Received: 14 May 2024 | Revised: 17 June 2024 | Accepted: 26 June 2024

DOI: 10.1002/emp2.13241

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
WILEY

ORIGINAL ARTICLE

Pediatrics

Epidemiology and risk stratification of young infants presenting to the emergency department with hypothermia

Michelle L. Wang BA[1] | **Indi Trehan MD, MPH**[2]

[1]University of Washington School of Medicine, Seattle, Washington, USA

[2]Departments of Pediatrics, Global Health, and Epidemiology, University of Washington, Seattle, Washington, USA

Correspondence
Indi Trehan, Departments of Pediatrics, Global Health, and Epidemiology, University of Washington, Seattle, WA, USA.
Email: indi@alum.berkeley.edu

Meeting: Presented at the Western Medical Research Conference, in Carmel, CA, USA, January 2024.

Funding information
Seattle Children's Hospital Pediatric Emergency Medicine Research Endowment

Abstract

Objective: Hypothermic infants are presumed to be at high risk for a serious bacterial infection (SBI) or herpes simplex virus (HSV) infection. In contrast to febrile infants, the emergency department (ED) management of hypothermic infants is variable in the absence of consensus guidelines, potentially resulting in low-value care and missed diagnoses. We investigated the diagnostic workup conducted for hypothermic infants in our academic pediatric ED, the incidence of SBI and HSV infection, and risk factors associated with infection.

Methods: We conducted a single-center retrospective study of infants ≤90 days of age with a rectal temperature ≤36.5°C in the ED between 2013 and 2022. From their medical records, we abstracted the type(s) of testing each infant received in the ED and the diagnosis of SBI and HSV, analyzing characteristics associated with each.

Results: Of 1095 hypothermic infants identified, 402 (37%) underwent testing for SBI or HSV. Among these, 34/402 (8.5%) had an SBI or HSV. A minimum temperature below 36°C and hospital admission were characteristics associated with higher rates of infectious testing. Infants aged 29–90 days, compared to 0–28 days, were more likely to have a urinary tract infection (odds ratio 3.28, 95% confidence interval 1.47–7.32).

Conclusions: Hypothermic infants have slightly lower rates of SBI or HSV than febrile infants, for whom infectious studies are widely recommended, but still high enough to warrant an infectious workup in most cases. Further research is required to risk stratify hypothermic infants in the ED to standardize care and improve outcomes while optimizing resource utilization.

1 | INTRODUCTION

1.1 | Background

Hypothermia can occur in infants due to a variety of factors, including environmental conditions, low weight, prematurity, and other non-infectious causes.[1–3] However, hypothermia may be the first and only presenting sign of a serious bacterial infection (SBI) (urinary tract infection [UTI], bacteremia, or bacterial meningitis) or herpes simplex virus (HSV) infection, all of which have the potential for significant morbidity and mortality if left undiagnosed and untreated.[4–7] Previous single- and multi-center studies have reported the prevalence of these infections in hypothermic infants to be 1.3%–8.3%, although these studies have been limited by sample size

Supervising editor: Katherine Edmunds, MD, MEd.

and have used varying inclusion criteria for hypothermia.[5,6,8–11] Prior studies have also suggested various clinical and laboratory features, such as absolute neutrophil count, leukocytosis, and platelet count, may be associated with an increased likelihood of these infections.[11–14]

1.2 | Importance

While national consensus clinical practice guidelines have been established and updated recently for managing febrile infants presenting to the emergency department (ED),[15] no national evidence-based guidelines regarding the management of hypothermic infants in the ED exist, leaving significant room for clinical practice variation among and within institutions, which may contribute to increased cost, complications, and inequitable care.[16] In addition, no prediction models with high sensitivity and specificity for SBI have been developed for risk-stratifying hypothermic infants.[17,18] The variation in care of hypothermic infants has been observed in multiple domains, including the threshold for hypothermia (eg, 36.0°C vs. 36.5°C), the amount of diagnostic workup pursued, the use of empiric antimicrobials, and disposition decisions.[7,19,20]

1.3 | Goals of this investigation

In this study, we aimed to investigate factors associated with the extent of diagnostic workup performed for hypothermic infants in a single ED at a freestanding children's hospital. Additionally, we attempted to identify the prevalence of, and investigate risk factors for, SBI and HSV infection among these patients.

The Bottom Line

Hypothermic infants are at high risk for a serious bacterial infection (SBI). In this single-center retrospective study of 1095 hypothermic infants ≤90 days of age, 402 underwent testing for SBI or herpes simplex virus (HSV), and among these, 8.5% had an SBI or HSV. A minimum temperature below 36°C and hospital admission were characteristics associated with higher rates of infectious testing. Further research is required to risk stratify hypothermic infants in the emergency department (ED) to standardize care and improve outcomes while optimizing resource utilization.

2 | METHODS

2.1 | Study design and setting

We conducted a retrospective study of all infants 0–90 days of age with a documented rectal temperature of ≤36.5°C while in the Seattle Children's Hospital ED between January 1, 2013, and December 31, 2022. Seattle Children's Hospital is an academic affiliate of the University of Washington and is a freestanding, quaternary care, urban teaching hospital. All patients are seen by a board-certified or board-eligible pediatric emergency physician, and nearly all are seen in conjunction with a resident physician (emergency medicine, family medicine, or pediatrics), an advanced practice provider (nurse practitioner or physician assistant), or fourth-year medical student. We received institutional review board approval as an exempt study. This study is being reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Supporting Information).

2.2 | Selection of participants

Eligible infants were identified through a search of the hospital electronic medical record (EMR), searching for any documented rectal temperature of ≤36.5°C at any time during their ED stay. We chose 36.5°C as the threshold for initial inclusion in order to be as broadly representative as possible and based on the World Health Organization's classification for hypothermia in newborns,[21] but with the intention to evaluate the threshold of 36.0°C as well, given the possible utility of that temperature threshold. Patients were excluded if they also had a documented rectal temperature of ≥38°C during their ED visit, in accordance with the cutoff used by the American Academy of Pediatrics to define a fever among infants under 60 days of age,[15] as their evaluation and management would then be guided based on principles applied to febrile infants.

2.3 | Data acquisition

We manually extracted clinical and laboratory data from the EMR. Clinical data included patient age in days, sex, date of presentation, chief complaint, disposition, and minimum and maximum rectal temperature documented in the ED. Laboratory data included results of blood, urine, and cerebrospinal fluid (CSF) cultures, HSV testing, complete blood count (CBC), urinalysis, respiratory viral panel, glucose, and C-reactive protein (CRP) levels.

2.4 | Outcomes

The outcomes of primary interest were the types of diagnostic testing ordered in the ED, the rates of SBI and HSV positivity, and the risk factors for SBI and HSV positivity. Any diagnostic testing performed was defined as having at least one of the following ordered by the ED provider: any HSV test, urine culture, blood culture, CSF culture, uri-

nalysis, upper respiratory infection panel (BIOFIRE Respiratory Panel, bioMérieux), CBC, CRP, or glucose test. Any HSV test was defined as an HSV blood polymerase chain reaction (PCR) test, HSV CSF PCR test, or HSV rapid PCR swab test from a skin or ocular site.

Bacteremia and bacterial meningitis were defined by growth of a pathogenic organism in blood or CSF cultures. UTI was defined as urine culture results with ≥100,000 CFU/mL of a single pathogen on a catheterized sample, following the American Academy of Pediatrics UTI Clinical Practice Guidelines.[22]

2.5 | Analysis

We summarized demographic, clinical, and testing statistics for the entire cohort, as well as for subgroups stratified by age in days (0–7, 8–28, 29–60, and 61–90), making comparisons between subgroups using χ^2 tests. We report the prevalence of SBI and HSV among patients who received relevant testing. Additionally, we report the prevalence of these infections among all patients, assuming all infants who did not receive testing did not have an infection. These analyses were conducted for the entire cohort and for the same age subgroups. We used Fisher's exact test to identify factors associated with the outcomes, reporting *p*-values, odds ratios, and 95% confidence intervals.

3 | RESULTS

3.1 | Characteristics of study subjects

A total of 1147 ED patients aged ≤90 days with a documented rectal temperature of ≤36.5°C during their ED course were initially identified by a search of the EMR. Of these, 1095 (48% female, median age 9.8 days, interquartile range 4.6–30.7 days) were ultimately included, as 52 patients were excluded due to also having a documented rectal temperature of ≥38°C during their time in the ED (Table 1 and Figure S1). Most patients ($n = 790$ [72.1%]) were ≤28 days old at presentation, and the majority ($n = 677$ [61.8%]) had a minimum temperature in the ED of 36°C–36.5°C, inclusive. Of the 1095 patients, 721 (65.8%) were admitted to the hospital.

3.2 | Rates of testing

A total of 850 patients (77.6%) had at least one of the following tests performed in the ED: CBC, CRP, glucose, HSV, urinalysis, urine culture, blood culture, CSF analysis and culture, and/or upper respiratory panel (Table 2 and Figure S2). However, only 402 patients (36.7%) had a urine culture, blood culture, CSF culture, or HSV testing performed; 326 (29.8%) had a urine culture, 326 (29.8%) had a blood culture, 193 (17.6%) had a lumbar puncture for CSF analysis, and 107 (9.8%) underwent HSV testing.

3.3 | Factors associated with testing

A number of predictors for the diagnostic workup for SBI and HSV were identified (Figure 1 and Figure S3). A minimum temperature below 36°C, compared to 36°C–36.5°C, and admission to the hospital or intensive care unit, as opposed to discharge, were associated with higher rates of all bacterial cultures (Tables S1–S3) and HSV testing (Tables S4–S7). Infants 0–28 days of age, in contrast to those 29–90 days of age, were more likely to have blood cultures, CSF cultures, and HSV testing done. Females had higher rates of urine cultures performed than males.

3.4 | Rates of SBI and HSV infection

Of patients who underwent the respective testing, 27/326 (8.3%) had a UTI, 7/326 (2.1%) had bacteremia, and 4/107 (3.7%) had a HSV infection (Table 3). Four of these patients had concurrent UTI and bacteremia. No hypothermic infants (0/193) were found to have bacterial meningitis. In total, 34/402 (8.5%) of patients who received any cultures or HSV testing or 34/1095 (3.1%) of all patients in the entire cohort, had an SBI or HSV infection (Table S8 and Figure S4). *Escherichia coli* was the most common pathogen identified among all patients with SBI ($n = 14$ [47%]) (Table S9).

3.5 | Characteristics associated with infection

Among patients who underwent urine culture, those 29–90 days of age, compared with those 0–28 days of age, were more likely to have a diagnosed UTI. No other factors investigated were found to be predictive of bacteremia, UTI, or HSV infection (Figure 2 and Tables S10 and S11).

4 | LIMITATIONS

There are several limitations to our study findings. The absence of a universally agreed-upon definition of hypothermia in neonates may impact the generalizability of our findings, given our use of the broader cutoff of 36.5°C suggested by the World Health Organization,[21] rather than the more commonly used 36°C threshold identified by a recent national survey of pediatric emergency providers.[19] By including patients who had a documented temperature of 36.5°C or lower at any point during their ED stay, rather than limiting it to only those who presented with such hypothermia, we also potentially included well-appearing patients who were not clinically identified or considered initially to be hypothermic, thus capturing many infants who did not undergo laboratory or infectious testing. Some infants with a chief complaint of fever at home or in a pre-referral setting were included in our study as long as they did not have a temperature of 38°C or greater during their ED stay.

TABLE 1 Characteristics of hypothermic infants, stratified by age.

Patient characteristics	Overall ($n = 1095$)	0–7 days ($n = 476$)	8–28 days ($n = 314$)	29–60 days ($n = 215$)	61–90 days ($n = 90$)
Female sex, *n* (%)	524 (47.9)	234 (49.2)	141 (44.9)	104 (48.4)	45 (50.0)
Minimum temperature in ED (°C), *n* (%)					
<35	30 (2.7)	18 (3.8)	6 (1.9)	2 (0.9)	4 (4.4)
35–35.9	388 (35.4)	214 (45.0)	104 (33.1)	53 (24.7)	17 (18.9)
36–36.5	677 (61.8)	244 (51.3)	204 (65.0)	160 (74.4)	69 (76.7)
Maximum temperature in ED (°C), *n* (%)					
≤36.5	400 (36.5)	213 (44.7)	84 (26.8)	66 (30.7)	37 (41.1)
36.6–37.9	695 (63.5)	263 (55.3)	230 (73.2)	149 (69.3)	53 (58.9)
Season, *n* (%)[a]					
Spring	274 (25.0)	122 (25.6)	77 (24.5)	51 (23.7)	24 (26.7)
Summer	241 (22.0)	109 (22.9)	67 (21.3)	47 (21.9)	18 (20.0)
Fall	267 (24.4)	112 (23.5)	74 (23.6)	58 (27.0)	23 (25.6)
Winter	313 (28.6)	133 (27.9)	96 (30.6)	59 (27.4)	25 (27.8)
Pre-COVID-19 pandemic, *n* (%)[b]	995 (90.9)	420 (88.2)	293 (93.3)	199 (92.6)	83 (92.2)
Chief complaint, *n* (%)					
Decreased oral intake	38 (3.5)	16 (3.4)	9 (2.9)	7 (3.3)	6 (6.7)
Emesis	79 (7.2)	13 (2.7)	27 (8.6)	28 (13.0)	11 (12.2)
Fever	84 (7.7)	16 (3.4)	34 (10.8)	26 (12.1)	8 (8.9)
Hyperbilirubinemia	223 (20.4)	193 (40.5)	28 (8.9)	2 (0.9)	0 (0)
Hypothermia	38 (3.5)	26 (5.5)	10 (3.2)	1 (0.5)	1 (1.1)
Respiratory distress	79 (7.2)	16 (3.4)	23 (7.3)	25 (11.6)	15 (16.7)
Other	554 (50.6)	196 (41.2)	183 (58.3)	126 (58.6)	49 (54.4)
Admitted to hospital, *n* (%)	721 (65.8)	337 (70.8)	218 (69.4)	120 (55.8)	46 (51.1)

Note: Comparisons by χ^2 test.

[a]Seasons defined by date of emergency department (ED) presentation. January 1 to March 30 considered winter, April 1 to June 30 considered spring, July 1 to September 30 considered summer, and October 1 to December 31 considered fall.

[b]Pre-COVID-19 pandemic defined as presentation to the ED before March 11, 2020.

Our study also focused on a cohort from a single academic urban pediatric hospital, potentially limiting the generalizability of our results. However, the variability in provider management decisions observed within our cohort implies that the variations in the management of hypothermic patients extend beyond the institutional level down to the provider level, as identified previously.[19]

Additionally, although the size of our overall cohort was relatively large, the relatively small number of positive infections may limit the robustness of our analysis, especially with regards to meningitis. This speaks to the need for large multicenter retrospective and prospective studies in order to have sample sizes large enough to more accurately assess risk factors for severe infections in this age group.

We intentionally evaluated only a limited set of variables, which did not capture other vital signs, clinical gestalt, medical history, or additional laboratory results that could potentially be associated with an increased level of diagnostic workup or the occurrence of SBI or HSV infection. This was done because the ultimate clinical goal would be to develop simple risk stratification tools that could be used at the point of triage or even in the pre-referral setting for evaluation of hypothermic infants.

We also do not have data on the clinical trajectory of infants after ED discharge, either to home or during admission. Our assumption that all patients who did not undergo microbiological testing did not have an SBI or HSV infection may have led to an underestimation of the true incidence of infections, as some may have returned for care at other facilities. Similarly, calculating the incidence of these infections among only patients who received testing potentially results in an overestimate of the rate of these serious infections among all hypothermic neonates. Despite these limitations, our findings from this large patient cohort provide valuable insights for future research on the management and risk stratification of hypothermic neonates in the ED and the epidemiology of SBI and HSV infection among this population.

TABLE 2 Rates of testing ordered in emergency department, stratified by age.

Variable	Overall ($n = 1095$)	0–7 days ($n = 476$)	8–28 days ($n = 314$)	29–60 days ($n = 215$)	61–90 days ($n = 90$)	*p*-Value
SBI or HSV testing, *n* (%)[a]	402 (36.7)	181 (38)	119 (37.9)	76 (35.3)	26 (28.9)	0.379
Blood culture	326 (29.8)	161 (33.8)	95 (30.3)	52 (24.2)	18 (20.0)	0.011
Urine culture	326 (29.8)	146 (30.7)	101 (32.2)	58 (27.0)	21 (23.3)	0.304
CSF culture	193 (17.6)	107 (22.5)	63 (20.1)	19 (8.8)	4 (4.4)	<0.001
Any HSV test	107 (9.8)	68 (14.3)	28 (8.9)	9 (4.2)	2 (2.2)	<0.001
Blood PCR	61 (5.6)	44 (9.2)	16 (5.1)	0 (0)	1 (1.1)	<0.001
CSF PCR	83 (7.6)	51 (10.7)	22 (7.0)	8 (3.7)	2 (2.2)	0.002
Skin/eye PCR swab	78 (7.1)	54 (11.3)	22 (7.0)	1 (0.5)	1 (1.1)	<0.001
Other diagnostic studies, *n* (%)						
CBC	448 (40.9)	191 (40.1)	148 (47.1)	81 (37.7)	28 (31.1)	0.021
CRP	54 (4.9)	21 (4.4)	12 (3.8)	14 (6.5)	7 (7.8)	0.284
Glucose	680 (62.1)	370 (77.7)	178 (56.7)	90 (41.9)	42 (46.7)	<0.001
Urinalysis	321 (29.3)	137 (28.8)	98 (31.2)	63 (29.3)	23 (25.6)	0.747
Respiratory PCR panel	270 (24.7)	87 (18.3)	91 (29.0)	64 (29.8)	28 (31.1)	0.003
Any test, *n* (%)[b]	850 (77.6)	403 (84.7)	247 (78.7)	142 (66.0)	58 (64.4)	<0.001

Note: Comparisons by χ^2 test.

Abbreviations: CBC, complete blood count; CRP, C-reactive protein; CSF, cerebrospinal fluid; HSV, herpes simplex virus; PCR, polymerase chain reaction; SBI, serious bacterial infection.

[a]Defined as at least one of the following: blood culture, urine culture, CSF culture, or any HSV test.

[b]Defined as at least one of the following: blood culture, urine culture, CSF culture, any HSV test, CBC, CRP, glucose, urinalysis, or upper respiratory panel. Does not include patients who only underwent other testing (e.g., bilirubin).

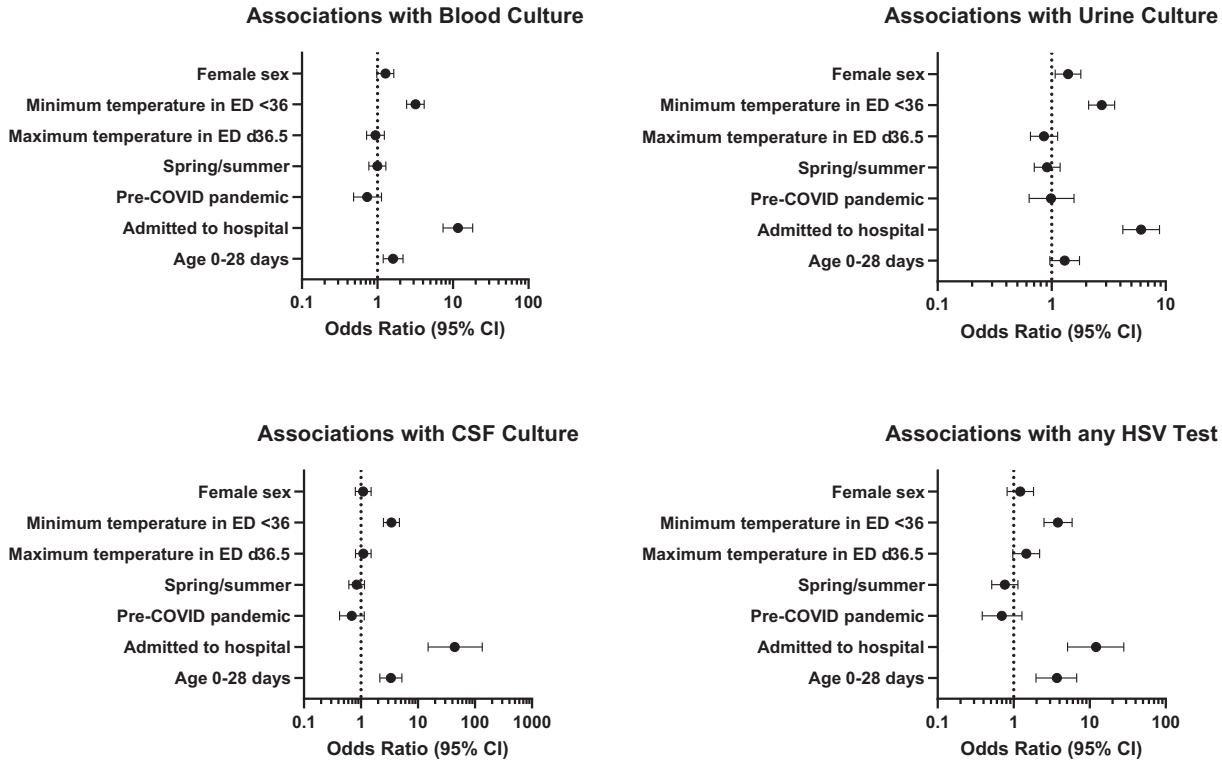

FIGURE 1 Characteristics associated with diagnostic testing for hypothermic infants in the emergency department (ED). Comparisons by Fisher's exact test. Seasons defined by date of ED presentation. January 1 to March 30 considered winter, April 1 to June 30 considered spring, July 1 to September 30 considered summer, and October 1 to December 31 considered fall. Pre-COVID-19 pandemic defined as presentation to the ED before March 11, 2020. CI, confidence interval; CSF, cerebrospinal fluid; HSV, herpes simplex virus.

TABLE 3 Rates of serious bacterial infection (SBI) and herpes simplex virus (HSV) infection among tested patients, stratified by age.

Infection	Overall	0–7 days	8–28 days	29–60 days	61–90 days	*p*-Value
Any SBI or HSV, *n* (%)	34/402 (8.5)[a]	5/181 (2.8)	15/119 (12.6)	10/76 (13.2)	4/26 (15.4)	0.003
Bacteremia	7/326 (2.1)	1/161 (0.6)	4/95 (4.2)	1/52 (1.9)	1/18 (5.6)	0.194
UTI	27/326 (8.3)	2/146 (1.4)	12/101 (11.9)	9/58 (15.5)	4/21 (19.0)	0.0004
Bacterial meningitis	0/193 (0)	0/107 (0)	0/63 (0)	0/19 (0)	0/4 (0)	–
HSV	4/107 (3.7)	2/68 (2.9)	1/28 (3.6)	1/9 (11.1)	0/2 (0)	0.669

Note: Comparisons by χ^2 test.
Abbreviation: UTI, urinary tract infection.
[a]Concurrent UTI and bacteremia present in four patients.

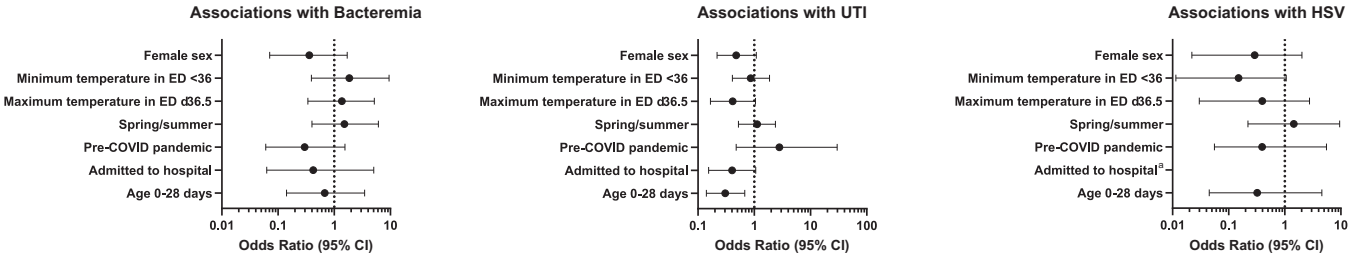

FIGURE 2 Characteristics associated with diagnosis of SBI and HSV infection among hypothermic infants who underwent directed testing in the emergency department (ED). Comparisons by Fisher's exact test. [a]Unable to plot odds ratio of ∞. Seasons defined by date of ED presentation. January 1 to March 30 considered winter, April 1 to June 30 considered spring, July 1 to September 30 considered summer, and October 1 to December 31 considered fall. Pre-COVID-19 pandemic defined as presentation to the ED before March 11, 2020. CI, confidence interval; HSV, herpes simplex virus; UTI, urinary tract infection.

5 | DISCUSSION

In our retrospective cohort study of infants ≤90 days of age with documented hypothermia in the ED, we found that 36.7% of patients received any SBI or HSV testing. Within this group, 8.5% tested positive for SBI or HSV, corresponding to 3.1% of all patients included in the study. Lower temperature and hospital admission were associated with increased rates of testing for SBI and HSV. Female sex was associated with higher rates of testing for UTI. Younger age was associated with higher rates of blood cultures, CSF cultures, and HSV testing. Presentation at an older age was associated with an increased incidence of UTIs. We did not identify any additional risk factors associated with SBI or HSV infection.

Our reported rates of SBI and HSV testing were comparable to those reported in other studies that also used a temperature cutoff of ≤36.5°C as inclusion criteria.[7,9] In contrast, studies that exclusively included patients with temperatures below 36°C reported markedly higher testing rates of approximately 70%–90%.[8,9,19,20,23] Other studies and surveys have also corroborated the association we observed between younger age at presentation and higher testing rates.[8,9,19,23]

Our reported rate of SBI and HSV among tested patients (8.5%) is slightly higher than that reported by Money et al. (6.1%), which similarly used 36.5°C as inclusion criteria but did not report HSV infection.[14] While our reported rate of SBI and HSV infection among all patients (3.1%) is lower than those reported by Ramgopal et al.[11] and Raffaele et al.[10] (8.3% and 5.7%, respectively), which also had cohort sizes of over 1000 patients, those studies exclusively included patients with temperatures below 36°C. Given the continued variability and uncertainty among pediatric emergency medicine practitioners as to which temperature threshold to use for optimal risk stratification for hypothermia,[19] we feel that providing information about those infants with temperatures ≤36.5°C is useful. Although we did not find minimum temperature to be associated with increased SBI or HSV infection, Wood et al. reported an association between a minimum temperature ≤34.4°C and these infections,[5] although that threshold is so low as to likely remove most clinical practice variation.

Most importantly for clinical practice, our SBI and HSV infection prevalence (whether using 3.1% or 8.5%), and even using a threshold of 36.5°C for hypothermia, is similar to the 2%–8% range reported by studies involving febrile neonates,[12,24–28] an incidence that generally continues to meet the threshold for a broad diagnostic workup for serious infections.[15] However, directly applying febrile infant decision tools to hypothermic infants has low specificity, suggesting the need for the creation of new algorithms specific to the hypothermic infant population.[18]

Although we identified multiple factors associated with SBI and HSV testing, the only factor we found to be associated with actual infection rates was older age in the case of UTIs. Other studies have reported an association of SBI and HSV infection with repeated temperature instability, higher white blood cell count, younger age, abnormal platelet count, abnormal urinalysis, and lower temperature.[5,9–11,14] Differences in our findings compared to others could be attributed

to differences in study design or due to the small number of patients with SBI and HSV infection in any given study. Until comprehensive large-scale, standardized, multicenter studies are conducted to further identify which infants are at greatest risk for infection, our findings support the continued widespread use of SBI and HSV testing for hypothermic neonates in the ED as there are insufficient clinical or screening laboratory markers to identify those with serious infections.

In summary, hypothermic infants appear to have rates of SBI and HSV infection slightly lower than febrile infants, in whom infectious studies are widely recommended. Nevertheless, the rate of these severe infections in our cohort (3.1%–8.5%) is arguably still higher than the threshold needed to warrant testing in most situations. Due to the low incidence of hypothermia among infants, a multicenter study is required to risk stratify hypothermic infants in the ED to standardize care and improve outcomes while minimizing excessive testing, which should also include cost-effectiveness analyses. Eventually, an algorithm for clinical management should be developed in a manner similar to febrile infants.

AUTHOR CONTRIBUTIONS

Michelle L. Wang collected and analyzed the data and drafted the manuscript. Indi Trehan conceived and designed the study, supervised data analysis, and takes responsibility for the paper as a whole. Both authors contributed substantially to manuscript revision and have approved the final submitted version.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

FUNDING INFORMATION

Supported by the Seattle Children's Hospital Pediatric Emergency Medicine Research Endowment.

DATA AVAILABILITY STATEMENT

The deidentified dataset and data dictionary are available upon request from the date of article publication by contacting Indi Trehan at indi@alum.berkeley.edu to investigators who provided an IRB letter of approval.

ORCID

Indi Trehan MD, MPH https://orcid.org/0000-0002-3364-6858

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wang ML, Trehan I. Epidemiology and risk stratification of young infants presenting to the emergency department with hypothermia. *JACEP Open*. 2024;5:e13241. https://doi.org/10.1002/emp2.13241

AUTHOR BIOGRAPHY

Indi Trehan, MD, MPH is a Professor of Pediatrics in the Divisions of Emergency Medicine and Infectious Diseases at the University of Washington in Seattle, WA, USA.