



Serious infections are rare in well-appearing neonates with hypothermia identified incidentally at routine visits

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ABSTRACT

Objectives: It is not established whether diagnostic testing and antimicrobial treatment are warranted in well-appearing neonates without other signs or symptoms who have hypothermia identified incidentally at a routine visit with their primary care provider.

Methods: This was a retrospective observational study of well-appearing neonates who were noted at a routine visit to be hypothermic (<97.7°F or <36.5°C) and referred to a pediatric emergency department over an 8.5-year period. Excluded were those transferred from an outside hospital and those with signs of illness, including apnea, bradycardia, fever, hypoglycemia, ill appearance, lethargy, poor feeding, respiratory distress, tachycardia, or vomiting. Patient characteristics, laboratory results, antimicrobial treatment, and clinical outcomes were recorded.

Results: Among a final cohort of 212 neonates with incidental hypothermia, no urine ($n = 195$) or blood ($n = 198$) culture grew a bacterial pathogen. No CSF culture ($n = 168$) grew a bacterial pathogen and no CSF PCR test ($n = 142$) was positive for herpes simplex virus. Contaminants were isolated in 3 urine and 3 blood cultures. **Conclusion:** Well-appearing neonates with incidentally noted hypothermia at a routine visit are at low risk for serious infection and may not warrant a full sepsis evaluation.

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1. Introduction

1.1. Background

Serious infection, defined as urinary tract infection (UTI), bacteremia, meningitis, or invasive herpes simplex (HSV) infection, has been reported to occur in 2.6–7.9% of neonates with hypothermia evaluated in an emergency department (ED) and/or admitted to a hospital [1,2]. However, these investigations did not make a distinction between hypothermia identified incidentally in well-appearing neonates at routine visits versus neonates evaluated for other signs or symptoms of illness.

Abbreviations: CSF, Cerebrospinal fluid; CNS, Central nervous system; ED, Emergency Department; EDH, Epidural hematoma; HSV, Herpes Simplex virus; IQR, Interquartile range; NEC, Necrotizing enterocolitis; PCP, Primary care practitioner; PCR, Polymerase chain reaction; UTI, Urinary tract infection; WBC, White blood cell.

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Neonates with incidental hypothermia identified by their primary care practitioner (PCP) and referred to EDs may represent a different population from hypothermic neonates who present directly to the ED. This distinction is relevant because normal neonates have limited ability to thermoregulate and are susceptible to environmental temperature stress and hypothermia [3–5].

The American Academy of Pediatrics neonatal well-visit guidelines do not provide recommendations for measuring body temperature [6]. In addition, a large, retrospective analysis using administrative data from 32 U.S. children's hospitals found notable variability in diagnostic testing and treatment of these patients [7].

This variability may result, in part, because there has been uncertainty whether neonatal hypothermia mandates a comprehensive evaluation for herpes simplex virus (HSV) infection, including lumbar puncture (LP) to identify central nervous system (CNS) disease. However, in a case-control study of neonates with documented HSV infection, though 27% of patients with disseminated disease were hypothermic, none with isolated CNS disease presented with hypothermia [8]. Other signs and symptoms were common in those with CNS disease, including vesicular rash (60%), poor feeding (43%), fever (36%), seizures (36%), irritability (21%), and lethargy (14%).

Moreover, iatrogenic complications are not uncommon after LP. Ultrasound diagnosed epidural hematoma (EDH) was identified after 31% of unsuccessful LP's in infants <6 months (40% among those with a traumatic LP), with complete effacement of the thecal sac in 17% [9]. Although the spinal canal is wide enough to accommodate EDH without sequelae, intramedullary hemorrhage of the conus medullaris resulting in paraplegia has been reported [10].

1.2. Objectives of this study

To our knowledge there are no reports of outcomes in well-appearing neonates with hypothermia identified incidentally at a routine visit. We sought to examine the prevalence of serious infection in this sub-population of hypothermic neonates.

2. Methods

2.1. Study design

We performed a retrospective observational study of all well-appearing neonates (≤ 28 days of age) who were noted to be hypothermic ($< 97.7^\circ\text{F}$ or $< 36.5^\circ\text{C}$) by their primary care provider (PCP) at a routine visit and referred to our tertiary children's hospital ED between January 2011 and June 2019. Routine visits were defined as a scheduled well visit, weight check, or jaundice check. Patients were identified using query functions of the electronic medical record. Each patient record was reviewed to ascertain these inclusion criteria that initially included all neonates evaluated in our ED for fever or hypothermia. We then excluded patients who were transferred from an outside hospital or who had signs of illness including: apnea, bradycardia, fever, hypoglycemia, ill appearance, lethargy, poor feeding, respiratory distress, tachycardia, or vomiting.

During the study period, consensus practice for hypothermic neonates in our urban, academic children's hospital ED was to obtain blood, urine, and CSF studies and to initiate antimicrobial treatment with ampicillin, gentamicin, and acyclovir. For the years 2015–2019 this practice was recommended in a clinical practice guideline.

We recorded age, sex, race, season of encounter, corrected gestational age, birthweight, weight at presentation, temperature reported by the PCP, rectal temperature at ED triage, antimicrobial administration, and laboratory results including nasopharyngeal respiratory pathogen panel (RPP) using polymerase chain reaction (PCR), white blood cell (WBC) count, urine culture, blood culture, and cerebrospinal fluid (CSF) results (bacterial culture, cell count, and HSV PCR). Bacteremia and bacterial meningitis were defined as growth of a single organism from blood or CSF culture, respectively, or detection of a pathogen from CSF using a commercially available multiplex PCR meningitis encephalitis panel, which was implemented during the last year of the study period. (All CSF samples were assayed using the BioFire FilmArray meningitis encephalitis panel [MEP] beginning May 2018) UTI was defined as $\geq 50,000$ cfu/ml on urine obtained by urethral catheterization using sterile technique [11].

2.2. Data analysis and reporting

Data were analyzed with STATA v.14.2 (StataCorp, College Station, TX). We report categorical variable as percentages and continuous variables as median [IQR]. This report conforms to the 22 items of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for observational studies.

2.3. Human research subjects protection

This research was approved by our Institutional Review Board (protocol # 191435).

3. Results

3.1. Characteristics of study subjects

During the 8.5-year study period 723 neonates were evaluated with a chief complaint of hypothermia. Among these, 212 well-appearing neonates were referred for evaluation after hypothermia was noted incidentally at a routine visit and met all inclusion criteria (Fig. 1). Clinical and demographic characteristics of these neonates are displayed in Table 1. Median [IQR] gestation was 37 [36, 39] weeks and most were in the first week of life, admitted to hospital, and treated with antimicrobials.

3.2. Main results

Blood, urine, and CSF acquisition and results are displayed in Fig. 1. There were no positive CSF bacterial cultures or positive CSF PCR tests for bacteria or HSV. Blood cultures from three patients grew *Staphylococcus epidermidis*, determined to be contaminants. One urine culture grew *Bacillus megaterium*, determined by infectious disease consultants to be a contaminant. Among 45 nasopharyngeal specimens tested by PCR for a panel of bacterial and viral pathogens that included HSV, one was positive for Rhinovirus.

There were no serious infections and no deaths reported. Among patients discharged from the ED, none returned within 72 h with an infection. Among 201 patients admitted to the hospital from the ED, 9 returned to the ED and were readmitted to the hospital (Table 2). One patient who initially presented at 35.6 weeks corrected gestational age and was treated with parenteral antibiotics returned 10 days after initial admission with bloody stools and abdominal radiograph concerning for necrotizing enterocolitis (NEC). This patient was managed with bowel rest and 5 days of antibiotics and discharged in improved condition. None of the other eight had evidence of systemic infection during the readmission.

4. Discussion

Our study suggests that serious infections are rare in well-appearing neonates with hypothermia noted incidentally at a routine visit. To our knowledge, this is the first study to examine this population. We speculate that incidentally identified hypothermia in otherwise well-appearing neonates most often reflects their normal, limited thermoregulatory capacity [3,4].

Sepsis evaluations and antimicrobial administration incur significant resource utilization and are not without potential complications.

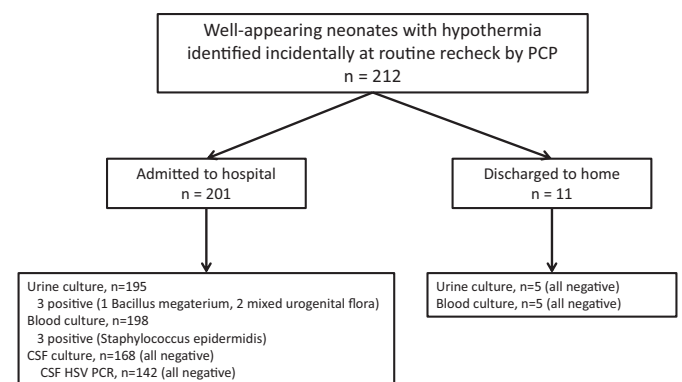


Fig. 1. Well-appearing neonates evaluated in a children's hospital emergency department after referral from PCP for hypothermia (core temperature $< 97.7^\circ\text{F}$ or 36.5°C) noted incidentally during routine well check. Abbreviations: CSF, cerebrospinal fluid; HSV, Herpes simplex virus; PCP, primary care practitioner; PCR, polymerase chain reaction.

Table 1

Characteristics of 212 well-appearing neonates with hypothermia (<97.7 °F or <36.5 °C) noted during a routine recheck.

Characteristic	Value
Age (days), median [IQR]	5 [4,6]
Male sex	107 (50.5)
Race	
White	139 (34.4)
Black	36 (16.9)
Pacific Islander	1 (0.5)
Asian	10 (4.7)
Unknown/undeclared	26 (12.3)
Season of encounter	
Winter	64 (30)
Spring	48 (23)
Summer	46 (22)
Premature (< 37 weeks)	74 (34.9)
Gestational Age (weeks.days), median [IQR]	
At birth	37 [36, 39]
At time of ED evaluation	37.5 [36.5, 39.4]
Twin gestation	20 (9.4)
Birth weight (kg), median [IQR]	2.75 [2.32, 3.12]
Temperature, median [IQR]	
Primary care practitioner	95.9 [95.0, 96.4]
ED triage, rectal	97.0 [96.3, 97.7]
Admitted to hospital from ED	201 (94.8)
Hospitalized patients, length of stay (d)	2.1 [2.0, 2.8]
Received empiric antimicrobial treatment	199 (93.9)

Abbreviations: ED, Emergency Department; IQR, Interquartile Range °C, Degrees Centigrade; °F, Degrees Fahrenheit; PCP, primary care provider.

Values are n (%) or Median [Interquartile range, IQR] unless otherwise specified.

Antibiotic treatment has also been associated with potential harm, including alterations of gut microbiota and antibiotic resistance in neonates and increased risk for NEC in premature newborns [12–14]. Though we cannot imply causality, it is notable that one neonate born at 35 weeks gestation developed NEC 10 days after sepsis evaluation and antibiotic treatment during a two-day admission.

Efforts are warranted to better identify well-appearing neonates with hypothermia but no other signs or symptoms who benefit from diagnostic and treatment interventions. These investigations might clarify when a sepsis evaluation is indicated, with or without an LP. Inflammatory biomarkers, in particular serum procalcitonin, may contribute to this decision making. However, procalcitonin, C reactive protein and absolute neutrophil count have low sensitivity to detect invasive bacterial infection in febrile neonates <21 days of age, and we are not aware of similar investigations among hypothermic neonates [15].

Future investigations might examine approaches that include HSV PCR testing of skin, eye, nasopharynx, and blood to identify well-appearing neonates in this sub-population who may benefit from blood, urine, and CSF analyses to identify serious infection. In addition, analyses of existing, large datasets of neonatal HSV infections might inform better diagnostic approaches to these patients [8,16]. Of particular

interest is examination of the laboratory and clinical outcomes of neonates with hypothermia but no other signs, symptoms, or laboratory abnormalities (e.g., transaminitis, thrombocytopenia, neutropenia, hypoglycemia). Finally, we believe the results of this study should prompt primary care clinicians to reconsider checking temperature in well-appearing neonates at routine visits.

5. Limitations

Our study has limitations, including retrospective data acquisition at a single center. There was likely variability in temperature measurement technique between our ED and PCP clinics. Additionally, some patients with incidentally noted hypothermia may not have been referred to our ED. Finally, some patients with serious infection may have been missed among the 5.2% discharged from the ED. However, none of these patients returned to our children's hospital ED, the primary referral center for our region, with an infection within 72 h.

6. Conclusion

Well-appearing neonates with incidentally noted hypothermia at a routing visit with their PCP are at low risk for serious infection and may not warrant a full sepsis evaluation.

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Article summary

This study found no serious infections in 212 well-appearing neonates who had hypothermia incidentally identified at a routine visit with their primary care practitioner and were referred to the emergency department for further evaluation.

Author contributions

Dr. Jain created the REDCap database, oversaw data acquisition and cleaning, and drafted the initial version of manuscript. Dr. Anderson assisted with data cleaning, interpretation of analyses, and critical review and manuscript revisions. Dr. Mikhail assisted with data acquisition and REDCap data entry, data cleaning, and critical review and revisions of manuscript. Dr. Arnold conceptualized and designed the study, conducted analyses, assisted with interpretation of analyses, and assisted with drafting, review, and revision of the manuscript.

Table 2

Characteristics of 9 neonates admitted to hospital for hypothermia who returned to the ED and were readmitted to hospital.

Age, 1st admission (days)	Age, 2nd admission (days)	Corrected GA (wks) at 1st admission	Reason for re-hospitalization	Outcome
6	19	35.6	Bloody stool, pneumatisis	Blood culture no growth; tx 10 days piperacillin-tazobactam
5	8	35.5	Abdominal distension, guaiac positive stool, normal KUB	Observed overnight without sepsis evaluation or antibiotic
4	21	35.4	Abnormal eye movements	Diagnosed with GERD
4	30	35.4	Projectile emesis	Pyloric stenosis
4	41	37.4	Fussiness	Diagnosed with GERD
2	73	36.2	Fever, dehydration	Rhinovirus infection
2	5	36.2	Hypothermia, hypoglycemia	Treated with radiant warmer without further infectious evaluation or treatment
6	8	37.6	Hypothermia, apnea	Admit to NICU; normal head ultrasound; treated with caffeine
7	11	35.6	Hypothermia	Isolette and bundling with resolution of hypothermia

Abbreviations: ED, Emergency Department; GA, gestational age; GERD, gastroesophageal reflux.

CRediT authorship contribution statement

Sweeti Bhakta Jain: Investigation, Data curation, Conceptualization.
Tucker Anderson: Writing – review & editing, Validation, Data curation.
Daniel Mikhail: Writing – review & editing, Project administration, Investigation, Data curation.
Ritu Banerjee: Writing – review & editing, Data curation.
Donald H. Arnold: Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article to disclose.

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