



# Entering the Icy Waters of Viral Testing and Infant Hypothermia

Kaitlyn Philips, DO, MS, and Alyssa H. Silver, MD

Temperature changes may be the only sign of infection in young infants. Whether hyper- or hypothermia occurs, the prevalence of serious or invasive bacterial infections is well-reported, ranging from 2.1% to 13.5%.<sup>1</sup> For decades, scholars have studied ways to risk-stratify infants with hyperthermia, or fever. The Rochester criteria, first published in 1985, was followed by the Boston criteria in 1992 and Philadelphia criteria in 1993. Most recently, the American Academy of Pediatrics' 2021 "Clinical Practice Guideline on the Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old" provided clinicians with the highly sought-after, evidence-based guidance for management of this vulnerable population.<sup>2</sup> The pediatric scientific community's next step is to expand this guidance to infants with hypothermia. These efforts are underway, thanks to the Hypothermic Young Infant Research Collaborative, a 9-site research group whose initial findings were published recently in *The Journal*.<sup>1</sup>

In this secondary analysis from the aforementioned collaborative, Prasad et al assess the role of viral respiratory pathogen (RP) testing in risk stratification for infants with hypothermia.<sup>3</sup> The authors performed a retrospective cohort study of infants included in the multicenter, parent study ( $\leq 90$  days old presenting to an emergency department or directly admitted with hypothermia  $\leq 36^\circ\text{C}$  between September 2016 and May 2021) who had RP testing. The authors tested the association between a positive RP test and presence of serious bacterial infection (SBI, defined as urinary tract infection, bacteremia, and/or meningitis) or invasive bacterial infection (IBI, defined as bacteremia and/or meningitis) in young infants with hypothermia using unadjusted bivariate analyses. Of the 1098 infants in the parent study, 446 had RP testing. Of those with RP testing, 7.4% had an SBI and 4.5% had an IBI. The prevalence of SBI or IBI did not differ significantly based on RP positivity, and the authors concluded that RP testing status should be used cautiously in making decisions for infants with hypothermia.

Some may view the article by Prasad et al as a large negative study with key methodologic weaknesses. The parent collaborative lacks community hospitals, where most children get their care, and so may not truly reflect the current prevalence of hypothermia and practices of RP testing. The population's overall prevalence of hypothermia is low, and SBI or IBI prevalence is even lower, limiting the power of the study. As such, multivariable analyses are not valid. There is tremendous

variation in RP testing practices between sites and between age ranges. The authors attempt to explore some of the demographic and clinical characteristics of RP testing status as well as frequency of detected pathogens, which leads to more questions than answers.

The reality is that the article by Prasad et al is a starting point. It took almost 5 years and an extensive research collaborative to characterize how RP testing was even being performed in infants with hypothermia. Including multiple large institutions across the nation helps capture the variability in management practices at these centers. Using both diagnostic codes and actual infant temperatures and reviewing cases to exclude any history of any fever is a robust process to confirm eligibility. Although larger, more expensive, prospective studies are needed to help clinicians safely incorporate RP testing status when risk-stratifying infants with hypothermia, the work by Prasad contributes to important, foundational literature.

In comparison, consider the modest beginnings of the young febrile infant literature. In 1977, Roberts and Borzy entered the untapped research trove of the young febrile infant with an observational study of only 61 infants.<sup>4</sup> They highlighted the "limitation of clinical judgment in assessing febrile infants in the age group studied and supported an aggressive approach in the management of very young febrile infants."<sup>4</sup> Several subsequent studies aimed to answer the question of how to identify SBI risk in febrile infants in the absence of any other data.<sup>5,6</sup> These now "landmark" studies were relatively small, single center, and retrospective. The often-cited Rochester Criteria, published in 1985, was among the first prospective study widely used to guide clinical management, despite studying only 233 infants from a single center.<sup>7</sup> These early studies were crucial in fueling the young febrile infant literature to the robust evidence we have today.

It took nearly 50 years of science to help clinicians appropriately manage febrile infants. During this time, the landscape of pathogens causing SBI and IBI changed, particularly in older infants, with the widespread use of vaccines and disease-prevention practices. Characterizing the clinical importance of viral testing in young infants who are febrile or with hypothermia is as important as ever. Clinicians are encouraged to incorporate RP testing in febrile

IBI	Invasive bacterial infection
RP	Respiratory pathogen
SBI	Serious bacterial infection

From the Department of Pediatrics, Joseph M. Sanzari Children's Hospital, Hackensack Meridian Children's Health, Hackensack, NJ

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infants 29-60 days old when making management decisions.<sup>2</sup> Although more studies are needed, Prasad et al's examination of RP testing in infants with hypothermia is a step in informing a parallel recommendation.

This study is an effort to enter the unexplored, perhaps icy, waters of infant hypothermia and viral testing. Although certainly not the conclusive study to guide clinical decision-making, the work of Prasad et al is a solid starting point, critical to inform future work to determine the utility of RP viral testing in infants with hypothermia. ■

### **CRedit authorship contribution statement**

**Kaitlyn Philips:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Alyssa H. Silver:** Conceptualization, Methodology, Writing – review & editing.

### **Declaration of Competing Interest**

K.P. and A.S. have no conflicts of interest to disclose.

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Reprint requests: Kaitlyn Philips, DO, MS Hackensack Meridian Children's Health, 30 Prospect Ave, Hackensack, NJ 07601. E-mail: [kaitlyn.philips@mhnh.org](mailto:kaitlyn.philips@mhnh.org)

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