Association between Clinical Outcomes and Hospital Guidelines for Cerebrospinal Fluid Testing in Febrile Infants Aged 29-56 Days

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Objective To describe the association between clinical outcomes and clinical practice guidelines (CPGs) recommending universal cerebrospinal fluid (CSF) testing in the emergency department for febrile infants aged 29-56 days.

Study design Using 2007-2013 administrative data from 32 US children's hospitals, we performed a difference-in-differences analysis comparing 7 hospitals with CPGs recommending universal CSF testing for older febrile infants aged 29-56 days (CPG group) with 25 hospitals without such CPGs (control group). We compared differences in clinical outcomes between older febrile infants with the corresponding differences among younger febrile infants aged 7-28 days. The primary outcome was the occurrence of an adverse event, defined as a delayed diagnosis of bacterial meningitis, mechanical ventilation, placement of a central venous catheter, extracorporeal membrane oxygenation, or in-hospital mortality. Analyses were adjusted for race/ethnicity, sex, median annual household income by zip code, primary insurance source, discharge season, and discharge year.

Results The proportion of older febrile infants undergoing CSF testing was higher ($P < .001$) in the CPG group (64.8%) than the control group (47.8%). CPGs recommending universal CSF testing for older febrile infants were not associated with significant differences in adverse events (difference-in-differences: +0.31 percentage points, 95% CI −0.18 to 0.85; $P = .22$).

Conclusions Hospital CPGs recommending universal CSF testing for febrile infants aged 29-56 days were not associated with significant differences in clinical outcomes. *(J Pediatr 2015;167:1340-6)*.

According to several clinical practice guidelines (CPGs) based on expert opinion, infants aged 0 through 28 days who are brought to the emergency department (ED) for evaluation of fever should undergo urine, blood, and cerebrospinal fluid (CSF) testing to facilitate prompt diagnosis of urinary tract infections, bacteremia/septicemia, and meningitis.[1-3] However, the management of older febrile infants aged 29-56 days in the ED has been debated in the literature for decades.[4-10] Although there is general agreement that these infants should undergo urine and blood testing, no such consensus exists for CSF testing.[1,2] Universal CSF testing for older febrile infants theoretically could prevent missed or delayed diagnoses of bacterial meningitis, leading to better clinical outcomes. On the other hand, if providers can accurately identify which older febrile infants need CSF testing after considering clinical presentation and results from other laboratory testing, universal CSF testing could lead to unnecessary stress for families, a higher risk of procedural complications, and hospitalizations of otherwise low-risk infants following traumatic lumbar punctures.[11-13]

Because of the lack of evidence supporting national guidelines on the management of older febrile infants, many US children's hospitals have implemented institution-specific CPGs to standardize clinical practice. Based on well-known but differing criteria to identify febrile infants at low-risk for serious bacterial infections, some US children's hospitals have adopted CPGs recommending universal CSF testing in the ED for febrile infants aged 29-56 days, and others have adopted CPGs recommending selective CSF testing after considering other factors.[14] To date, no study has compared the clinical benefits of these approaches. Although randomization would be ideal for causal inference, such an approach would be infeasible because of the practical and ethical difficulties of enrolling a large number of infants to potentially undergo an invasive procedure like lumbar puncture.

CPG	Clinical practice guideline
CSF	Cerebrospinal fluid
ED	Emergency department
ICD-9	*International Classification of Diseases, Ninth Revision*
PHIS	Pediatric Health Information System

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The objective of this study was to evaluate the association between clinical outcomes and hospital CPGs recommending universal CSF testing in the ED for older febrile infants aged 29-56 days. We used a strong quasi-experimental approach that exploited the variation in CSF testing recommendations among CPGs for older febrile infants at US children's hospitals. Specifically, we examined hospitals with and without CPGs recommending universal CSF testing and compared the differences in clinical outcomes between these hospital groups among older febrile infants with the corresponding differences among younger febrile infants.

Methods

We compared 7 hospitals with CPGs recommending universal CSF testing for older febrile infants in the ED (CPG group) with 25 hospitals without such CPGs (control group). In the control group, 8 hospitals had CPGs recommending selective CSF testing for older febrile infants meeting specific criteria, and 17 did not have CPGs guiding management of older febrile infants (de facto selective CSF testing). We included the 17 hospitals without CPGs based on a previous study showing no changes in rates of CSF testing for febrile infants after implementation of a care process model that recommended selective CSF testing.[15] This finding suggests that there is a similar CSF testing approach among hospitals without CPGs for older febrile infants and hospitals with CPGs explicitly recommending a selective CSF testing approach.

We used a difference-in-differences analysis to estimate differences in clinical outcomes between the CPG and control groups among older febrile infants that were not predicted by the corresponding differences among younger febrile infants. An important advantage of this approach is that it adjusted for differences in patient characteristics between the CPG and control groups that did not vary with age. For example, even if infants' severity of illness at presentation differed systematically between the CPG and control groups, the effect of this confounder would be removed by our comparisons of older vs younger infants, as long as the difference in illness severity was the same in both age groups.

Data for this study were obtained from the 2007-2013 Pediatric Health Information System (PHIS), an administrative database containing encounter-level information from 45 nonprofit, tertiary US children's hospitals affiliated with the Children's Hospital Association (Overland Park, Kansas). Participating hospitals provide discharge data for inpatient, ED, and observation unit visits, including demographic information, *International Classification of Diseases, Ninth Revision* (ICD-9) diagnosis codes, ICD-9 procedure codes, and charges for clinical services.[16] Because the PHIS contains de-identified data, the Institutional Review Board of Boston Children's Hospital deemed this study exempt from review.

We defined older febrile infants as ages 29-56 days and younger febrile infants as ages 7-28 days. We excluded infants ages 0-6 days because of the unique clinical circumstances during the immediate perinatal period.[5] Following other studies, we excluded 7 of the 45 PHIS hospitals with missing ED visit data and 1 hospital with ED and inpatient records that could not be linked.[17] To assign the remaining hospitals to the CPG and control groups, we determined the presence, content, and implementation year of CPGs for older febrile infants based on a previously administered survey of ED medical directors at PHIS hospitals (89% response rate).[14] Of the 37 hospitals in the survey, we excluded 4 because of survey nonresponse and 1 because of inaccurate discharge diagnosis information for ED visits, leaving 32 hospitals in the sample.

For hospitals implementing CPGs, we excluded data from years before the CPGs were implemented. We further excluded records with discharge diagnosis codes indicating a complex chronic condition[18] (eg, congenital heart disease) because febrile infants with these conditions often undergo nonstandard evaluations in the ED.[17] After these exclusions, there were 415 280 potentially eligible records for infants aged 7-56 days who were evaluated in the ED of the 32 hospitals.

Following previous research on the management of febrile infants, we restricted the sample to records with 1 of the following 4 fever-related codes in an admission or discharge diagnosis field: 780.6 (fever and other physiologic disturbances of temperature regulation), 780.60 (fever, unspecified), 780.61 (fever presenting with conditions classified elsewhere), and 778.4 (other disturbances of temperature regulation of infant).[3,17] To capture febrile infants with records containing infection-related codes but not fever-related codes, we also included records with an infection-related admission or discharge diagnosis code that predicted a complete sepsis evaluation (urine, blood, and CSF testing) for at least 50% of infants aged 7-28 days (**Appendices 2** and **3**; available at www.jpeds.com). This strategy was based on the assumption that complete sepsis evaluations are good proxies for fevers among infants aged 7-28 days. In support of this assumption, previous research indicates that most febrile infants ≤28 days old undergo these evaluations in PHIS hospital EDs.[3] Complete sepsis evaluations are less likely to predict fevers among febrile infants age 29-56 days, who less frequently undergo these evaluations.[17] As such, we did not include these infants when screening diagnosis codes.

In sensitivity analyses, we used cut-offs of 25% or 75% instead of 50%, restricted the sample to records with any of the 4 fever-related diagnosis codes in an admission or discharge diagnosis field, and excluded infants who underwent no urine, blood, or CSF testing (because these infants may not have been truly febrile).