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Hypothermia in Young Infants: Frequency and Yield of Sepsis Work Up

Michelle C Perry, MD^a, Susan K Yaeger, MD^b, Katie Noorbakhsh, MD^a, Andrea T Cruz, MD,MPH^c, Robert W Hickey, MD^a

Michelle C Perry: michelle.perry2@chp.edu; Susan K Yaeger: susan.k.yaeger@gmail.com; Katie Noorbakhsh: Katie.Noorbakhsh@chp.edu; Andrea T Cruz: atcruz@texaschildrens.org; Robert W Hickey: Robert.hickey@chp.edu

^aChildren's Hospital of Pittsburgh of UPMC, Department of Pediatrics

^bLehigh Valley Health Network, Department of Emergency Medicine

^cBaylor College of Medicine, Department of Pediatrics

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hypothermia; infant; bacterial infection

Introduction

Signs of infection in children less than 60 days old may include fever or hypothermia. Published data of febrile infants show an incidence of serious bacterial infection (SBI) of approximately 9%¹. SBIs include meningitis, bacteremia, urinary tract infection (UTI) and bacterial pneumonia. In comparison, documentation of SBI in hypothermic patients is limited. El-Radhi reported a 60% rate of infectious etiology for hypothermia of infants less than 4 weeks old but the generalizability of the study is limited because the population included home-born infants in one of the poorest areas of Baghdad from 1978–1980.² In a study examining the incidence of SBI in infants presenting with apparent life threatening event (ALTE) (study was published based on old nomenclature diagnosis) three of the five patients with SBI presented with a temperature <36.5°C.³

The issue is further confounded by thresholds for hypothermia ranging from 35.0–36.5°C.^{2,4–10} The World Health Organization defines hypothermia in newborns as mild 36.0–36.5°C, moderate 32.0–36.0°C and severe <32.0°C¹¹. The International Pediatric Sepsis

Address correspondence to: Robert Hickey Department of Pediatrics, Children's Hospital of Pittsburgh, 4401 Penn Ave, Pittsburgh, PA 15224 [Robert.hickey@chp.edu], 412-692-7692.

Author Contributions:

MCP, SKY, AC and RWH conceived and designed the study. MCP, SKY and KN conducted record review. MCP analyzed the data with the assistance of SY and RWH. MCP, AC and RWH drafted the manuscript, and all authors contributed substantially to its revision.

Conflict of Interest:

The authors have indicated that they have no potential conflicts of interest to disclose.

Meetings:

The preliminary data was presented as a poster at Pediatric Academic Societies Conference in Baltimore, Maryland in May 2016.

Consensus Conference considers 36.0°C as the threshold for hypothermia for all age groups.⁴ The normal temperature range measured by rectal thermometer is 36.6–37.9°C.¹²

Our objective was to determine the incidence of SBI discovered during the evaluation of infants <60 days old presenting to a pediatric emergency department (PED) with an initial temperature demonstrating hypothermia. We sought to determine the frequency and extent of evaluation in these hypothermic patients as well as to compare characteristics of hypothermic patients with and without SBI.

Methods

Study Site

The study was performed in the PED at a single tertiary care hospital, The Children's Hospital of Pittsburgh, with an annual volume of approximately 85,000 visits. The hospital has a wide referral base and serves a broad socioeconomic and demographic spectrum including urban, suburban, and rural population.

Patients

Children ages 0–60 days visiting the PED between January 2013 and December 2014 with initial rectal temperature (T) <36.5°C were identified through a query of our electronic health record repository. Patient inclusion was determined by chart review performed by one of four reviewers. Visits were determined ineligible if the presenting chief complaint was trauma, the patient was transferred from an outside hospital following evaluation for an SBI, had known diagnosis of SBI, or if temperature was not a rectal temperature.

Data Collection

A standard data collection instrument was completed for each patient using information from the electronic medical record. Data were entered into SPSS database (v23.0; SPSS Inc., Chicago, IL) for analysis. Four investigators extracted the data. Variables included: age, gender, race, ethnicity, chief complaint, past medical history, gestational age, birth weight, circumcision, maternal GBS status, initial vital signs (temperature, blood pressure, heart rate, respiratory rate and pulse oxygenation), final PED vital signs, weight, complete blood cell count (CBC), blood culture, urinalysis (UA), urine culture, cerebrospinal fluid (CSF) parameters and culture, viral testing, chest x-ray, antibiotic therapy received in the PED, PED diagnosis, discharge diagnosis, admission status and unit care level.

A SBI evaluation was defined as a full evaluation (blood, urine and CSF cultures) or partial evaluation (<3 cultures). SBI was defined as a culture growing an organism that was considered by the care provider to be pathogenic as documented in PED or discharge note. UTI was defined as a urine culture growing >50,000 colony forming units (CFU) of a pathogen or 10,000–50,000 CFU of a pathogen with urinalysis positive for UTI (leukocyte esterase, nitrites, >5 WBC/HPF, or bacteria on Gram stain).¹³ The Pittsburgh low-risk criteria (Rochester criteria with enhanced urinalysis) for evaluation of the febrile infant was applied to infants who underwent SBI evaluation to determine the sensitive, specificity, and predictive values of this tool when applied to hypothermic infants.¹⁴ Immature neutrophils

(band cells, myelocytes and metamyelocytes) to total neutrophils ratio (I:T ratio) was calculated: a ratio greater than 0.2 is often used as an indication of infection in infants.¹⁵

Outcome Measures

The primary outcome was diagnosis of SBI based on a positive blood, urine or CSF culture or chest x-ray. Secondary outcomes were factors predictive of SBI evaluation and SBI diagnosis.

Data Analysis

The variables of the group with SBI were compared with the group with a negative SBI evaluation by Fisher Exact test and Mann-Whitney U test. Odds ratio with 95% intervals were calculated for categorical data. Effect size $r = z / \sqrt{n}$ was calculated for continuous variables with the p resulting from Mann-Whitney U test less than 0.05. Demographic and clinical characteristics of patients were reported as median values or proportions as appropriate. Pair-wise Pearson correlation was used to assess correlation between demographic variables. Confidence intervals of Pearson's coefficient were calculated using a calculator available at <http://www.vassarstats.net/rho.html>.¹⁶ Statistical significance was defined as a P < 0.05. All data were analyzed using SPSS statistical software (v.23.0; SPSS Inc.) The hospital's institutional review board approved this study.

Results

In 2013 and 2014, 487 infants presented to the PED with initial temperature <36.5°C. Fifteen percent (73 patients) were excluded for non-rectal thermometry (49 patients), chief complaint of trauma (18 patients), rule-out sepsis evaluation completed at transferring ED (5 patients) or undergoing treatment for Herpes Simplex Virus encephalitis (1 patient)(Figure 1). Twenty five percent of patients (104 patients) underwent a SBI evaluation. The remaining 75% of patients (310 patients) had no cultures drawn. None of the 310 patients who did not undergo a SBI evaluation returned within 72 hours with a subsequent diagnosis of SBI.

In the subset of patients who received a SBI evaluation, 42% (44 patients) only had one or two cultures obtained. Fifty-eight percent (60 patients) underwent blood culture, urine culture and CSF culture. SBIs were identified in 9/104 (8.7%) of infants undergoing SBI evaluation and in 2.2% of all hypothermic young infants.

Clinicians' Decision to Pursue SBI Evaluation

In order to assess why clinicians decided to pursue a SBI evaluation, the patients who underwent SBI evaluation were compared to patients who did not (Table 1). The patients who underwent SBI evaluation were younger, weighed less at birth, weighed less in the ED, were more likely pre-term at birth, and more likely Caucasian. With the exception of race, many of these variables are correlated with each other. For example, ED weight correlated with age ($\rho=0.59$, CI 0.52, 0.65), birth weight ($\rho=0.75$, 95% CI 0.68, 0.81) and gestational age ($\rho=0.47$, 95% CI 0.37, 0.56). The mean temperature of patients undergoing SBI was statistically, but not clinically, lower than patients without work up

(35.9 vs. 36.2 deg C). Figure 2 displays the frequency of initial temperatures. All patients with a temperature less than 35°C underwent sepsis evaluation.

The Identification of Patients with SBIs

Amongst patients receiving a sepsis evaluation, only age was associated with positive SBI (Table 2). Of note, the association of age with frequency of sepsis work up and yield had an inverse relationship with younger age associated with more frequent work up while older age is associated with more positive cultures (Figure 3). Taken together, these results suggest that factors associated with impaired ability to maintain homeothermy (prematurity, young age, lower weight, etc.) prompted the clinician to pursue a work up for SBI. In contrast, older patients have more developed fat stores, are more resistant to environmental hypothermia, and thus more likely to have an infectious etiology.

Frequency and results of laboratory testing of those diagnosed with SBI and no SBI are presented in Tables 5 and 6. Patients diagnosed with SBI had statistically higher absolute band counts and immature:total white count ratio. However, the diagnostic utility of these tests is very limited (only 3 of 9 patients with SBI had an elevated I:T ratio, while 7 of 94 patients without SBI had elevated I:T ratio).

Low risk criteria

The Pittsburgh low-risk criteria for *febrile* infants was retrospectively applied to the 104 patients undergoing complete or partial sepsis work up. None of the nine patients with SBI would have been classified as low-risk patients, whereas 25 of the 95 patients (26%) without SBI would have been classified as low risk. Discharge from the PED was not associated with meeting low-risk criteria, but only 6 of the 104 patients who underwent evaluation were discharged from the PED. All patients with SBI were admitted during their index PED visit, and seven of nine patients had antibiotics initiated in the ED. Sixty percent of patients who would be classified as low risk received antibiotics.

Diagnosis and outcome of patients with SBI

Tables 3 and 4 shows additional details of the patients diagnosed with SBI. Patient 5 died as a result of GBS meningitis and is the only patient who died as a result of an SBI. While alpha hemolytic streptococcus is not commonly considered a urinary pathogen, we included patient 3 as an SBI because the treating team choose to treat it as an SBI in the setting of urinalysis positive for UTI and positive urine culture.

Discussion

This is the first study to examine hypothermia as a sign of serious bacterial infection in infants <60 days of age. Our finding of approximately 200 patients per year with hypothermia in a PED shows that this is not an uncommon clinical finding. Yet, management of these patients occurs in a vacuum of clinical data: who do you evaluate and what is the yield? In a study of preterm infants residing in a NICU who developed sepsis after 3 days of life (average gestational age of approximately 30 weeks; average onset of sepsis on DOL 10), 2.2% had hypothermia (<36°C).⁶ Our finding of SBI in 2.2% of patients

with hypothermia in the PED collaborates that this is an important clinical presentation of SBI and potentially sepsis.

Seventy five percent of hypothermic infants in our cohort were not evaluated for SBI. Many of the variables that were associated with increased likelihood of undergoing sepsis evaluation are interrelated. Preterm and low birth weight infants often lag behind in feeding skills, temperature regulation, and weight gain than full term and normal birth weight infants. While a febrile infant's history of prematurity has been identified as an exclusion criteria for application of the Rochester and Pittsburgh criteria, and low birth weight has been identified as a risk factor of late-onset sepsis,¹⁵ these variables have not been examined for predicting SBI in hypothermic infants. We found that patients with evaluation for SBI were Caucasian, younger, weighed less, and were more likely to be premature yet these variables did not correlate with higher likelihood of having an SBI, suggesting that hypothermia in young, small and premature infants is more likely caused by low stores of body fat and immature temperature regulation rather than SBI. It is possible that clinicians preferentially worked up younger infants because of the concern for "immature immune system." Paradoxically, older patients have more developed fat stores, are more resistant to environmental hypothermia, and thus more likely to have an infectious etiology (thus explaining the higher yield of pathogens in older infants). The higher rate of work up in Caucasian infants is worrisome because of the disparity in care based upon race that has been well-documented for other clinical scenarios.

Although we cannot say with certainty that none of our patients without an SBI evaluation had a SBI, none of them returned to our ED with a diagnosis of SBI and we are the only children's hospital within our region. Thus, clinicians appear to be accurate when they decide to forgo sepsis evaluation in 75% of hypothermic infants, although very young infants with low weight may be receiving unnecessary evaluation.

Even though clinicians correctly "triaged" 75% of infants without a sepsis evaluation, 95 of 104 patients (91%) worked up for SBI were subsequently found to be without SBI. Among these 95 patients, 94% were admitted to the hospital and 64% received unnecessary antibiotics. Thus, there is room for improvement in our clinical decision making. When the Pittsburgh low-risk criteria is applied to these patients 25 (26%) could have been discharged from the ED. The data from the low-risk criteria, while promising, are preliminary in nature and require a larger, prospective study for validation.

Limitations

This study suffers from all of the expected limitations of a retrospective study including reporter bias, recorder bias, missing data, and post-hoc testing. We attempted to mitigate these limitations through standardized case report forms and pre-defined data elements.

Strictly speaking, we cannot conclude that hypothermia is associated with an increased risk for SBI, because the comparison group (children with normothermia) do not undergo evaluation for SBI. Similarly, we do not know for certain that our hypothermic infants without sepsis work up did not have SBI—however, not one of these infants returned to our facility with a diagnosis of SBI and there are very few other hospitals within our region

that admit young infants. Unfortunately, these limitations are insurmountable; it would be unethical to design prospective studies requiring sepsis work up in *normothermic* children or work up of *all* hypothermic children regardless of physician preference.

The analysis of the low-risk criteria is especially limited. This is a post-hoc analysis in a population set with a very low number of children with SBI. Larger, prospective studies are certainly needed and we believe that this analysis can serve as preliminary data.

Even with its limitations, this study is the first and only study to provide data for clinical decision-making when managing a young infant with hypothermia. We describe several important findings that can help the clinician assess risk and formulate a management plan. Specifically, we found that 1) most infants in the first week of life are not hypothermic because of bacterial infection, and 2) almost all children with bacterial infection had clinical or laboratory findings consistent with the adage that sick children look sick.

Conclusion

Hypothermia can be a presenting sign of sepsis in infants <60 days with approximately 2% having SBI. Additional prospective studies are needed to develop and validate a risk-stratification tool for young patients with hypothermia.

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Figure 1:
Study Flow Diagram

Figure 2:
Frequency of Initial temperature of patients who did and did not undergo SBI evaluation

Figure 3:
The evaluation and diagnosis of SBI organized by the patients' age.

Table 1:

Demographics and presentation of patients who were and were not evaluated for SBI.

	No SBI Work Up (%) or [IQR]	n	SBI Work Up (%) or [IQR]	n	p	Odds Ratio (95% CI)
Age (d)	17 [6.0–39.0]	310	10 [4–30]	104	0.03	
Male	177 (57.1)	310	59 (57)	104	1.00	0.9 (0.6–1.4)
Caucasian	217 (72.8)	298	88 (86)	102	0.01	2.4 (1.3–4.4)
Pre Term (<37w)	41 (14.1)	292	49 (46)	104	<0.001	5.2 (3.2–8.7)
GA (w)	38.0 [37–39]	168	36.9 [35–38]	86	<0.001	
BW (g)	3189 [2780–3541]	122	2690 [2398–3151]	42	<0.001	
Low BW (<2.5kg)	10 (8.2)	122	19 (45)	42	<0.001	9.3 (3.8–22.5)
ED Weight (g)	3380 [2875–4118]	308	2705 [2278–3158]	102	<0.001	
Initial T (°C)	36.2 [36.0–36.4]	310	35.9 [35.3–36.2]	104	<0.001	
Initial sBP (mmHg)	87 [82–92]	304	86 [81–94]	98	0.58	
Initial HR	154 [140–164]	309	147 [131–160]	102	0.004	
Initial RR	42 [36–48]	309	40 [36–48]	102	0.27	

BW: birthweight; CI: confidence interval; ED: emergency department; GA: gestational age; HR: heart rate; IQR: interquartile range; N: number of infants in which variable was documented; No sig: no significant difference between groups $p>0.05$; RR: respiratory rate; SBI: serious bacterial infection; sBP: systolic blood pressure; T: triage temperature; w: weeks

Statistically significant differences $p<0.05$ are bolded.

Table 2:

Demographics and presentation of patients with sepsis evaluation who were and were not diagnosed with SBI

	SBI (%) or [IQR]	n	No SBI (%) or [IQR]	n	p	Odd Ratio (95% CI)
Age (d)	18 [12–49]	9	8 [4–29]	95	0.03	
Male	3 (33)	9	56 (59)	95	0.17	0.4 (0.1–1.5)
Caucasian	8 (89)	9	80 (86)	93	1.00	1.3 (0.2–11.3)
Pre Term (<37w)	3 (33)	9	46 (48)	95	0.50	0.5 (0.1–2.3)
GA (w)	37.3 [36.0–38.8]	8	36.6 [35.0–38.0]	78	0.26	
BW (g)	3033 [2430–3390]	7	2550 [2290–3110]	35	0.27	
ED Weight (g)	2930 [2130–4140]	9	2690 [2290–3110]	93	0.78	
Initial T (°C)	36.1 [34.0–36.4]	9	35.9 [35.4–36.2]	95	0.86	
Initial sBP (mmHg)	82[80–95]	9	89 [81–94]	89	0.48	
Initial HR	151 [128–160]	8	146 [132–161]	94	0.84	
Initial RR	44 [36–48]	8	40 [36–48]	94	0.49	
Initial O2 Sat	93 [70–98]	5	100 [98–100]	61	0.001	

BW: birthweight; CI: confidence interval; ED: emergency department; GA: gestational age; HR: heart rate; IQR: interquartile range; N: number of infants in which variable was documented; No sig: no significant difference between groups $p>0.05$; RR: respiratory rate; SBI: serious bacterial infection; sBP: systolic blood pressure; T: triage temperature; w: weeks

Statistically significant differences $p<0.05$ are bolded.

Table 3:

Demographics and characteristics of patients diagnosed with SBI

	T (°C)	Age (d)	Sex	Gestational Age at Birth	Medical History	Chief Complaint
1	36.4	49	Female	39	Hypoplastic left heart syndrome, bilateral hydronephrosis	Cyanosis, low temperature
2	36.4	11	Female	37.3	Twin gestation, bradycardia	Bradycardia alarms
3	36.2	48	Female	unk	None	Vomiting, diarrhea, fever
4	36.1	7	Female	41	None	Abdominal distension, fussy with feeds
5	35.9	18	Male	36	GBS positive mother, untreated; hypoglycemia, hospitalized for dehydration	Refusal to feed
6	35.8	27	Female	36	Right dysplastic kidney	Lethargy, poor eating, hypothermia
7	34	12	Male	38.1	None	Cyanosis
8	34	16	Female	37.3	None	Cough, color change
9	33.3	57	Male	35	Intubated upon delivery, hyperbilirubinemia, hypoglycemia secondary to hyperinsulinism	Decreased oral intake

GBS: group B streptococcus; T: triage temperature; unk: unknown variable

Table 4:

Evaluation of patients diagnosed with SBI

	Initial O2 Sat	Documented ill-appearing	WBC	ANC	Immature Neutrophils	Low-risk exclusions	SBI
1	93	Ill	9900	5600	0	Chronic illness, NICU stay, perinatal abx, abx <7d, ill-appearing	CONS bacteremia
2	98	Well	8900	2310	0	NICU stay, elevated uWBC	<i>Enterococcus faecalis</i> UTI
3	unk	Well	8500	2380	0	Elevated uWBC	α -Hemolytic Streptococcus UTI
4	unk	Well	16700	6340	170	Elevated WBC	Non-hemolytic Strep Bacteremia
5	unk	Grey, poor alertness	2100	550	170	Premature, inpatient stay, ill-appearing, elevated WBC & CSF WBC	GBS Bacteremia & Meningitis
6	97	Decreased interaction	13400	9110	130	Premature, right dysplastic kidney, ill, elevated WBC & uWBC	<i>E. coli</i> UTI
7	64	Limp, blue-grey, poor respiratory effort	11200	4500	2230	Ill-appearing, elevated ABC	Pneumonia
8	76	Withdrawn	6700	2920	1370	Ill-appearing, elevated uWBC, abnormal CXR	GBS UTI
9	unk	Moderate distress, ill	5600	1860	160	Preterm, NICU stay, perinatal abx, abx <7d, ill-appearing, elevated uWBC, abnormal CXR	Multi-organism UTI, pneumonia

Abx: antibiotics; ANC: absolute neutrophil count; CONS: coagulase-negative staphylococci; CSF: cerebrospinal fluid; CXR: chest radiograph; GBS: group B streptococcus; NICU: neonatal intensive care unit; UTI: urinary tract infection; uWBC: urine white blood cell count; WBC: white blood cell

Table 5:

Evaluation findings of patients who were and were not diagnosed with SBI

	SBI n=9 (%)	No SBI n=95 (%)	p	Odds ratio (95% CI)
CBC	9 (100)	95 (99)	1.00	
UA	8 (89)	79 (83)	1.00	1.6 (0.2–13.9)
LP	5 (56)	56 (59)	1.00	0.9 (0.2–3.5)
Bld Cx	9 (100)	88 (93)	1.00	
CXR	7 (78)	34 (36)	0.03	6.3 (1.2–31.9)
Viral Testing	6 (67)	47 (50)	0.50	2.0 (0.5–8.7)

Bld Cx: blood culture; CBC: complete blood count; CI: confidence interval; CXR: chest x-ray; LP: Lumbar Puncture; n: number of infants; SBI: serious bacterial infection; UA: urinalysis

Statistically significant differences $p < 0.05$ are bolded.

Table 6:

Evaluation findings and treatment decisions of patients who were and were not diagnosed with SBI

	SBI (%) or [IQR]	n	No SBI (%) or [IQR]	n	p	Odds ratio (95% CI)
WBC	8900 (6150–12300)	9	8550 (6800–11400)	93	0.95	
ANC	2920 (2085–5970)	9	2610 (1660–4245)	94	0.40	
ABC	130 (0–620)	9	0 (0–43)	94	0.01	
I:T ratio	0.03 (0–0.28)	9	0.00 (0–0.02)	94	0.01	
Elevated I:T	3 (33)	9	7 (7)	94	0.04	6.2 (1.3–30.3)
Antibiotics	7 (78)	9	61 (64)	95	0.49	2.0 (0.4–9.9)
Low Risk Criteria	0 (0)	9	25 (26)	95	0.11	0.9 (0.8–1.0)
Admitted	9 (100)	9	89 (94)	95	1.00	1.1 (1.0–1.2)

ABC: Absolute band count; ANC: absolute neutrophil count; CI: confidence interval; IQR: interquartile range; I:T ratio: immature to total white count ratio; No sig: no significant difference between groups $p>0.05$; SBI: serious bacterial infection; WBC: white blood count

Statistically significant differences $p<0.05$ are bolded.