Citrobacter koseri meningitis and septicemia in a neonate with borderline fever at home

Mark Keith Hewitt MD BMSc, Jennifer Ann Klowak MD MSc, Jeffrey M. Pernica MD MSc, James Leung MD

Cite as: *CMAJ* 2021 October 18;193:E1592-4. doi: 10.1503/cmaj.210285

A 13-day-old boy presented to the pediatric emergency department with a chief complaint of fussiness and shivering overnight. The patient felt hot to his parents' touch; his axillary temperature, measured at home, was 37.7°C while bundled and was 37.5°C a few hours later when unbundled, which prompted the visit. The baby continued formula feeding frequently, but with slight decreases in volume, and was stooling and voiding appropriately (> 6 full diapers in the preceding 24 h). He was somewhat sleepy, but easily rousable and consolable with his parents.

At triage, the patient's vitals were within age-appropriate ranges, with a rectal temperature of 37.4°C, respiratory rate of 48 (normal 40–60) breaths/min, oxygen saturation 98% on room air, heart rate 152 (normal 100–160) beats/min and blood pressure 82/50 mm Hg. His weight at presentation was 3.44 kg; birth weight was 3.25 kg. Clinical examination was otherwise unremarkable; specifically, he had normal tone, brisk perfusion, no neck stiffness, no rash and a level fontanelle. We did not identify any overt sources of infection on examination.

The patient had been born at 38+3 weeks' gestation via normal vaginal delivery to a seroprotected, transmasculine father (assigned female at birth). The father had vaginal colonization of group B *Streptococcus* (GBS) and type 2 diabetes mellitus requiring insulin during pregnancy. Pregnancy was also complicated by a chlamydia infection in the third trimester that was treated with unknown antibiotics and confirmed resolved with a negative result on retest before delivery. Birth was uncomplicated, with appropriate peripartum prophylaxis with GBS penicillin, and routine monitoring for hypoglycemia. The newborn was discharged 24 hours after birth with no concerns. We noted no other risk factors for early neonatal sepsis; specifically, prolonged ruptured membranes, previous infant with GBS meningitis or maternal fever.

Considering the reported axillary temperature higher than 37.5°C at home, we conducted a full septic workup, consisting of blood culture, viral nasopharyngeal swab, urine culture and lumbar puncture with cerebrospinal fluid (CSF) analysis. We admitted our patient and treated him empirically with intravenous ampicillin, cefotaxime (both at 50 mg/kg) and acyclovir (20 mg/kg) pending culture results. Results of investigations are presented in Table 1.

Key points

- In infants younger than 3 months old, an axillary temperature higher than 37.5°C should be treated as a fever when considering sepsis as a differential diagnosis.
- Even if infants with reported fever at home are found to be afebrile in the emergency department, clinicians should ask about risk factors and examine for signs of serious bacterial infection; given the higher prevalence of infection in this age group, consider further investigation.
- White blood cell count and C-reactive protein may be normal when measured early in the course of illness in a neonate with serious bacterial infection.
- Clinical decision tools vary in the recommended cut-off for fever thresholds in the infant population; the Canadian Paediatric Society recommends thresholds of higher than 38°C for rectal temperatures and higher than 37.5°C for axillary temperatures.

Given abnormal CSF results, we increased the antibiotic dose to meningitis doses at 100 mg/kg/dose for both ampicillin and cefotaxime. Ten hours after presentation, we recorded a rectal temperature of 39.0°C. Laboratory values worsened over the next 24 hours to a peak white blood cell count of 18.8×10^9/L, C-reactive protein of 48.2 mg/L and venous lactate of 4.1 mmol/L. The blood culture returned positive for *Citrobacter* spp., and we changed the patient's antibiotics to meropenem on the advice of our microbiologist. Polymerase chain reactions of CSF for herpes simplex virus, enterovirus and parechovirus were negative, and cultures of both blood and CSF grew *Citrobacter koseri*.

Our patient's fevers stopped after 4 days of antimicrobial therapy. He did not have any seizures and his neurologic status did not worsen during the admission. Initial cranial ultrasound and follow-up magnetic resonance imaging did not show any evidence of brain abscess or structural abnormalities. As the isolated *Citrobacter* strain was cefotaxime-sensitive, we stopped meropenem and restarted cefotaxime, which was continued until the child reached 1 month of age when we changed it to ceftriaxone for ease of dosing, for a total of 3 weeks of treatment. Over the subsequent 2 years, the patient had no repeat admission to hospital, standard postmeningitis auditory screening has been normal, and the parents have not reported any concerns about growth or delayed milestones.

Table 1: Laboratory investigations of a febrile neonate

Test	Patient result (age-appropriate reference range)
Serology	
WBC	11.8 (5–20) × 10^9/L
ANC	8.4 (1.0–9.5) × 10^9/L
Hemoglobin	186 (125–205) g/L
Platelets	466 (150–400) × 10^9/L
CRP	5.6 (< 6.2) mg/L
Venous lactate	2.0 (< 2.2) mmol/L
CSF	
Colour	Yellow, xanthrochromia present
Leukocyte count	3361 (0–20) × 10^6/L
Protein	2.07 (< 0.45) g/L
Glucose	1.8 mmol/L (0.6 × serum glucose [3.2 mmol/L])
Blood	< 1000 × 10^6/L (none)
Other investigations	
Urinalysis	Negative WBC, nitrites, RBC, leukocytes, bacteria, protein
Nasopharyngeal swab	Negative

Note: ANC = absolute neutrophil count, CRP = C-reactive protein, CSF = cerebrospinal fluid, RBC = red blood cell count, WBC = white blood cell count.

Discussion

Neonatal sepsis is a life-threatening diagnosis, with a reported incidence of 1–4 per 1000 live births in the United States.[1] Common culprit bacteria in the neonatal (< 30 d) age group include GBS, *Escherichia coli* and other gram-negative bacilli, thought to be acquired through vertical transmission from the maternal genitourinary tract.[2] In Canada, missed meningitis is a common complaint to the Canadian Medical Protection Association, with most cases concerning children aged 0–4 years.[3] *Citrobacter koseri* is a gram-negative bacterium that is universally resistant to penicillin; it is a rare cause of neonatal meningitis. Case-fatality rates in neonates are about 30%, with 70% of cases developing brain abscess and 50% of survivors left with long-term neurologic sequelae.[4]

In neonates presenting with parental concerns of fussiness, clinicians should ask about increased lethargy, change in behaviour, decrease in wet diaper frequency and volume, reduced feeding and antenatal risk factors for serious bacterial infection. The patient should be examined for clinical signs of serious bacterial infection, such as tachypnoea, tachycardia, fever, signs of dehydration (e.g., delayed capillary refill, lethargy), signs of an intracranial process (e.g., atonia, irritability, inconsolability, bulging fontanelles), increased work in breathing (e.g., tachypnea, recessions, head bobbing) and jaundice.

Clinical features of serious bacterial infection may be subtle, and several clinical decision tools have been derived to aid clinicians in diagnosing serious bacterial infection in infants. Classically, the Rochester, Philadelphia and Boston criteria have been used to determine risk in infants younger than 90 days with fever without a source.[5] Since these decision tools were validated, however, the prevalence of serious bacterial infection has decreased because of the routine administration of additional vaccinations for *Hemophilus influenzae B* and *Streptococcus pneumoniae* (pneumococcal vaccine), and antenatal screening protocols. Newer clinical decision tools have been derived to reflect this reduced prevalence, such as the "Step-by-Step Approach" to febrile infants, and the Pediatric Emergency Care Applied Research Network (PECARN) rule for low-risk infants.[6,7] These newer tools use novel sepsis biomarkers, such as procalcitonin, tests for which are presently not widely available for clinical use.

Crucially, all these clinical decision tools rely on appropriate identification of fever to initiate investigations. Frequently, clinicians face a dilemma of initiating invasive investigations for serious bacterial infection in infants with unclear symptomology and borderline temperatures measured at home, around the commonly used 38°C fever threshold. A challenge in implementing clinical decision tools relates to accurate temperature measurement. Although the Canadian Paediatric Society recommends rectal temperatures as the gold standard, this method is perceived to be invasive. Parents frequently use different methods of measuring temperatures at home, such as axillary or forehead methods. Axillary temperatures have a lower fever threshold (37.5°C) than rectal temperatures (38°C); therefore, using lower cut-offs for fever with axillary temperatures is suggested.

The parents of our patient reported axillary temperatures of 37.5 and 37.7°C, which did not classify as febrile based on definitions in clinical decision tools. The "Step-by-Step Approach" defines fever as rectal or axillary temperatures higher than 38.0°C, the PECARN and Rochester rules use a rectal temperature higher than 38.0°C, the Philadelphia criteria defines it as a rectal temperature higher than 38.2°C, and the Boston rule uses a rectal temperature higher than 38.0°C or "equivalent" at home.[5–7] A key determinant in our management stemmed from the Canadian Paediatric Society's position statement on temperature monitoring, which recommends, on expert opinion, that an axillary temperature higher than 37.5°C constitutes a fever.[8] This recommendation is supported by literature suggesting a lower threshold for fever for axillary temperatures.[9] Furthermore, a secondary analysis of 1233 prospectively enrolled infants younger than 60 days old with fever at home, but not in the emergency department, found that 8.8% were subsequently diagnosed with a serious bacterial infection, prompting a recommendation that these patients be treated as if they had a fever documented by a health care provider when applying clinical decision tools to risk-stratify patients.[10]

Our patient initially presented with normal laboratory values for common infection markers used by clinical decision tools, namely white blood cell count and C-reactive protein. A recent prospective observational study of febrile infants younger than 90 days showed that commonly used thresholds for white blood cell and absolute neutrophil counts fail to identify infants at risk of serious bacterial infections with a high degree of accuracy.[11] Large-scale research has found C-reactive protein values below 20 mg/L

to be associated with a negative likelihood ratio of 0.25 for invasive infection.[12] However, recent literature suggests that this cut-off may have only a 77% sensitivity and 77% specificity for invasive bacterial infection; furthermore, it varies with time, peaking 36–72 hours after the initial inflammatory or infectious stimulus.[13] Of note, we did not have access to procalcitonin testing; the "Step-by-Step Approach" uses a procalcitonin value greater than 0.5 ng/mL to identify a high-risk neonate, and the PECARN tool uses a cut-off of less than 1.71 ng/mL to identify infants at low risk.[6,7]

In our patient, neonatal age (< 30 d) was the only definitive risk factor for serious bacterial infection according to the clinical decision tools. Ultimately, the patient's age and home temperature led us to classify this neonate as febrile, prompting workup, which led to early diagnosis and rapid initiation of antibiotics, potentially avoiding complications such as brain abscess and septic shock. Though most febrile infants will not have bacterial infections, clinical examination and widely available biomarkers do not permit the reliable identification of those with viral infections who do not require empiric antibiotics.[7] Further research should prioritize methods of home temperature monitoring commonly used by parents to be safely incorporated into clinical decision tools and minimization of antibiotic use to improve antimicrobial stewardship in this patient population.

Conclusion

Neonatal and infant sepsis is life-threatening and carries substantial risk of long-term neurologic morbidity or death. Although multiple clinical decision tools are available to aid in managing infants with fever without source, diagnosis can still be challenging with borderline temperatures. We reported the case of a neonate with meningitis who presented with a maximum axillary temperature of 37.7°C at home, few clinical features suggesting serious bacterial infection, and without evident risk factors for sepsis. The temperature monitoring statement of the Canadian Paediatric Society, and literature suggesting high rates of serious bacterial infection in neonates with documented fever at home, were paramount in our decision to perform a full septic workup in this patient. Front-line clinicians should be familiar with various modalities of temperature monitoring and have a high index of suspicion for serious bacterial infection in neonates presenting with fussiness and any definition of fever, not just rectal temperatures.

References

1. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. *Lancet* 2017;390:1770-80.
2. Swanson D. Meningitis. *Pediatr Rev* 2015;36:514-24, quiz 525-6.
3. Meningitis: understanding the vulnerabilities. Ottawa: Canadian Medical Protective Association; 2015:6-8.
4. Doran TI. The role of citrobacter in clinical disease of children: review. *Clin Infect Dis* 1999;28:384-94.
5. Diagnosis and management of febrile infants. 2012; Rockville (MD): Agency for Healthcare Research and Quality; reviewed August 2018. Available: https://www.ahrq.gov/research/findings/evidence-based-reports/er205-abstract.html (accessed 202X May 25).
6. Gomez B, Mintegi S, Bressan S, et al. Validation of the "step-by-step" approach in the management of young febrile infants. *Pediatrics* 2016;138:e20154381.
7. Kuppermann N, Dayan PS, Levine DA, et al.; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN). 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.
8. Leduc D, Woods S; Community Paediatrics Committee. Temperature measurement in paediatrics. *Paediatr Child Health* 2000;5:273-84.
9. Oguz F, Yildiz I, Varkal MA, et al. Axillary and tympanic temperature measurement in children and normal values for ages. *Pediatr Emerg Care* 2018;34:169-73.
10. Ramgopal S, Janofsky S, Zuckerbraun NS, et al. Risk of serious bacterial infection in infants aged ≤ 60 days presenting to emergency departments with a history of fever only. *J Pediatr* 2019;204:191-5.
11. Cruz AT, Mahajan P, Bonsu BK, et al.; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network. Accuracy of complete blood cell counts to identify febrile infants 60 days or younger with invasive bacterial infections. *JAMA Pediatr* 2017;171:e172927.
12. Gomez B, Bressan S, Mintegi S, et al. Diagnostic value of procalcitonin in well-appearing young febrile infants. *Pediatrics* 2012;130:815-22.
13. Lanziotti VS, Póvoa P, Soares M, et al. Use of biomarkers in pediatric sepsis: literature review. *Rev Bras Ter Intensiva* 2016;28:472-82.

Competing interests: Jeffrey Pernica reports a grant from MedImmune and an honorarium from the Canadian Paediatric Review, outside the submitted work. No other competing interests were declared.

This article has been peer reviewed.

The authors have obtained patient consent.

Affiliations: Division of Emergency Medicine (Hewitt), Department of Medicine, McMaster University, Hamilton, Ont.; Division of Pediatric Intensive Care (Klowak), Department of Pediatrics, Ottawa University, Ottawa, Ont.; Divisions of Pediatric Infectious Disease (Pernica) and Pediatric Emergency Medicine (Leung), Department of Pediatrics, McMaster University, Hamilton, Ont.

Contributors: All authors contributed substantially to the acquisition and analysis of the data. Mark Hewitt and Jennifer Klowak drafted the manuscript. All of the authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Correspondence to: James Leung, Leungj16@mcmaster.ca