COMMENTARY

Febrile Infant Hospitalizations: When Is the Right Time to Discharge?

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Early in their training, pediatricians come to grips with a scary fact about young febrile infants <3 months of age: they can be sick without looking sick.[1–3] Until the early 1990s, both well- and ill-appearing young febrile infants were managed conservatively, with the same cookbook strategy: hospitalization for 48 to 72 hours on empirical parenteral antibiotics as urine, blood, and spinal fluid cultures marinated.[4,5] Pediatric house staff became proficient at spinal taps but also learned that most infants had cultures that tested negative. This "rule out sepsis" recipe clearly subjected many infants to the risks and costs of unnecessary hospitalization and treatment.[6] At least 2 questions ensued: which infants could be spared hospitalization? And, if an infant was hospitalized, when could she or he be safely discharged?

With regard to the first question, in 2012, the US Agency for Healthcare Research and Quality published a comprehensive review of the myriad of approaches to this conundrum,[7] and most are familiar with the current state of affairs.[8] First, pediatric trainees still learn the algorithms developed decades ago in Boston,[9] Milwaukee,[10] Philadelphia,[11] and Rochester,[12] which teased out a subpopulation of "low-risk" febrile infants who might safely be spared tests, antibiotics, and/or hospitalization. In other studies, authors supported intramuscular ceftriaxone and close follow-up as an alternative to hospitalization for selected infants 28 to 90 days of age.[13] Second, despite changes in bacteriology, such as the virtual disappearance of *Listeria* and *Haemophilus influenzae*, and the impressive reduction in group B streptococcal and pneumococcal infections,[14,15] the overall ball park rates of serious bacterial infection in young febrile infants remain stubbornly unchanged: 5% to 10% have a urinary tract infection, ~1.5% to 2% are bacteremic, and 0.5% have meningitis.[7] Third, researchers confirm the risks are higher for ill-appearing infants (~10% have bacteremia) and those <1 month of age[7] and are lower for infants with bronchiolitis,[16,17] enterovirus[18] or influenza,[19] or reassuring c-reactive protein[20] and/or procalcitonin.[21] Finally, although some clinicians now manage well-appearing febrile infants with urinary tract infections as outpatients,[22,23] many febrile neonates and non–low-risk febrile infants 28 to 90 days of age are hospitalized for the same old reason: you just can't reliably tell who is sick.

So, when can you stop worrying and safely discharge a hospitalized infant who does not appear ill? This question rightly presumes that if follow-up is assured, the sooner the better, given hospitalization's financial costs, iatrogenic risks, and emotional toll on families.[6,24–27] Discharge after 48 to 72 hours of negative cultures became a de facto rule of thumb when cultures were read manually, once daily, because cultures that turned positive later were almost always with a nonpathogen or contaminant.[28] Studies of actual "time to positivity" became possible when laboratories began using microbial detection systems that provide immediate notification of a culture turning

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positive. Kaplan et al[28] found 93% of blood cultures that became positive with a pathogen did so within 28 hours of incubation. Evans and Fine[29] reported 97% positive within 36 hours. Biondi et al[30] reported 91% positive within 24 hours, 96% within 36 hours, and 99% within 48 hours. Lefebvre et al[31] reported 96% positive within 24 hours. All concluded that the old 48- to 72-hour rule could safely be shaved by a day or 2.

In this current issue of *Hospital Pediatrics*, Aronson et al[32] report somewhat lower rates of positivity within 24 to 36 hours. They retrospectively reviewed the microbiology database and medical records on infants 60 days or younger who were brought to the emergency department at 1 of 10 children's hospitals from 2011 to 2016. They identified 360 cases of bacteremia and 62 cases of culture-proven meningitis and subdivided each group into those who were ill appearing on presentation and those who were not. After 24 hours of culture incubation, 85% of the bacteremic patients had cultures that tested positive if they were not ill appearing on presentation versus 93% if they were ill appearing. After 36 hours, 95% in both groups of bacteremic patients were positive. For meningitis, the infant's appearance did not affect the time to positivity, which was 89% in 24 hours and 95% in 36 hours.

Extrapolating from these data, if the baseline rate of bacteremia is ∼10% for an ill-appearing febrile young infant and 2% for one that is well appearing, then ∼0.7% (1:140) of ill-appearing infants will have their culture turn positive within 24 hours (7% of 10%), and 0.5% (1:500) will turn positive after 36 hours (5% of 10%). For the infants who appeared well on presentation, 0.3% (1:333) will have their culture turn positive within 24 hours (15% of 2%), and 0.1% will turn positive after 36 hours (5% of 2%). The numbers are even smaller for meningitis.

Depending on one's view of acceptable risk, these back-of-the-napkin calculations provide support for many options: discharging all well-appearing infants at 24 hours, always waiting 36 hours, or sometimes waiting 36 hours, such as when a patient appeared ill on presentation or in neonates, who have a relatively higher baseline rate of bacteremia. All of these strategies are defensible, especially considering that practicing pediatricians often do not follow academic febrile infant guidelines and their patients do not suffer.[33] Where you stand depends on where you sit.

As a practical matter, where the clinician rests on the risk tolerance spectrum may not matter much because the time the cultures were obtained will likely determine the discharge timing decision. Assume the infant's cultures were obtained at 11 PM. No one is going to discharge an infant home with parents in the middle of the night. So even if a clinician supports discharging a well-appearing infant after 24 hours of cultures that tested negative, the infant is not going home until the community physician or academic care team rounds the next day (say at 9 AM [34 hours]) and enters discharge orders that a nurse executes even later in the morning. Perhaps the current study will be used to persuade the 48-hour believer that it is safe to discharge somewhat sooner, say at 5 PM (42 hours), instead of insisting the infant and parent stay another night in the hospital because the discharge process isn't going to start at 11 PM (the nursing change of shift in many hospitals). Patient follow-up is another practical issue. Clinicians ought to be more conservative if they have misgivings about the parent's ability to recognize their infant is sick and/or return to the office or clinic.

Clinicians often express risk in personal terms, as if they are accepting the medical risk on behalf of the patient or parent, despite that the physician's true risk is limited to feeling awful or getting sued for malpractice if the rare event occurs. The rule-out-sepsis quandary seems a ripe area for shared decision-making, and the time to positivity studies can be used to allow clinicians to express risk with increased precision. An open question is to what extent these risk refinements will help frightened, sleep-deprived parents who have seen their new infant subjected to bladder catheterization, venipuncture, spinal tap, hospitalization, and treatment, all because we've told them their infant might have a life-threatening condition.[34]

Unfortunately missing from this entire discussion is an answer to the most pertinent question: what if we and/or the parents make the wrong decision about testing, treatment, or hospital discharge? What is the risk of death or disability if you discharge from the hospital (or don't hospitalize in the first place) an infant who turns out to have meningitis or bacteremia and gets readmitted (or admitted) for full treatment within the next 24 hours? Unfortunately, neither the febrile infant nor the time to positivity studies are designed to answer this question. Still, provided in most of the febrile infant studies are some clinical outcome information on infants whose cultures unexpectedly turned positive. It's a small, heterogeneous group of young febrile infants: low risk and initially untreated, low risk and given an initial shot of ceftriaxone, treated and untreated hospitalized infants discharged before 36 to 48 hours with cultures that tested negative, and those managed by community pediatricians who may or may not follow any recommended algorithms. Spoiler alert: bad outcomes have not been reported.[7] Nonetheless, as with everything in life, the risk must be non-zero. Intuitively, the small risk will likely be further mitigated if a discharged infant whose culture unexpectedly turns positive gets proper treatment expeditiously, which will depend on the parent's compliance with follow-up plans. It is reassuring that several studies reveal that parents are highly reliable under these circumstances,[7] but this is a judgment the clinician must make on a case by case basis.

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