RESEARCH ARTICLE

Clinical Characteristics and Health Outcomes of Neonates Reporting to the Emergency Department With Hypothermia

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ABSTRACT

OBJECTIVES: Although hypothermia has long been considered a sign of serious bacterial infection (SBI) in neonates, there is a lack of medical literature on this topic, and little is known about the prevalence of serious infection in these patients. Our primary objective was to assess the prevalence and type of serious infection in neonates with hypothermia. Our secondary objective was to describe the prevalence and type of significant pathology overall in this cohort.

METHODS: We examined neonates (≤28 days old) evaluated in the emergency department and/or admitted to the hospital with hypothermia over a 3-year period. Demographics and relevant clinical data were extracted from the medical record. Fisher's exact test was used to determine differences in the prevalence of clinical and demographic characteristics in patients with and without a diagnosis of serious infection.

RESULTS: Sixty-eight neonates met inclusion criteria, and 63 (93%) were admitted. Of those admitted to the hospital, 5 (7.9%) had a diagnosis of serious infection, including SBI ($n = 4$) and disseminated herpes simplex virus ($n = 1$). The types of SBI included urinary tract infection, septicemia, and meningitis. Eighty percent and 60% of neonates with hypothermia and diagnosed with serious infection had a temperature ≤34.4°C and ill appearance, respectively. Significant pathology was found in 9 (14.3%) patients and included both infectious and noninfectious diagnoses.

CONCLUSIONS: Neonates presenting with hypothermia have a substantial risk for SBI or other significant pathology. This population merits further investigation; a multicenter prospective study should be conducted to better understand associations between risk factors and outcomes.

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Fever is the most common reason for an infant to present to the emergency department (ED) for evaluation.[1] There is an abundance of literature with regard to the workup and management of the febrile neonate.[2–5] It is the current standard of care to evaluate for serious bacterial infection (SBI) and admit these patients to the hospital for empirical antibiotic treatment given the challenge of reliably recognizing those neonates with SBIs.[6–10] Upward of 10% of febrile neonates will have an SBI, whereas the remainder will have nonbacterial etiologies, such as viral illness, as the cause of their fever.[11]

Fever may not be observed in neonates who are later diagnosed with severe infection; in 1 cohort of patients with bacteremia, 13% were afebrile at presentation.[12] In fact, neonates who are diagnosed with an infection may initially present with hypothermia.[13] Generally, infection may lead to hypothermia by increasing the catabolic state.[14] Despite the extensive literature dedicated to the risk of serious infection in febrile neonates, there is scant research or guidance regarding the workup and outcomes of neonates presenting with hypothermia. Researchers in 3 studies published in the 1960s and 1980s describe a risk of eventual diagnosis of severe infection in neonates presenting with hypothermia, but these are not generalizable to our population because of the advancement in vaccinations and the geographic location of the cohorts recruited in these studies.[14–16] There is also literature published with regard to hypothermia and neonatal herpes simplex virus (HSV) infection that in which researchers describe a sepsislike syndrome with hypothermia as a presenting risk factor for an eventual diagnosis of HSV in neonates.[17,18] In 1 retrospective prevalence study, 1.1% of neonates presenting with hypothermia had an eventual diagnosis of HSV infection.[17] Still, the question of the type and extent of workup for neonates with hypothermia remains.

It is the standard of care at our institution to initiate the same infectious workup in neonates who present to the ED with hypothermia as we do in those who present with fever. We set out to understand if such cautious and extensive evaluations were needed for these neonates. Because there is a paucity of literature with regard to this subset of patients, we initiated this study to better understand the hypothermia in neonates who present to our institution. Our purpose in this study was to determine the prevalence and types of serious infection (SBI or HSV) in neonates with hypothermia presenting to the ED and describe differences in selected patient demographics and characteristics that exist between those with serious infection and those without. Secondarily, we also sought to identify the prevalence and type of significant pathology, including noninfectious etiologies, overall in neonates with hypothermia.

METHODS

Study Design, Setting, and Population

A single-center retrospective chart review of neonates, defined as infants born at any gestational age who are ≤28 days of age, who were evaluated in the ED at Brenner Children's Hospital for reported or documented hypothermia over a 3-year period (September 1, 2013–September 1, 2016) was conducted. Brenner Children's Hospital at Wake Forest Baptist Health is a tertiary-care academic children's hospital in Winston-Salem, North Carolina.

Inclusion criteria encompassed neonates ≤28 days old with documented or reported hypothermia presenting to the ED. Documented hypothermia was defined as hypothermia found during temperature monitoring at the primary care physician's office or on triage in the ED. Reported hypothermia was defined as having a low temperature found during home temperature monitoring by the parent or caregiver by any means (temporal, rectal, or axillary).

Patient charts were identified by using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) billing codes for "hypothermia, newborn or disorder of temperature regulation" (codes 778.3 and 778.4 from the ICD-9-CM and codes P808 and P818 and 819 from the ICD-10-CM), and the temperature used to ensure that the ED visit was truly for hypothermia was ≤36.1°C. Exclusion criteria included neonates who did not truly have hypothermia (incorrect billing code used).

The electronic medical record was queried by using the above codes, and these charts were manually reviewed to ensure they met inclusion criteria. Subsequently, the electronic medical record was queried for all patients admitted to our hospital who were ≤28 days of age over the same 3-year period to ensure that administrative and billing data did not exclude any patients. The Wake Forest School of Medicine Institutional Review Board approved this study protocol (00041291).

Data Collection

All eligible charts were reviewed by the study team members, who were trained on data abstraction by the principal investigator before data collection. Discrepancies with regard to data were proposed to the entire study team, and consensus decisions were made with the input of all members after review.

Medical record review was used to record deidentified patient characteristics, including demographic, clinical, and laboratory details as well as hospital course and outcomes. Data were abstracted on patient age, sex, race, and duration of gestation. Clinical data included temperature on presentation as well as appearance of patient and abnormal physical examination findings. Laboratory data collected included complete blood cell count with differential, complete metabolic panel, HSV testing on blood and cerebrospinal fluid (CSF), urinalysis with microscopy, urine culture, CSF profile and culture, and blood culture. Hospital course and outcomes included admission location (floor unit, intermediate care unit [IMC], or PICU), admission service (pediatric hospitalist, pediatric subspecialist, or pediatric intensivist), use of antimicrobial agents, length of stay (LOS) in hours, and discharge diagnosis.

Definitions

Patients were classified as having an SBI if they had a discharge diagnosis of urinary tract infection (UTI), bacteremia and/or septicemia, or bacterial meningitis.[19] UTI was defined as ≥50 000 colony-forming units/mL of a single pathogen on a catheterized sample with a concomitant urinalysis with pyuria.[20] Bacteremia and/or septicemia were defined as blood culture growth of bacteria (not determined to be a contaminant in laboratory workup) or a diagnosis of bacteremia and/or septicemia with negative culture results as determined by a patient who met systemic inflammatory response criteria with suspected infection but without bacterial growth on culture.[21] Bacterial meningitis was defined as CSF culture growth of bacteria (not determined to be a contaminant in laboratory workup), whereas viral meningitis was defined by CSF pleocytosis with positive viral testing results, and CSF pleocytosis was defined as abnormal white blood cell (WBC) counts on CSF without an identified pathogen. A planned rule out SBI was defined as a clinical and laboratory workup (blood, urine, and CSF cultures) and receipt of antimicrobial agents, and it was determined by review of ED physician medical decision-making in the patient chart. Serious infection was defined as an SBI or HSV infection. Pneumonia was defined as new, discrete infiltrates on chest radiography and was only considered to be an SBI if a known respiratory pathogen was isolated concurrently from the neonate's blood culture.

Ill appearance of the patient was defined as the attending physician's (ED or admitting) note including words such as "ill-appearing" or "toxic" or a description of the patient as being less arousable, weak, or mottled, as described in the severe impairment category on the Yale Observation Scale.[22] There were no discrepancies between the ED and admitting staff with regard to the appearance of a patient. Significant pathology was defined as a discharge diagnosis that required hospitalization for treatment or monitoring (excluding those that just required monitoring of temperature) as determined by the study team. Also excluded from the definition of significant pathology were neonates with the sole diagnosis of jaundice who needed phototherapy. LOS was calculated in hours as the number of hours from hospital admission (time admission order placed) through hospital discharge (time discharge order placed).

Outcome Measures

Primary outcomes were the prevalence and type of serious infection (SBI or HSV) in neonates with hypothermia. The prevalences of associated clinical and patient characteristics were described. Secondary outcomes included the prevalence and type of significant pathology overall in this cohort.

Statistical Methods

Fisher's exact test was used to determine differences in clinical and demographic patient characteristics in patients with and without an eventual diagnosis of serious infection. $P < .05$ was considered statistically significant. We calculated 95% confidence intervals (CIs) for prevalence estimates and proportions. Regression analysis to control for confounding variables was planned, but a small number of events of serious infection prevented this. SAS (version 9.4; SAS Institute, Inc, Cary, NC) statistical software was used for analysis.

RESULTS

Cohort

We identified 69 neonates via ICD-9-CM and ICD-10-CM codes; 64 of these met inclusion criteria on manual chart review, with 5 excluded for lack of hypothermia, defined by reviewers as a temperature ≤36.1°C. Subsequently, we identified 730 patients ≤28 days of age admitted for any reason to our hospital over the same time frame. We manually reviewed these charts for admission reason to ensure that billing and administrative data were not excluding any patients; only 4 (0.5%) of these neonates met inclusion criteria for our study. We did not manually review the charts of all neonates seen in the ED (and sent home) during the same 3-year period because, on the basis of our review of all admitted patients, billing codes seem to capture this population well and outcome measures were only to be analyzed on admitted patients. Thus, a total of 68 neonates met inclusion and exclusion criteria for analysis (Fig 1).

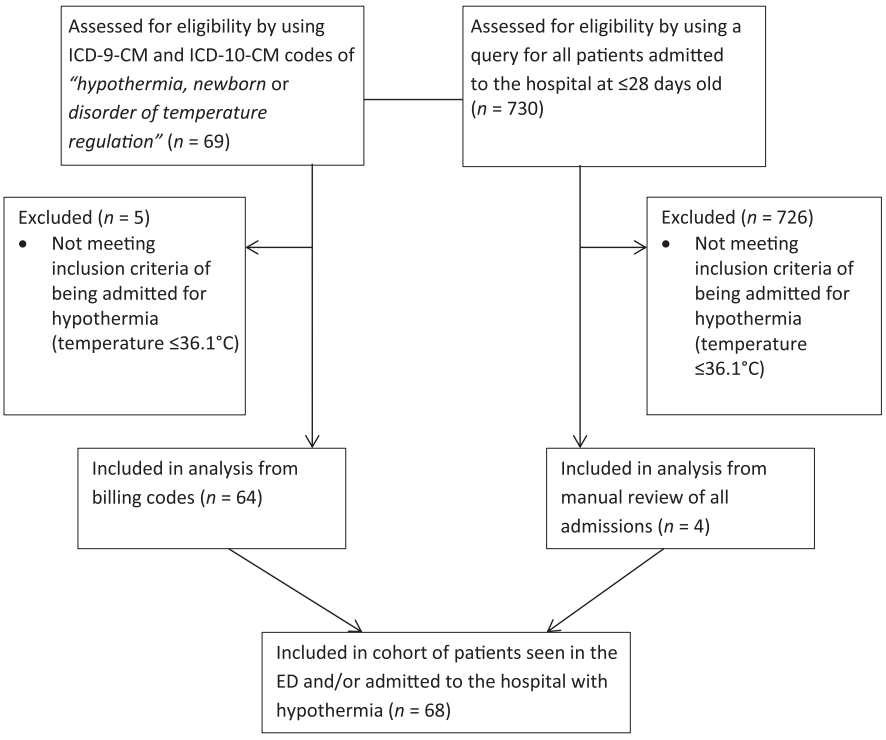

FIGURE 1 Flow diagram of cohort determination for analysis.

Patient Characteristics

Of the 68 neonates in our cohort, 63 (93%) were hospitalized and were included in analysis. All patients who were sent home from the ED had documented temperatures >36.1°C in the ED. On chart review, there were no repeat visits to the ED in the subsequent weeks for this cohort of patients who were sent home from the ED after a brief period of observation only.

Table 1 reports the clinical characteristics of our participants. There were 36 girls (53%), and 42 (62%) neonates were born at term. Eighteen (27%) of these patients were seen in the winter months, defined as dates from December 1 through February 28. The median age of all patients was 4.5 days, and 56 (82%) neonates were ≤7 days of age.

Evaluation and Hospital Course of Neonates

Table 1 reports the evaluation and clinical course of admitted patients ($n = 63$). Nine (14%) patients were ill-appearing on presentation. The ED course for admitted patients included a planned SBI evaluation (blood, urine, and CSF cultures) followed by starting antimicrobial agents in all neonates. CSF was able to be obtained in 51 (81%) patients, and thus 12 patients (19%) had an incomplete workup for SBI. The majority of patients (83%) were admitted to the general pediatric floor, whereas 17% were admitted to either the IMC or PICU on the basis of criteria at our institution involving discussion between the hospitalist and intensivist and the needs of the patient, including more frequent vital signs or laboratory draws, concern for decompensation, or need for heated and humidified high-flow nasal cannula or intubation. For admitted patients, the median age and temperature at presentation were 4 days and 35.5°C (range: 33.4°C–36.0°C), respectively. The median LOS was 53 hours, and there was 1 patient death due to multiorgan failure as a result of disseminated HSV.

TABLE 1 Characteristics of All Neonates and Those Patients Who Were Admitted Shown in Absolute Numbers and Percentages

	n	%
All patients ($N = 68$)		
Age, ≤7 d	56	82
Female sex	36	53
Race and/or ethnicity		
White	30	44
African American	15	22
Hispanic	11	16
Other or unknown	12	18
Length gestation, wk		
≥37	42	62
<37	26	38
Seasonality at presentation		
Winter (December 1 to February 28)	18	27
Not winter	50	73
Admitted patients ($n = 63$)		
Ill-appearing	9	14
CSF culture obtained	51	81
Blood and urine cultures obtained	63	100
HSV blood and CSF obtained	50	79
Admit location		
Floor unit	53	84
IMC	8	13
PICU	2	3
Diagnosis of serious infection (SBI or HSV)	5	8
Diagnosis of serious pathology	9	14
Death	1	2

Primary and Secondary Outcome Results

Five (7.9%; 95% CI: 3.4%–17.3%) of our patients had a diagnosis of serious infection, including 4 (6.4%: 95% CI: 2.5%–15.2%) with SBI and 1 (1.6%: 95% CI: 0.3%–8.5%) with disseminated HSV. Nine (14.3%: 95% CI: 7.7%–25%) of our patients had a diagnosis of significant pathology. The diagnoses of significant pathology (other than SBI or HSV) included other bacterial infection ($n = 1$), inborn error of metabolism ($n = 1$), esophageal cyst requiring surgical repair with associated dehydration ($n = 1$), and cardiomyopathy ($n = 1$).

Description of Patients With Serious Infection or Significant Pathology

Table 2 reports the characteristics and outcomes of the 9 patients determined to have a diagnosis of significant pathology, including organisms that grew from cultures with a positive result. Of the 5 neonates with an eventual diagnosis of serious infection (SBI or HSV), 3 were ill-appearing, with attending admission notes describing neonates who were "mottled," "ill-appearing," "lethargic," "floppy," or "difficult to arouse." The 2 neonates with SBI who were not ill-appearing had an eventual diagnosis of UTI. For those 5 patients diagnosed with serious infection, age ranged from 4 to 17 days and median LOS was 119 hours. Their median temperature at presentation was 34.4°C.

Table 3 reports differences in demographic and clinical characteristics in patients with serious infection versus those without serious infection. Those that met statistical significance include admission age, lower temperature, ill appearance, and elevated absolute band count.

TABLE 2 Characteristics, Laboratory Values, LOS, and Diagnoses of Patients Found to Have Serious Infection or Other Significant Pathology

	Age, d	Sex	Gestation, wk	Minimum Temperature, °C	Ill-Appearing	Serum WBC Count, Cells/μL	Bandemia	LOS, h	Diagnosis	Culture Growth
Patients diagnosed with serious infection										
Patient 1	4	F	34–37	34.4	No	9600	No	101	SBI: UTI	*Enterococcus faecalis*
Patient 2	8	F	≥37	35.6	No	7600	No	64	SBI: UTI	*E faecalis*
Patient 3	17	M	≥37	33.4	Yes	34 700	Yes	157	SBI: sepsis	Culture result negative[a]
Patient 4	4	F	34–37	34.4	Yes	5700	No	504	SBI: meningitis	Culture result negative[b]
Patient 5	9	F	34–37	34.4	Yes	10 900	Yes	119	Disseminated HSV	HSV-2 blood and/or CSF
Patients diagnosed with other significant pathology										
Patient 6	4	M	≥37	35.4	No	7700	No	119	Bacterial pneumonia	—
Patient 7	8	F	≥37	34.9	Yes	10 500	No	78	Propionic acidemia	—
Patient 8	3	F	≥37	35.9	No	17 000	No	384	Esophageal cyst	—
Patient 9	11	F	≥37	35.8	Yes	21 000	No	555	Cardiomyopathy	—

F, female; HSV-2, herpes simplex virus 2; M, male; —, not applicable.
[a] Culture result negative for sepsis as determined by clinical and laboratory characteristics.
[b] Probable bacterial meningitis as determined by CSF profile; antibiotics given before CSF collection and patient characteristics.

DISCUSSION

In this study, we have described the clinical outcomes, including the prevalence of SBI, in a cohort of neonates with hypothermia. To our knowledge, this is the only recent study to be focused on outcomes for this specific population. The prevalence of serious infection was 7.9%, whereas significant pathology overall involved 14.3% of our cohort.

At the onset of our study, we questioned whether extensive, invasive, and cautious testing, as is the standard of care at our institution, needed to be performed on neonates ≤28 days old presenting to the ED with hypothermia. Our hypothesis was that the majority of neonates presenting with hypothermia were not infected but rather had temperature dysregulation because of a larger ratio of surface area to body mass as well as decreased glycogen stores to support heat production. However, our results reveal that these patients do often have diagnoses of significance. Although this is a small sample size, the percentage of patients with an eventual diagnosis of SBI (6.4%) is similar to the reported percentage of febrile neonates found to have SBI.[11] In addition to SBI, we also had 1 patient with an eventual diagnosis of disseminated HSV who presented with hypothermia and a sepsislike syndrome, as described by the work of Caviness et al[18] on the subject of neonatal HSV. Lastly, we found that neonates with hypothermia may have temperature dysregulation for reasons other than infection, as demonstrated by our cohort, with ultimate diagnoses as varied as infection, inborn error of metabolism, congenital gastrointestinal tract anomaly, and heart failure.

A discussion surrounding the initial appearance of the infant and a possible decision point to pursue workup and treatment of serious infection is of interest to us. In our study, all patients had a planned evaluation for SBI regardless of initial appearance. This resulted in 177 bacterial cultures of blood, urine, and CSF. Although this model may end up being the standard of care after further study and elucidation of risk factors, the question surrounding risk stratification is important to pursue in this population. Notably, risk stratification has been studied extensively in the febrile infant, and a febrile infant who is not well appearing would immediately be stratified into the high-risk category.[2,23–27] Our results reveal that each hypothermic patient with invasive or HSV infection was identified as ill-appearing at presentation. Importantly, only a small percentage (10%) of our patients without an eventual diagnosis of serious infection were noted to be ill-appearing at presentation. Thus, ill appearance of a patient may be an important risk factor to focus on in future studies to determine the need for full infectious workup for neonates with hypothermia.

It is also worth noting that the neonate with hypothermia may have eventual diagnoses other than infection. Unlike the febrile neonate who likely either has SBI or viral infection, the hypothermic neonate may have a wide variety of serious pathology as seen by our cohort. The provider must avoid anchoring to the diagnosis of infection and remain open to a variety of eventual pathologies.

On the basis of the results from our study, this cohort requires more expansive research attention, including a multicenter prospective study to provide evidence-based guidance for physicians caring for neonates presenting with hypothermia. The continued interest in the febrile neonate has advanced our knowledge of this population and has allowed physicians to reduce invasive and extensive testing in some members of this population.[28,29] Indeed, after the implementation of a care process model for febrile infants, outcomes improved and costs were reduced.[30] It may be possible to involve risk stratification and provide care pathways to neonates with hypothermia if sufficient evidence is produced by subsequent and larger studies.

Limitations to this study include the small sample size and single-center results that may not be generalizable. In addition, our definition of significant pathology is

TABLE 3 Differences in the Prevalence of Clinical and Patient Characteristics of Neonates With Eventual Diagnosis of SBI or HSV (Serious Infection)

	n	Yes SBI or HSV (*n* = 5) % (95% CI)	*n*	No SBI or HSV (*n* = 58) % (95% CI)	*P*
Age, d					.03
≤7	2	40 (12–77)	51	88 (77–94)	
>7	3	60 (23–88)	7	12 (6–23)	
Admission temperature, °C					.004
≤34.4	4	80 (38–96)	7	12 (6–23)	
34.5–35	0	0 (0–43)	8	14 (7–25)	
35.1–35.5	0	0 (0–43)	20	34 (24–47)	
35.6–36.1	1	20 (4–62)	23	40 (28–53)	
Lowest temperature ≤34.4°C					.003
Yes	4	80 (38–96)	7	12 (6–23)	
No	1	20 (4–62)	51	88 (77–94)	
Sex					.36
Female	4	80 (38–96)	30	52 (39–64)	
Male	1	20 (4–62)	28	48 (36–61)	
Gestation, wk					.36
≥37	2	40 (12–77)	37	64 (51–75)	
<37	3	60 (23–88)	21	36 (25–49)	
Ill-appearing					.02
Yes	3	60 (23–88)	6	10 (5–21)	
No	2	40 (12–77)	52	90 (79–95)	
Bandemia[a]					.005
Yes	2	40 (12–77)	0	0 (0–6)	
No	3	60 (23–88)	57	100 (94–100)	
WBC count <5000 cells/μL or >15 000 cells/μL[b]					.51
Yes	1	20 (4–62)	7	12 (6–23)	
No	4	80 (38–96)	50	88 (77–94)	

[a] Bandemia absolute band count is >1500 cells/μL.
[b] Numbers do not equal 63 (entire cohort) because 1 patient did not have a complete blood count.

subjective and may not be agreed on by all providers. Also, the definition and literature surrounding cultures that have negative results for sepsis are controversial, and not all providers may choose to include these patients in the category of SBI. Our patient who was classified as having likely bacterial meningitis on the basis of CSF pleocytosis and CSF profile with no culture growth after 24 hours of antibiotics may have actually had viral meningitis. Because our study was observational, there may be additional predictors that we were unable to measure. In addition, we were limited by the variables available in the medical record. Omitting a review of all charts of patients seen in the ED during the time frame of our study may have omitted some patients not captured by our chosen billing codes. Retrospective chart reviews are also able to suggest associations and not causations. However, given the paucity of recent literature on the epidemiology of significant pathology in neonates with hypothermia, our study is an important first step in generating interest and describing the prevalence of serious infection in this population.

CONCLUSIONS

We found that neonates presenting with hypothermia may have significant pathology, and such pathology may be infectious or noninfectious. In our cohort, the majority of these neonates were admitted. All those who were admitted had a planned rule out for SBI and were started on broad-spectrum antimicrobial agents. We believe that a larger study and the inclusion of hypothermia in administrative databases are important next steps to generating the data and evidence needed to produce clinical practice guidelines that will improve patient care and lower costs for this cohort.

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