Boston Febrile Infant Algorithm 2.0: Improving Care of the Febrile Infant 1–2 Months of Age

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INTRODUCTION

Fever in young infants is a common indication for acute medical evaluation. Approximately 500,000 febrile infants present to emergency departments (EDs) and outpatient clinics annually for evaluation.1,2 The diagnostic evaluation of young febrile infants remains challenging, but important as 7%–11% of well-appearing infants will have a serious bacterial infection (SBI), including bacteremia, meningitis, and urinary tract infection (UTI).3 Multiple studies have demonstrated that clinical appearance alone is an insensitive determinant for bacterial meningitis and bacteremia, with only 58% of infants with invasive bacterial infection (IBI; bacteremia and/or meningitis) presenting as ill-appearing.4–7 For these reasons, risk stratification algorithms have been developed to guide the evaluation and management of febrile infants, including the Boston,4 Philadelphia,8 and Rochester10 criteria and the step-by-step approach11 and Pediatric Emergency Care Applied Research Network (PECARN) febrile infant rule.2 Despite establishing these strategies, significant variation in management continues, particularly among infants between 1 and 2 months of age.12 Over the decades since these strategies were implemented, there has been a shift in SBI epidemiology with an increased predominance of UTI and a decrease in both bacteremia and meningitis without a change in the overall SBI rate.13 This shift, in conjunction with identifying novel biomarkers for SBI, has prompted a revision of our standardized approach. Procalcitonin (PCT) and C-reactive protein (CRP) are diagnostically superior to the traditionally used white blood cell count (WBC) and WBC differential in the risk stratification for SBI, especially for IBI.14–16 Newer biomarkers have been widely used in Europe and are increasingly deployed in the
United States. The most recently reported strategies, step-by-step, and PECARN rules, have incorporated CRP and PCT into their risk assessment for SBI.2,11

Other institutions have modified existing strategies based on available evidence and local experience to reduce testing and decrease hospitalization.17 At our institution, a 30-year-old protocol for well-appearing febrile infants 1–2 months of age (specifically 31–60 days) without a localized source of infection recommended examination of blood, urine, and cerebrospinal fluid (CSF), empiric antibiotics, and discharge home if the infant was considered low-risk for SBI by laboratory parameters.8 We chose to focus on the 1–2 month age group as this is the population with the greatest variability in management across centers and one in which we felt we had the most opportunity locally to improve care. Based on mounting evidence for the use of PCT and the desire to stay current in our approach, we revised our algorithm in 2018 by incorporating PCT aiming to more accurately identify low-risk infants to safely decrease lumbar punctures (LPs) and antibiotic administration without increasing hospitalizations, ED revisits, or missed IBI.

METHODS

Context
We conducted this quality improvement (QI) project at a single urban, tertiary children’s hospital with an annual ED volume of 61,000 visits. The ED initiated a clinical pathway program in 2011 and currently utilizes an array of 28 standardized clinical pathways that are readily available in the electronic clinical systems and aligned with order sets. Each pathway has an expert panel that regularly reviews emerging evidence and communicates with clinical staff through standard communication channels. Once approved by local leadership, all revisions are discussed with the faculty at in-person group meetings and reinforced through individual faculty performance feedback and online case-based education.

According to the policy for activities that constitute research at Boston Children’s Hospital, this research met the criteria for operational improvement activities exempt from ethics review. Specifically, this project was approved by the hospital’s Department of Pediatrics Performance Excellence Group as a QI initiative.

Population
The target study population included febrile infants 31–60 days of age with a rectal temperature ≥38.0 °C (documented at home or in ED), well-appearance, and no signs of focal bacterial infection by examination. Exclusion criteria for the revised pathway were the same as for the prerevision pathway. They included prematurity (<37 weeks), immunodeficiency, significant pre-existing medical condition (complicated perinatal course, prior surgery, prior bacterial infection, major congenital anomalies), or prolonged fever (>120 hours) as determined by chart review. The study population will be referenced as 1–2 months throughout the remainder of the article.

The Intervention—Planning and Implementation
The process of revising the febrile infant clinical pathway started in 2017 based on local pediatric emergency medicine expert review of published evidence regarding diagnostic performance of PCT for IBI in febrile infants. We had some local expertise as we had previously published a research investigation of optimal PCT thresholds for detecting SBI and IBL.18 Although in development, the pathway was reviewed with key stakeholders in emergency medicine and hospitalist medicine and communicated with the outpatient network of referring providers. One of our pathway experts (M.B.H.) is also an infectious disease expert. Laboratory medicine leaders were also engaged in ensuring PCT results would return in a consistent, timely manner (processing and reporting goal of 60 minutes). The hospital information technology support team incorporated the revised pathway into the existing order set for ordering ease. The proposed pathway was presented at faculty meetings and educational conferences, and feedback was encouraged. With the consensus of the expert team, the revised pathway and supporting electronic health record order set was launched in June 2018 (Figure S1, Supplemental Digital Content, http://links.lww.com/PQ9/A438). Importantly, two key changes were instituted simultaneously: (1) the low-risk criteria were redefined to include normal results of a urinalysis (≤5 WBC/high power field, negative nitrite, and leukocyte esterase), plasma WBC count (5,000–15,000 cells/µL), a PCT level (≤0.2 ng/mL), and routine CSF analysis was no longer part of the risk stratification and (2) empiric antibiotics were no longer recommended for low-risk infants before discharge. Before pathway revision, low-risk criteria were: UA with ≤ 5 WBC/hpf, plasma WBC 4,000–20,000 cells/µL, and CSF cell count ≤ 10 cells/hpf. The revised pathway reflected our belief that the addition of PCT would safely define a subset of the low-risk patients that could be managed safely as outpatients without routine LP and empiric antibiotics. If PCT testing was unavailable, providers were instructed to default to the previous version of the pathway.

Once launched, the pathway was published on the clinical pathways intranet site and on the mobile smartphone application available within the hospital network. To disseminate the revised pathway and reinforce uptake, implementation strategies included electronic communications, case-based discussions at ED educational conferences, monthly review of accumulated data with regular updates at faculty meetings, and interactive sessions with ED nursing and sessions targeted to referring outpatient providers. The associated electronic order set was adapted to encourage the recommended testing and treatment.
Assessing the Intervention
The care of the target population was reviewed retrospectively for the 18 months preimplementation (January 2017–June 2018) and prospectively for the 24 months postimplementation (July 2018–June 2020) of the revised pathway. Eligible infants were identified from the clinical data warehouse using a pick-list chief complaint of fever or a recorded rectal temperature of 38.0 °C or higher at any time during their ED visit. Available coded data were acquired by an automatic data feed into a Health Insurance Portability and Accountability Act–compliant, password-protected RedCap database, followed by a manual chart review. Age at presentation and other demographic information, maximum measured temperature in the ED, laboratory results (WBC, absolute neutrophil count, PCT, WBC on microscopic urinalysis, and results of urine and blood cultures, and CSF culture), ED diagnoses and antibiotics prescribed were collected automatically into RedCap. The manual chart review was completed to discern specific inclusion/exclusion criteria, appearance of the patient (well—active, alert, no irritability, appears normal, normal tone and perfusion; nonwell—fussy but consolable, somnolent, poor feeding, mild tachypnea or tachypnea, no emergent intervention required; or toxic, critically ill—apnea, poor perfusion, emergent interventions), and disposition of the patient (admitted to floor, admitted to ICU, or discharged), and pathway adherence. Pathway adherence was defined by obtaining all recommended laboratory studies and cultures, performing an LP, administering antibiotics in high-risk patients, and discharging low-risk patients without an LP or antibiotics. The attending physicians making the determination of well-appearance were essentially the same before and after the intervention. Final diagnoses were recorded from the index visit and any revisits within 14 days. All manually extracted data was entered into RedCap.

After the revised pathway was implemented, data were compiled monthly by our quality analysts and reviewed by the ED quality team and ED pathway experts, who ultimately performed the chart reviews and recorded pathway adherence. An additional review was available from the authors for any conflicting information in the record or uncertainty of variable coding—in this rare instance, a second author reviewed the record, and discussions continued until consensus was reached.

Measures
The primary outcome measure was the proportion of infants 1–2 months of age with LPs performed. The proportion of infants 1–2 months of age who received antibiotics was a secondary outcome measure. Deviations from the pathway occurred primarily due to an alternative source of fever (eg, recent immunization) or a recognizable infection (eg, bronchiolitis) or presumed source of infection such as UTI. Based on the published data of PCT in febrile infants and with the addition of PCT to the low-risk criteria, we anticipated that a fraction of the patients could be safely managed without a lumbar puncture or empiric antibiotics as the risk of IBI, including meningitis, would be exceedingly low. Published studies suggest that a cut point of 0.12 ng/mL, PCT has a sensitivity of 95.2% for SBI/IBI and a sensitivity of 90% at a cut point of 0.3 ng/mL.16,18 Our expert advisors chose a threshold of 0.2 ng/mL for classifying risk—specifically PCT ≤0.2 ng/mL was considered low risk. Admission rates, 72-hour ED revisits for the same chief complaint related to initial presenting chief complaint (ie, fever), and missed diagnosis of SBI and IBI over the subsequent 30 days were monitored as balancing measures.

SBI was defined as a positive blood or CSF culture result with a known pathogen or a positive urine culture result (>50,000 colony forming units per mL of pathogenic bacteria from a catheterized specimen). IBI was defined as a positive blood or CSF culture with a known pathogen. Other proven or potential bacterial diagnoses were recorded (eg, pneumonia, osteomyelitis, deep abscess).

Analysis
We used summary statistics to describe patient-related and clinical factors. Demographic and clinical characteristics, process measures, and balancing measures were compared between the pre- and post-implementation groups by using chi-square tests. A P chart depicted the impact of interventions on the outcome and process measures in the postimplementation period. Control limits were set 3 SDs from the mean. Standard rules were used to determine special cause variation.19

As a secondary approach to assess the pathway’s impact on LP use, we conducted an interrupted time series (ITS) analysis. Calendar month was used as the unit of time, comparing 18 months of the preimplementation period to 24 months of the postimplementation period. We estimated a logistic regression model with LP utilization as the dependent variable and time, intervention period (pre versus post), and the time-by-period interaction as the independent variables. We also included age (0–28 versus 29–60 days) as a covariate. This logistic ITS model compared the preintervention to the postintervention rates (ie, comparison of slopes) and the pre- versus postintervention intercepts (ie, the level change) while accounting for pre-existing trends in the outcome. These analyses were performed using the software package STATA SE, version 16.0 (StataCorp, College Station, Tex.). All tests were two-tailed, and alpha was set at 0.05.

RESULTS
Among the 676 infants under study, 60 patients were excluded based on aforementioned inclusion and exclusion criteria after detailed review in the postimplementation period, leaving 290 preimplementation and 326 postimplementation patients for analysis. The pre- and postimplementation groups were similar in demographic and clinical characteristics including in age, sex, maximum ED temperature, and
prevalence of SBI and IBI (P = 0.08 preintervention versus postintervention time period for IBI) (Table 1). PCT was obtained in 293 patients (89.8% of patients evaluated after revised pathway implementation). With the revised algorithm, the proportion of infants who underwent lumbar puncture decreased from 66.2% to 31.9%, (34.3% absolute reduction, P < 0.001; Fig. 1). ITS analysis revealed a small, not statistically significant preperiod slope, trending downward [odds ratio (95% confidence interval) = 0.96 (0.92, 1.00)] with a significant level change comparing the pre- to postperiods [intercept comparison: odds ratio = 0.29 (0.16, 0.50) implying the postintervention result is not simply due to secular trends] (Fig. 2).

In addition, antibiotic administration decreased by 26.2% (prerevision 62.4% to postrevision 36.2%, P < 0.001; Fig. 1). Among infants discharged from the ED, antibiotic administration decreased by 40.1% (60.8% prerevision to 20.7% postrevision, P = 0.001).

Although unanticipated, the admission rate postrevision decreased by 8.1% (34.8% to 26.7%, P = 0.03) without an increase in 72-hour ED revisits (8.4% prerevision to 10.3% postrevision, P = 0.50) or revisits within 72 hours requiring admission (2.6% prerevision to 6.3% postrevision, P = 0.07). Importantly, postrevision, there have been no adverse outcomes related to missed SBI or IBI cases.

The revised clinical pathway led to a sustained reduction in LP, antibiotic administration, and admission over the 24 months since pathway revision (Fig. 1). After implementation of the revised protocol, 35.4% of infants were classified as high risk; pathway adherence for these infants included lumbar puncture in 74.7% and antibiotic administration in 75.8%, addressing the challenges of implementing pathways in practice, especially when implementation includes obtaining an LP (ie, LP adherence often lower due to LP declined or failed attempt). Among the low-risk infants (64.6% of infants) for which LP and antibiotics were not routinely recommended, 7.2% had a lumbar puncture, and 12.2% received antibiotics.

DISCUSSION

We report the successful implementation of a clinical pathway for febrile infants 1–2 months of age, resulting in a safe and substantial reduction in LPs and antibiotic administration without increasing hospitalizations, ED revisits, or missed IBIs. We believe several key strategies were essential for acceptance and adherence to the protocol: (1) early engagement of key stakeholders to review the published evidence and support the modification of a deeply rooted protocol; (2) the clinical expert team facilitated iterative, open discussions among the physician faculty to review this supporting evidence and offer their input on the revised protocol; (3) an explicit commitment to report outcomes to the staff regularly; and (4) the electronic order set was modified to mirror the pathway revisions and guide utilization of PCT for risk stratification.

For many years, there has been high variability in the ED management of febrile young infants without significant differences in outcomes. Most emergency physicians align with a particular established strategy but deviate frequently concerning testing, antibiotic use, and disposition. The historical argument to routinely perform LPs in 1- to 2-month-old febrile infants was due to the sequelae of delayed or missed diagnoses of bacterial meningitis despite a relatively low (0.2%) rate. Routine performance of CSF testing in this age group has been associated with higher costs, increased hospitalization rates, and significant parental stress without improved outcomes compared to selective CSF testing—leading some to question the need for routine testing in this age group. The poor diagnostic performance of WBC counts for detecting IBI has been a primary factor in the conservative testing and management in this population. For these reasons, as well as an attempt to standardize care, numerous risk stratification algorithms for febrile infants 1–2 months of age have been developed or adapted. Studies suggest PCT is superior for the diagnosis of IBI, and most modern risk stratification algorithms have included PCT to improve performance. The modification of our pathway was prompted by a desire to safely reduce the number of LPs in well-appearing febrile 1- to 2-month-old and the accessibility of rapid PCT results. In an attempt to simplify the protocol and align with other risk stratification systems used nationally, we adjusted the WBC parameters of 5–15,000 wbc/hpf to designate low risk when modifying our pathway. Our pathway differs from many others in relying on rapid PCT testing in addition to CBC and UA and its focus on the 1- to 2-month-old population.

Similarly, the AAP recently published guidelines in this population of 1- to 2-month-old infants with fever to designate a low-risk population who can be managed without routine LP. The AAP guidelines propose a similar combination of UA, PCT when available, and either absolute neutrophil count or CRP to guide the need for LP. Although the cut points vary between the guidelines, they serve a similar intent to reduce unnecessary LPs, antibiotic use, and hospitalizations in this population. Although we have not adopted the AAP guideline at our institution, we support using PCT and other biomarkers to guide

Table 1. Demographic Information for Patients Pre- and Postintervention

|                | Preintervention (n=290) | Postintervention (n=326) |
|----------------|------------------------|-------------------------|
| Median age (IQR), d | 46 (39–54)             | 45 (38–53)              |
| Female sex (N, %)   | 148 (61)               | 152 (46.1)              |
| Median maximum temperature in ED (IQR), °C | 38.0 (37.5–38.5)      | 38.1 (37.6–38.5)        |
| SBI (N, %)         | 26 (9)                 | 38 (11.5)               |
| IBI (N, %)         | 1 (0.34)               | 6 (1.8)                 |
| LP (N, %)          | 102 (66.2)             | 104 (31.9)              |
| Antibiotic administration (N, %) | 181 (62.4)       | 118 (36.2)              |
| Admission (N, %)   | 101 (34.8)             | 87 (26.7)               |

IQR, interquartile range.
**Fig. 1.** P charts demonstrating percentage of well-appearing patients 1-2 months of age with fever. Figure A is percentage of febrile infants who had a lumbar puncture. Figure B is percentage of febrile infants who received antibiotics. X axis is time in months pre- and postrevision with each hash mark representing 1 month.

**Fig. 2.** Interrupted time series analysis for well-appearing 1- to 2-month-old patients with fever undergoing lumbar puncture. Calendar month was used as the unit of time, comparing 18 months preimplementation to 24 months postimplementation.
the selected performance of LPs in the 1- to 2-month-old febrile infant.

In a recent effort, Widmer et al33 published their experience with the addition of PCT to their algorithm for 1- to 2-month-old febrile infants. They noted rapid adoption of PCT testing by clinicians. In contrast to our experience, however, they could not demonstrate any reduction in lumbar puncture, hospitalizations, or antibiotic use despite rapid adoption of PCT testing.33 The authors noted their study site already had a relatively low rate of lumbar puncture in the preimplementation period, and although low-risk infants had fewer LPs, the overall proportion of infants undergoing LPs did not change as more infants were classified as high-risk. In contrast, we demonstrated a decrease in LPs even with a more conservative PCT cut point.

In addition to the safe reduction of LPs and antibiotic use, we observed a decrease in admissions with the revised approach secondary to an increase in the proportion of low-risk infants and potentially fewer unplanned admissions secondary to traumatic or unsuccessful LPs. Our study has several limitations. It was conducted at a single academic pediatric ED with a decade-long familiarity and confidence with a process for the development and implementation of care pathways; this experience and culture may have accelerated the reassertion and acceptance of a change effort. Additionally, before the pathway revision, the physician group was primed by growing evidence to introduce a less invasive approach and greater antibiotic stewardship. The WBC was adjusted with the pathway revision to mirror the widely used WBC parameters for low risk (5–15,000 wbc/hpf)—the separate impact of this change was not separately analyzed. For dissemination across systems of care, there must be an acknowledgement that a basic premise for diagnostic strategies in this age group is the determination of well versus ill-appearance, which may depend on the pediatric expertise of the provider. In many regards, more discerning objective diagnostic tests are needed in settings with less experienced providers judging the illness severity of young infants. Although we did not observe any adverse outcomes related to missed SBIs or IBIs, our analysis was not designed or powered to detect a difference in these outcomes. There is the possibility that a patient returned to another facility for care, and was found to have SBI/IBI or required admission at that visit, which we would not have captured in our data. As part of the design of the QI intervention, we were able to track and complete an in-depth chart review conducted on the postrevision population resulting in the exclusion of 60 patients based on the aforementioned inclusion/exclusion criteria. The preintervention population was not designed in the same way thus this level of detailed review was not possible. Although we only performed detailed medical record reviews for exclusion criteria in the postintervention period, both populations had similar rates of IBI and SBI allowing fair comparison.

CONCLUDING SUMMARY

The addition of procalcitonin to our febrile infant pathway allowed the practice to change from routine LP to selective LP of high-risk 1- to 2-month-old infants. It resulted in a reduction in LPs, antibiotic administration, and hospitalization without increasing ED revisits or delayed diagnosis of serious infections.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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