 days undergoing evaluation for SBI, HRV was the most frequently detected virus; however, infants with HRV only detected or negative RP testing results were at greater risk of SBI compared with those with a non-HRV pathogen detected.[16] In our study, we also found HRV was the most frequently detected virus among infants with hypothermia diagnosed with SBI and IBI. As HRV often is detected in children without symptoms[32-35] and can be shed for a prolonged period of time,[33-36] positive HRV testing may have limited utility to distinguish between infants with hypothermia with and without SBI. Interestingly, in the

Table III. RPs detected in infants with hypothermia undergoing evaluation for SBI

Respiratory pathogen result	Total	Age category			*P* value
		≤28 d	29-60 d	61-90 d	
No.	446	339	72	35	
Any pathogen detected	111 (24.9)	55 (16.2)	38 (52.8)	18 (51.4)	<.001
Non-HRV pathogen	59 (13.2)	29 (8.6)	21 (29.2)	9 (25.7)	<.001
HRV alone	42 (9.4)	22 (6.5)	13 (18.1)	7 (20.0)	.01
HRV + ≥1 other pathogen	10 (2.2)	4 (1.2)	4 (5.6)	2 (5.7)	.64

Values are No. (%) unless otherwise indicated.

Table IV. Prevalence of RPs among infants with hypothermia with SBIs

Respiratory pathogen result	Total	Age category		
		≤28 d	29-60 d	61-90 d
Any SBI	33	25	5	3
Non-HRV +	2 (6.1)	2 (8)	0 (0)	0 (0)
HRV+	4 (12.1)	1 (4)	1 (20)	2 (66.7)
RP–	27 (81.8)	22 (88)	4 (80)	1 (33.3)
Any UTI	15 (45.5)	14 (56)	1 (20)	0 (0)
Non-HRV +	0 (0)	0 (0)	0 (0)	0 (0)
HRV+	1 (6.7)	1 (7.1)	0 (0)	0 (0)
RP–	14 (93.3)	13 (92.9)	1 (100)	0 (0)
Any bacteremia	18 (54.6)	13 (52)	3 (60)	2 (66.7)
Non-HRV +	2 (11.1)	2 (15.4)	0 (0)	0 (0)
HRV+	3 (16.7)	0 (0)	1 (33.3)	2 (100)
RP–	13 (72.2)	11 (84.6)	2 (66.7)	0 (0)
Any meningitis	5 (15.2)	2 (8)	1 (20)	2 (66.7)
Non-HRV +	0 (0)	0 (0)	0 (0)	0 (0)
HRV+	1 (20)	0 (0)	0 (0)	1 (50)
RP–	4 (80)	2 (100)	1 (100)	1 (50)
IBI (bacteremia/meningitis)	20 (60.6)	13 (52)	4 (80)	3 (100)
Non-HRV +	2 (10)	2 (15.4)	0 (0)	0 (0)
HRV+	3 (15)	0 (0)	1 (25)	2 (66.7)
RP–	15 (75)	11 (84.6)	3 (75)	1 (33.3)

Values are No. (%) unless otherwise indicated.

literature on febrile infants, positive HRV testing was only associated with IBI for infants 29-60 days but not infants ≤28 days.[16] In our cohort, HRV was more prevalent among children older than 29 days compared with ≤28 days; however, no difference by SBI/IBI outcome was detected. Future studies with larger cohorts of older infants could better assess associations between HRV positivity and SBI/IBI in this subpopulation, potentially facilitating a decrease in hospital stay and receipt of unnecessary antibiotics, as has been described for febrile infants.[30,37]

Several patient and clinical factors may affect the association between RP testing and incidence/prevalence of SBI. In our study, infants who were ill-appearing more frequently received RP testing and had positive testing results. Although ill appearance is a risk factor for SBI among febrile infants,[13] it was not independently associated with IBI among infants with hypothermia.[12] Accordingly, additional testing in this subpopulation of infants might guide risk stratification for SBI and IBI. The utility of RP testing in infants with hypothermia may be affected by the seasonality of respiratory viruses. Infants who were tested during fall and winter months more often had RP+ testing; because certain viruses such as influenza and respiratory syncytial virus are historically most prevalent in communities during the winter season,[38] the effect of RP+ results in modifying the post-test probability of an SBI/IBI may be limited during these times. The AAP febrile infant guidelines suggest that for febrile infants >28 days old, viral testing should be considered on an individual basis, however, if obtained, results should not affect entrance into a recommended care pathway.[13] Our data suggest that the decision to obtain RP testing and use the results to influence care should be determined on an individualized basis, as similarly suggested for febrile infants in the AAP febrile infant clinical practice guideline.

Our study is not without limitations. Although the data are from the largest research collaborative on infants with hypothermia with verified temperature data to date, the relatively low prevalence of SBI and IBI among the study cohort limits our statistical power to detect small but still potentially clinically important differences. In addition, not all infants underwent evaluation for all 3 sources of SBI or RP testing, so the point estimate of SBI prevalence may not be generalizable to all infants with hypothermia. However, no infants from the larger parent study cohort without a full or partial SBI evaluation returned with SBI or IBI within 30 days of the initial encounter.[20] Additional limitations pertained to the variation in RP testing performed for each infant. Although the majority of RP panels were similar across 7 of 9 sites, 2 sites did not include *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Bordetella pertussis*, or *Bordetella parapertussis* during the periods of the study. Further, younger infants were more likely to receive RP testing overall, and not all infants with RP testing were evaluated with panels of PCRs. As a result, we may have underestimated the prevalence of positive testing results and of individual pathogens among this cohort. We would not expect the lack of certain pathogens on a panel to significantly alter the association between testing and SBI/IBI, given these pathogens were not detected among the infants with more expansive testing. However, the observation that older infants had RP testing performed less often but more frequently had a pathogen detected may have biased our findings toward the null (ie, making it less likely to detect an association between SBI and RP testing). Lastly, although the participating sites in our study are geographically diverse, all the sites were large, tertiary medical centers; hence, data from our study may not be generalizable to community-based medical centers.

Conclusions

In this multicenter study of infants with hypothermia, we did not detect a difference in the prevalence of SBI or IBI between infants who were RP+ and RP–. The use of RP testing in infants with hypothermia to guide clinical decision-making surrounding evaluation for SBI should not yet be

implemented broadly. If implemented, there should be acknowledgment of uncertainty in the overall effect on an infant's risk for infection. Further research is needed to understand whether RP testing can aid in the risk stratification of infants with hypothermia. ■

CRediT authorship contribution statement

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Declaration of Competing Interest

Dr. Morrison was supported through the National Heart, Lung, and Blood Institute, National Institutes of Health, award 1K23HL163331.

All authors report no conflicts of interest to disclose.

We acknowledge Lauren Gabriel, Erin Schmidt, Hania Adib, Ali Sawani, Meghan Gray, Noah Hellermann, Elizabeth Rinaldi, Melissa Burns, Amber Domako Rachael Mullin, Kevin Basagio, and Stephanie Prudencio for their contributions to the Hypothermic Young Infant Research Collaborative.

Submitted for publication Sep 7, 2023; last revision received Dec 22, 2023; accepted Jan 8, 2024.

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References

1. Nigrovic LE, Mahajan PV, Blumberg SM, Browne LR, Linakis JG, Ruddy RM, et al. The Yale observation scale score and the risk of serious bacterial infections in febrile infants. Pediatrics 2017;140:e20170695.
2. 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.
3. Levine DA, Platt SL, Dayan PS, Macias CG, Zorc JJ, Krief W, et al. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. Pediatrics 2004;113:1728-34.
4. 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;173:342-51.
5. McCulloh RJ, McDaniel LM, Kerns E, Biondi EA. Prevalence of invasive bacterial infections in well-appearing, febrile infants. Hosp Pediatr 2021;11:e184-8.
6. Kasmire KE, Vega C, Bennett NJ, Laurich VM. Hypothermia: a sign of sepsis in young infants in the emergency department? Pediatr Emerg Care 2021;37:e124-8.
7. Perry MC, Yaeger SK, Noorbakhsh K, Cruz AT, Hickey RW. Hypothermia in young infants: frequency and yield of sepsis workup. Pediatr Emerg Care 2021;37:e449-55.
8. Ramgopal S, Walker LW, Vitale MA, Nowalk AJ. Factors associated with serious bacterial infections in infants ≤60 days with hypothermia in the emergency department. Am J Emerg Med 2019;37:1139-43.
9. Ramgopal S, Noorbakhsh KA, Pruitt CM, Aronson PL, Alpern ER, Hickey RW. Outcomes of young infants with hypothermia evaluated in the emergency department. J Pediatr 2020;221:132-7.e2.
10. Wang ME, Neuman MI, Nigrovic LE, Pruitt CM, Desai S, DePorre AG, et al. Characteristics of afebrile infants ≤60 days of age with invasive bacterial infections. Hosp Pediatr 2021;11:100-5.
11. 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.
12. Raffaele JL, Sharma M, Berger S, Mitchell M, Lee C, Morrison J, et al. Prevalence of invasive bacterial infection in hypothermic young infants: a multisite study. J Pediatr 2023;258:113407.
13. Pantell RH, Roberts KB, Adams WG, Dreyer BP, Kuppermann N, O'Leary ST, et al. Evaluation and management of well-appearing febrile infants 8 to 60 days old. Pediatrics 2021;148:e2021052228.
14. Lyons TW, Garro AC, Cruz AT, Freedman SB, Okada PJ, Mahajan P, et al. Performance of the modified Boston and Philadelphia criteria for invasive bacterial infections. Pediatrics 2020;145:e20193538.
15. Biondi EA, Byington CL. Evaluation and management of febrile, well-appearing young infants. Infect Dis Clin North Am 2015;29:575-85. https://doi.org/10.1016/j.idc.2015.05.008
16. Blaschke AJ, Korgenski EK, Wilkes J, Presson AP, Thorell EA, Pavia AT, et al. Rhinovirus in febrile infants and risk of bacterial infection. Pediatrics 2018;141:e20172384.
17. Krief WI, Levine DA, Platt SL, Macias CG, Dayan PS, Zorc JJ, et al. Influenza virus infection and the risk of serious bacterial infections in young febrile infants. Pediatrics 2009;124:30-9.
18. Aronson PL, Louie JP, Kerns E, Jennings B, Magee S, Wang ME, et al. Prevalence of urinary tract infection, bacteremia, and meningitis among febrile infants aged 8 to 60 days with SARS-CoV-2. JAMA Netw Open 2023;6:e2313354.
19. Gill PJ, Richardson SE, Ostrow O, Friedman JN. Testing for respiratory viruses in children: to swab or not to swab. JAMA Pediatr 2017;171:798-804.

20. Combs MD, Mitchell M, Molas-Torreblanca K, Lee C, Raffaele JL, Sharma M, et al. Variation in care of well-appearing hypothermic young infants: a multisite study. Hosp Pediatr 2023;13:742-50.
21. 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.
22. Lo YHJ, Graves C, Holland JL, Rogers AJ, Money N, Hashikawa AN, et al. Temperature threshold in the screening of bacterial infections in young infants with hypothermia. Emerg Med J 2023;40:189-94.
23. Sprecher A, Malin K, Finley D, Lembke P, Keller S, Grippe A, et al. Quality improvement approach to reducing admission hypothermia among preterm and term infants. Hosp Pediatr 2021;11:270-6.
24. Andrews C, Whatley C, Smith M, Brayton EC, Simone S, Holmes AV. Quality-improvement effort to reduce hypothermia among high-risk infants on a mother-infant unit. Pediatrics 2018;141:e20171214.
25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.
26. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr 2014;14:199.
27. Baskin MN, Goh XL, Heeney MM, Harper MB. Bacteremia risk and outpatient management of febrile patients with sickle cell disease. Pediatrics 2013;131:1035-41.
28. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011;128:595-610.
29. Aronson PL, Lyons TW, Cruz AT, Freedman SB, Okada PJ, Fleming AH, et al. Impact of enteroviral polymerase chain reaction testing on length of stay for infants 60 days old or younger. J Pediatr 2017;189:169-74.e2.
30. Byington CL, Reynolds CC, Korgenski K, Sheng X, Valentine KJ, Nelson RE, et al. Costs and infant outcomes after implementation of a care process model for febrile infants. Pediatrics 2012;130:e16-24.
31. Byington CL, Enriquez FR, Hoff C, Tuohy R, Taggart EW, Hillyard DR, et al. Serious bacterial infections in febrile infants 1 to 90 days old with and without viral infections. Pediatrics 2004;113:1662-6.
32. Jansen RR, Wieringa J, Koekkoek SM, Visser CE, Pajkrt D, Molenkamp R, et al. Frequent detection of respiratory viruses without symptoms: toward defining clinically relevant cutoff values. J Clin Microbiol 2011;49:2631-6.
33. Muller L, Mack I, Tapparel C, Kaiser L, Alves MP, Kieninger E, et al. Human rhinovirus types and association with respiratory symptoms during the first year of life. Pediatr Infect Dis J 2015;34:907-9.
34. van der Zalm MM, van Ewijk BE, Wilbrink B, Uiterwaal CS, Wolfs TF, van der Ent CK. Respiratory pathogens in children with and without respiratory symptoms. J Pediatr 2009;154:396-400.e1.
35. Byington CL, Ampofo K, Stockmann C, Adler FR, Herbener A, Miller T, et al. Community surveillance of respiratory viruses among families in the Utah Better Identification of Germs-Longitudinal viral Epidemiology (BIG-LoVE) study. Clin Infect Dis 2015;61:1217-24.
36. Loeffelholz MJ, Trujillo R, Pyles RB, Miller AL, Alvarez-Fernandez P, Pong DL, et al. Duration of rhinovirus shedding in the upper respiratory tract in the first year of life. Pediatrics 2014;134:1144-50.
37. Dorney K, Bachur RG. Febrile infant update. Curr Opin Pediatr 2017;29:280-5.
38. Neumann G, Kawaoka Y. Seasonality of influenza and other respiratory viruses. EMBO Mol Med 2022;14:e15352.