examples of the apparent value of these medications for individual patients. However, the accumulated published evidence is cause for concern and offers little guidance for clinicians. Given the challenges of equipoise and expense, it will not be easy to design and conduct prospective studies. However, continuing to expose highly vulnerable patients to furosemide and other loop diuretics without clarity of benefit and risk is concerning. We can and should do better. ■

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In Search of an Ideal Protocol to Distinguish Risk for Serious Bacterial Infection in Febrile Young Infants

The evaluation and management of the febrile young infant is commonly performed in the outpatient setting. The subset of those aged less than 8 weeks of age has traditionally been demarcated from relatively older febrile children by a variety of unique clinical factors affecting risk for serious bacterial infection (SBI). These include inadequately developed host defenses, difficulty in accurately grading patient clinical appearance because of neurologic immaturity, and a unique profile of potential bacterial pathogens causing SBI for which we lack preventative vaccines.

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Consensus regarding appropriate management has evolved over time. Initially, it was customary to perform a full sepsis evaluation and hospitalize all febrile infants aged 0-8 weeks for empiric parenteral antibiotics pending culture results. After determining that the rate of

CSF Cerebrospinal fluid
LP Lumbar puncture
SBI Serious bacterial infection

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SBI is approximately halved in those aged 4-8 weeks vs those <4 weeks of age, multiple outpatient studies tested SBI low-risk criteria protocols to accurately stratify infectious risk for relatively older febrile infants. The criteria used were similar in each study, including a combination of full-term birth history, no underlying medical conditions, appearing to be well with no focus of bacterial infection on physical examination, and a negative evaluation for sepsis. Several studies included the criteria of normal cerebrospinal fluid (CSF) analysis; others did not. A low-risk profile presentation was common, accounting for approximately 30% of all febrile infants aged 4-8 weeks. The effective utilization of these criteria promoted significant healthcare cost savings, and avoidance of unnecessary hospitalization for parenteral antibiotic therapy, without sacrificing sensitivity for SBI outcome. This approach seemed to be widely adopted for the outpatient management of febrile infants aged 4-8 weeks, although a 2016 report indicated management deviations are common with only 59% of febrile infants aged 0-4 weeks presenting to a large California health maintenance organization receiving a complete evaluation for sepsis.[1]

Additional protocols excluded performance of a lumbar puncture (LP)/CSF analysis, relying exclusively on analyzing patient clinical appearance, urinalysis, and blood test results (including serum inflammatory markers) to distinguish SBI risk. One such study from the Pediatric Emergency Care Applied Research Network[2] reported 99.6% negative-predictive value for their low-risk criteria for SBI outcome; they included febrile infants aged 0-4 weeks; and analyzed only 10 cases of bacterial meningitis. To highlight the difficulty in accurately applying such an approach, a subsequent study[3] testing these same criteria found that 10.2% of those with SBI were misclassified as "low risk," including 13% of infants with invasive bacterial infections (4 with bacteremia and 2 with bacterial meningitis) All 5 misclassified patients were clinically well-appearing and had "normal" values for complete blood count absolute neutrophil count and serum procalcitonin concentration.

The study by Coyle et al[4] in this volume of *The Journal* is a cost analysis of 5 such protocols defining low-risk for SBI in febrile infants aged 29-90 days. One can argue this cohort is not homogeneous with regard to SBI risk because at approximately the midpoint (8 weeks of age), we would anticipate transition to a different range of bacterial pathogens and commencement of the protective effect of antibacterial vaccines for *Streptococcus pneumoniae* and *Haemophilus influenzae* type b. As expected, protocols utilizing fewer interventions (no LP/CSF analysis, chest radiograph, or antibiotic therapy) had the lowest cost, seemingly without sacrificing sensitivity.

The issue of whether and when to perform CSF analysis in the outpatient evaluation of the febrile infant is controversial. For older children, effective antibacterial vaccines have dramatically diminished the prevalence of invasive bacterial infections. As such, fewer LPs are performed by resident trainees, which likely negatively impacts attaining technical proficiency in successfully executing this basic procedure as reported in this volume of *The Journal*.[5] It can be argued that the current standard of care for the febrile infants aged 0-4 weeks (SBI rate 12%) should continue to routinely include LP/CSF analysis and result in hospitalization for empiric antibiotic therapy pending culture results. Those aged 4-8 weeks (SBI rate 6%) are eligible for outpatient management if meeting all low-risk criteria: full-term birth history, no underlying medical conditions, appearing to be well with no focus of bacterial infection on physical exam, and a negative sepsis evaluation. Whether to perform CSF analysis routinely has become a matter of physician discretion. There are some factors to consider.

For the febrile young infant, the overall prevalence of bacterial meningitis is 1-2%; and the rate of traumatic LP nearly 40%.[6] The relative neurologic immaturity of the febrile young infant can confound accurate bedside assessment of the essential variables of patient clinical appearance and presence of nuchal rigidity. There is potential for creating a scenario of partially-treated meningitis for the outpatient-managed febrile young infant receiving empiric antibiotic therapy at the time of initial evaluation (no LP); who then receives repeat evaluation (with LP) for continued fever during the same illness. If the LP is traumatic, or the CSF profile suggests infection, the prior administration of antibiotics may confound the ability to make accurate clinical decisions based on negative CSF culture results. There is a considerable body of published literature making consistent recommendations regarding febrile young infant management, with important medical-legal implications.

The authors concluded "Based on the data from this study, clinicians can be reassured there are overall cost savings in the least aggressive approach, even if it means a small number of patients return for admission."[4] The ideal protocol achieves zero tolerance for a missed SBI because delay in initiating effective antibiotic therapy can result in devastating consequences. The quest for an ideal protocol for febrile infants minimizing intervention and, thus, limiting healthcare costs, is desirable but only if highly accurate in identifying infants with SBI. With each febrile young infant encounter, physicians must consider many individual factors in discerning whether to perform LP/CSF analysis. Healthcare cost consideration is certainly important, but by no means the ultimate arbiter of choosing a successful management strategy. ■

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Are Breastfed Infants Iron Deficient? The Question That Won't Go Away

Though iron is one of the most abundant elements in the earth's environment, iron deficiency is the most common single nutrient deficiency in the world. Given the very low iron content of human milk, there continues to be concern and controversy about the iron needs of the breastfed infant, particularly after 4-6 months of age when human milk alone will not supply the infant's requirement for iron.[1,2] In this volume of *The Journal*, Abrams et al[3] report on the potential iron deficiency in US breastfed infants 6-12 months of age, utilizing the database of dietary intakes from the 2016 Feeding Infants and Toddler Study (FITS).[4] This is a timely report as for the first time the Dietary Guidelines for Americans will include recommendations for the first 2 years of life when they are released in 2021. The guidelines for the intake of iron in breastfed infants will be controversial, no matter what is recommended. Compared with most other nutrients, iron has a narrow therapeutic window and historically there have been significant concerns for both too much and too little. The potential for both short- and long-term adverse neurodevelopmental outcomes of iron deficiency in infants continues to be an unresolved issue. This has lead the American Academy of Pediatrics to recommend universal iron supplementation for breastfed infants beginning at 4 months of age and continuing until appropriate iron-containing foods (including red meat and iron fortified cereals) are introduced into the diet.[1] These recommendations aim to minimize risks for iron deficiency with or without iron deficiency anemia, while waiting for unequivocal evidence that the very low iron content of human milk does not have an adverse impact on neurodevelopmental outcomes. The findings in this report give some support for this recommendation.

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It is significant that the recently published Scientific Report of the 2020 Dietary Guidelines Advisory Committee (to advise the Dietary Guidelines for Americans) concludes that "there is strong evidence that consuming complementary foods and beverages that contain substantial amounts of iron, such as meats or iron fortified cereals, helps maintain adequate iron status or prevents iron deficiency during the first year of life among infants with insufficient iron stores, or breastfed infants who are not receiving adequate iron from other sources." In this report, 2 nutrients, iron and vitamin D, are singled out for a discussion of dietary supplementation including food fortification, during the birth to 24 months life stage. However, the impact of iron supplements on neurodevelopmental outcomes in breastfed infants is not addressed.[2]

In the current report, the investigators examined the dietary intake data from infants 6-12 months of age who are either breastfed fed without infant formula (n = 296) or were mixed feeding (receiving both breast milk and infant formula) (n = 102).[3] It's notable that nearly all of the infants in both groups were also receiving complementary foods at the time of the FITS surveys. Though these investigators also looked at the formula-fed infants in the FITS survey, they concluded, as did the American Academy of Pediatrics[1] and the Dietary Guidelines Advisory Committee,[2] that infants fed formula (iron content 10-12 mg/L) but no breast milk, are at much less risk for significant iron deficiency and iron deficiency anemia. At present, approximately 75% of infants in the US are receiving some formula by 6 months of age, 43% receive formula without any breast milk, 32% receive both human milk and infant formula (mixed feeding); 25% are receiving no infant formula.[5]

Using the FITS data, Abrams et al calculated the iron intakes from 24-hour dietary recalls obtained by infant care providers. They then relied on the factorial modeling methodology utilized by the National Academy of Medicine (NAM) that determined the daily amount of iron needed to supply the estimated average requirement (EAR) in this age group is 6.9 mg per day.[6] This method takes into

EAR Estimated average requirement
FITS Feeding Infants and Toddler Study
NAM National Academy of Medicine

F.G. is co-author of the American Academy of Pediatrics position statement on iron deficiency and iron deficiency anemia in infants and toddlers.

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