

Length of Stay and Complications Associated With Febrile Infants <90 Days of Age Hospitalized in the United States, 2000–2012

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OBJECTIVES: It is not known how changes in the epidemiology of serious bacterial infection (SBI) and greater availability of rapid viral diagnostic tests have impacted the hospital length of stay (LOS) and associated complications among young infants with suspected SBI.

METHODS: We used national administrative data from the Healthcare Cost and Utilization Project Kids' Inpatient Database and other state-specific data to identify febrile infants <90 days of age hospitalized in 2000, 2003, 2006, 2009, and 2012. We used multivariate analysis to determine LOS, risk factors for prolonged LOS, and complications of care among infants with isolated fever or viral respiratory disease, without concomitant serious infection.

RESULTS: We identified 44 875 infants. LOS for each clinical group did not change over time in a clinically significant way. Mean LOS was ≤ 2 days for approximately two-thirds of all infants and ≥ 4 days for 11% in each clinical group. Factors associated with longer LOS included age <31 days, critical clinical status, concomitant chronic disease, and the presence of complications ($P < .05$). We identified 289 (0.8%) infants with 351 complications of care, 18 (6%) of whom had >1. These infants had longer LOS ($P < .001$), and those with chronic disease and older age were at increased risk ($P < .01$).

CONCLUSIONS: Despite the changing epidemiology of SBI and increased availability of viral diagnostic testing, we did not detect a clinically significant change in LOS for febrile infants with suspected SBI. Complications associated with hospitalization of these infants was associated with increased LOS.

ABSTRACT

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Defining the appropriate management of febrile infants <90 days of age has been a continuing topic of discussion in the literature since the 1970s.^{1–5} Approximately 7% to 11% of such infants will have a serious bacterial infection (SBI) (typically defined as urinary tract infection [UTI] or pyelonephritis or bacteremia or meningitis), and many of whom are less likely than older infants to exhibit classic symptoms and signs.¹ The generally accepted management approach, particularly for infants <30 to 45 days of age, is a full diagnostic evaluation followed by hospital admission for receipt of empirical antibiotic therapy and clinical monitoring while awaiting the final bacterial culture results.⁶ This approach reflects the reality that no definitive standard or algorithm exists that reliably excludes SBI in the ambulatory setting; management therefore may err on the side of admission.² Importantly, authors of small single-center studies have reported that hospitalization itself carries risk to the infant, and prolonged or unnecessary hospitalization necessarily increases that risk.^{7,8}

The proportion of SBI due to bacteremia or meningitis in young febrile infants has decreased substantially (relative to UTI)^{9,10} since the early 2000s, and the use of more sophisticated and rapid viral diagnostic testing has become commonplace.^{11–14} These realities might be expected to enable earlier hospital discharge for a potentially large subset of these hospitalized infants. There are, however, no national data that have been used to address this question. Our objective was to evaluate the hospital length of stay (LOS) and associated risk factors among young febrile infants hospitalized from 2000 to 2012.

METHODS

Setting and Study Population

We conducted a retrospective study of febrile infants from 2000 to 2012 using deidentified data for inpatient visits. The work was deemed “not human research” by the Institutional Review Board of the Los Angeles Biomedical Research Institute at the Harbor–University of California, Los Angeles Medical Center. We used inpatient data from the Kids’ Inpatient Database (KID), a publicly available resource administered by the

Healthcare Cost and Utilization Project (HCUP). The KID is the largest nationally representative sample of pediatric discharges (up to 21 years of age) from US community, nonrehabilitation hospitals and contains data on pediatric health care use and outcomes.¹⁵ The KID data subset is extracted from the HCUP State Inpatient Database (SID) discharge data set, which is a state-specific inpatient database that includes all inpatient discharges from participating states.¹⁶ KID data have been available every 3 years since 1997 and include ~3 000 000 records per year (80% pediatric discharges, 10% uncomplicated births). Weighted, it estimates ~7 500 000 hospitalizations per year. We obtained 2000, 2003, 2006, and 2009 KID data from HCUP. In 2012, the KID data no longer included variables to select patients by age in days or months. Therefore, we created a 2012 data set for comparison with 2000–2009 KID data. This included 2012 data from Arizona, Kentucky, Maryland, Michigan, New Jersey, New York, North Carolina, and Washington from the 2012 HCUP SID data. In addition, inpatient hospital discharge 2012 data from California, Illinois, Pennsylvania, and Texas (all unavailable in the 2012 SID) were obtained directly from the respective state agencies with approval from their associated institutional review boards; these are also deidentified data normally sent to the Agency for Healthcare Research and Quality for inclusion in HCUP data. We thereafter used data from 2000 to 2012 for this analysis. States in the 2000, 2003, 2006, and 2009 KID data sets that could not be matched to 2012 inpatient data were omitted during analyses such that results would be more directly comparable across the entire study period. Each record in the inpatient data set pertains to a single visit. The KID structure does not allow for the identification of repeat visits from the same individual.

Patients were divided into age categories of 1 to 30, 31 to 60, and 61 to 89 days of age. In this age group, we believe that infants with critical and/or chronic illness may confound the management decisions among infants with fever^{17,18}; therefore, we created a critical and a chronic illness variable to identify such infants. The former included

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnoses that we believed would reflect greater morbidity and/or mortality, modeled after the Pediatric Risk of Mortality score.^{18,19} We created 2 clinical groups on the basis of ICD-9-CM codes. The fever-only group included infants with only a fever diagnosis and no other associated infection. Infants in the viral respiratory group had a diagnosis of fever and viral respiratory infection without a serious infection (SI). We also identified and excluded infants in an SI group (all of whom had a diagnosis of fever and SI). We defined SI as bacterial meningitis, bacteremia, UTI, pyelonephritis, sepsis, herpes simplex infection, bacterial pneumonia, abscesses, and orthopedic infections. ICD-9-CM codes for the fever-only, viral respiratory, and SI groups, as well as for critical illness and chronic conditions are noted in Supplemental Tables 5 and 6; some codes were explicitly validated in our selected age group.^{20–23} LOS was defined in days (beginning at midnight), and we excluded hospital births, 0 days of age, and transfers to and from other facilities because no information was available from the other facility.

Outcome Measures and Statistical Analyses

The primary outcome measure for inpatients was hospital LOS for each clinical group. We performed descriptive statistics on LOS, disposition after hospitalization, and patient demographic characteristics. To determine how change over time predicts LOS in an adjusted model, we conducted a multivariable negative binomial regression. This model was used in preference to multivariable Poisson regression to lessen the impact of overdispersion that existed in the data. Complications were assessed via multivariable logistic regression. Using methodology provided by the HCUP, we applied nationally representative weights to the KID; inpatient 2012 data require no weights because the SIDs include nearly all community inpatient stays within each state. The final sample size for the 2012 data was comparable to the weighted annual 2000–2009 KID data. For the final models, analysis of the KID for 2000–2009 was

restricted to only those states available in 2012. Lastly, we identified complications of medical care related to the encounter using ICD-9-CM and E-codes in each data set on the basis of, in part, observed complications in earlier work in this age group^{7,8} (Supplemental Tables 5 and 6). All statistical analyses were conducted using Stata Statistical Software, release 14.2 (Stata Corp, College Station, TX).

RESULTS

Among 32 348 483 total weighted pediatric hospital discharges and after exclusions and application of the target ICD-9-CM codes, the study population included 44 875 infants (Fig 1). The demographic characteristics of the study population are noted in Table 1. Ninety-nine percent had a routine discharge, whereas 1% were transferred, received home health after discharge, or left against medical advice; 6 infants died. The distribution of clinical group by age was similar, and 74% of all infants were in the fever-only group. The absolute number of admissions by year did not appreciably change over the study period (data not shown).

Overall mean hospital LOS from 2000 to 2012 based on estimates from bivariate regression of LOS predicted by year is noted in Fig 2. Among all identified infants, LOS

ranged from an average of 2.61 days (95% confidence interval [CI] 2.55–2.67) in 2000 to 2.50 days (95% CI 2.47–2.55; $P = .02$) in 2012. For patients in the fever-only group, LOS ranged from 2.59 days (95% CI 2.53–2.66) to 2.51 days (95% CI 2.46–2.56; $P > .05$), and in the viral respiratory group, LOS ranged from 2.66 days (95% CI 2.56–2.76) to 2.50 days (95% CI 2.44–2.56; $P > .05$). In both clinical groups, overall LOS among infants ≥ 30 days of age was 10% shorter compared with the younger infant cohort ($P < .01$).

In the multivariate analysis, factors associated with a statistically significant (and at least $>10\%$) longer LOS included the youngest age group (1–30 days), concomitant critical status, or preexisting chronic illness (Table 2). Approximately 63% to 64% of infants in the fever-only and viral respiratory-only groups had hospital stays that were 2 days or fewer, respectively. Also, 11% in each of the fever-only and viral respiratory-only groups had an LOS of ≥ 4 days.

Other nonclinical characteristics associated with variability in LOS included multi-racial people and/or people of color (higher LOS), private insurance (shorter LOS), and regional location in the United States (Table 2). The maximal variation for any of

the nonclinical factors above, compared with the reference group, was not $>7\%$. We also assessed the potential independent effect of other selected risk factors not available (only) from our 2012 data. Among 36 289 infants admitted from 2000 to 2009, those in teaching hospitals had a 5% increased LOS than those in nonteaching hospitals ($P < .01$), infants admitted on Saturday or Sunday had a 4% shorter LOS ($P < .01$) than those not, and no significant difference between rural and urban hospital location was observed (the risk ratios for the variables in Table 2 did not change appreciably in this secondary analysis).

TABLE 1 Demographic Characteristics of the Inpatient Study Population, 2000–2012

Demographic Category	Inpatient 2000–2012, ^a n (%)
Age group, d	
1–30	19 216 (43.4)
31–60	19 058 (43.0)
61–89	6 013 (13.6)
Critical clinical status	7 056 (15.7)
Chronic disease	2 905 (6.5)
Complications	289 (0.8)
Sex	
Boy	24 385 (54.3)
Girl	20 487 (45.7)
Race	
White	14 401 (32.1)
African American	4 828 (10.8)
Hispanic	12 874 (28.7)
Other	4 723 (10.5)
Missing	8 049 (17.9)
Payer type	
Commercial or private	15 751 (35.1)
Medicaid	26 406 (58.9)
Medicare	21 (0.1)
Other	934 (2.1)
Self-pay	1 732 (3.9)
Hospital region	
Northeast	12 613 (28.1)
Midwest	5 513 (12.3)
South	9 703 (21.6)
West	17 045 (38.0)

Data were weighted as described in the Methods section.

^a Some categories may have missing values.

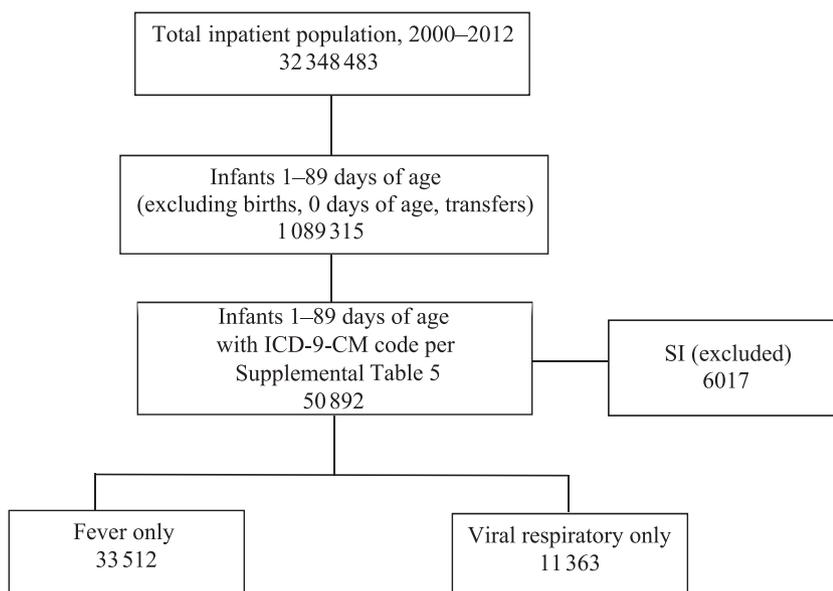


FIGURE 1 Patient cohort identification enrollment flow diagram.

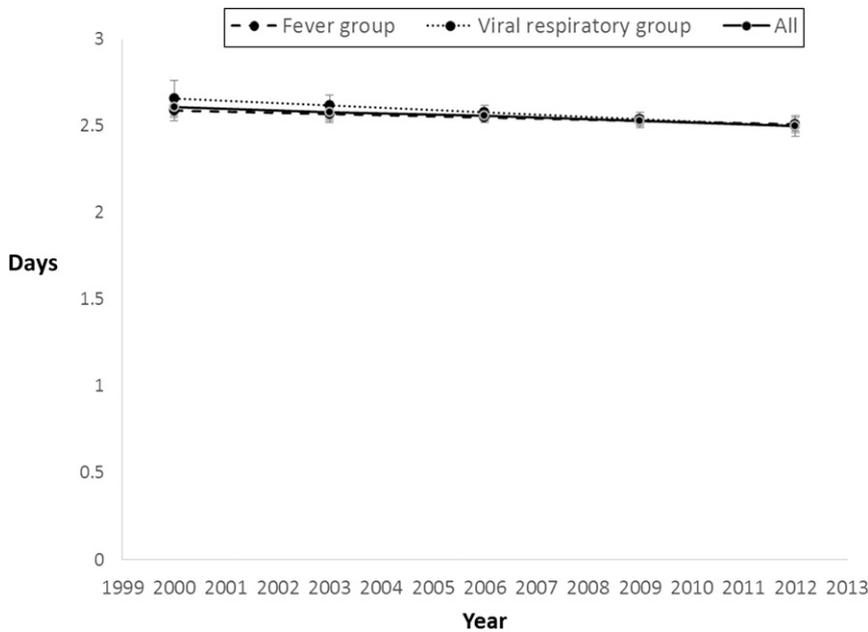


FIGURE 2 Hospital LOS, 2000–2012.

We identified 351 complication events among 289 (0.82%) patients during the entire study period. Among those with a specified cause, 223 of 289 (77%) complications were due to medications, and 35 (12%) were related to diagnostic and therapeutic interventions (Table 3). A total of 18 of 289 patients (6%) had ≥ 2 complications during the identified admission. The mean LOS for those with complications was 3.7 vs 2.5 days for those without complications ($P < .001$). In multivariate analysis, infants with chronic illness were nearly twice as likely as those without chronic illness to have a complication of hospitalization ($P < .01$). As well, infants 60 to 89 days of age were >3 times as likely as those 1 to 30 days of age to have a complication of care ($P < .01$) (Table 4).

DISCUSSION

Herein, we provide the first description of long-term national trends regarding certain characteristics of hospitalization for young febrile infants <90 days of age with suspected SBI. In this large US population including both community- and academic-based institutions, we found no clinically relevant change in the hospital LOS over the study period. Our hypothesis was that LOS in

these infants might slowly decrease over time because of clinicians' acknowledgment of ongoing changes in SBI epidemiology and increasing use of rapid viral diagnostic tests. In particular, the former reflects the experience that identifying a specific bacterial pathogen in blood or cerebrospinal fluid is an increasingly uncommon event.¹⁴ Since 2000, the decline in the incidence of SBI due to previous group B *Streptococcus*, *Listeria monocytogenes*, and pneumococcus has accelerated,^{11–13} and recent data have been used to note the value of rapid viral testing toward less overall diagnostic testing and therapy in those with suspected SBI.^{2,10,24,25} With our data, we suggest that clinicians' acceptance or awareness of such information is incomplete and/or is impacted by a lack of availability of viral diagnostics and/or perhaps some other factors that may encourage more conservative practice such as personal experience, practice-group dynamics, and other impacts of peer-to-peer practice or medicolegal concerns.²⁶

Previous studies of the hospitalization of young febrile infants have been focused on the likelihood of admission,^{27,28} antimicrobial use,²⁹ and outcomes,³⁰ with relatively little or no attention to LOS and its associated

TABLE 2 Multivariate Negative Binomial Regression Analysis of Hospital LOS, 2000–2012

Variable	Risk Ratio (95% CI)
Diagnosis group	
Fever only	Reference
Viral respiratory infection	1.01 (0.99–1.02)
Age group, d	
1–30	Reference
31–60	0.92 (0.90–0.94)**
61–89	0.88 (0.85–0.91)**
Year	0.99 (0.99–0.99)*
Critical clinical status	1.26 (1.22–1.30)**
Chronic disease	1.63 (1.54–1.74)**
Complications	1.45 (1.15–1.83)**
Girls	1.00 (0.98–1.02)
Insurance	
Public	Reference
Private	0.95 (0.93–0.98)*
No insurance	0.97 (0.93–1.01)
Other	1.03 (0.96–1.10)
Race	
White	Reference
African American	1.07 (1.03–1.12)**
Hispanic	1.03 (1.01–1.06)**
Other	1.05 (1.01–1.10)*
Missing	1.02 (0.99–1.05)
Hospital region	
West	Reference
Northeast	1.06 (1.04–1.09)**
Midwest	0.97 (0.94–0.99)*
South	0.99 (0.96–1.02)

Some categories may have missing values.

** $P < .01$; * $P < .05$.

predictors. We found certain patient characteristics to be associated with longer LOS including race and/or ethnicity, geographic location, and insurance type. It is clear, however, that LOS will also depend generally on specific clinical issues and nonmedical issues (eg, family dynamics), variables for which we did not have data. Regardless of the age group or condition for which LOS is studied, it is important to consider correlated outcomes at the practitioner, hospital, or other level.³¹ Nonetheless, relatively few empirical data exist regarding predictors of LOS for young infants admitted for nonsurgical conditions. Others have reported that prematurity and

TABLE 3 Complications of Care Identified Among Young Infants Who Are Febrile and Hospitalized, 2000–2012

	Frequency (%)
Complications due to medications	
Antibiotics	127 (36)
Dermatitis due to medication	59 (17)
Other ^a	37 (11)
Complications due to procedures	
IV catheter	17 (5)
Other ^b	18 (5)
Complications due to unspecified procedures and/or medical care	93 (27)
Total	351^c

IV, intravenous.

^a Each includes <10 observations: allergic reaction to medication, skin agent, antipyretics, cold and allergy medication, complication due to infusion or transfusion, cytopenia due to medication, cardiovascular medications, IV fluids, pain medications, and respiratory medications.

^b Each included <10 observations: lumbar puncture, catheter, and injury due to procedure.

^c A total of 351 complications were identified among 289 patients.

concomitant comorbidities were associated with prolonged LOS for infants <6 months of age with UTI,³² and the specific infecting pathogen was associated with an increased LOS in children <2 years of age with bronchiolitis.³³ We are not aware of any such study of infants and LOS, for any medical condition, performed on a large longitudinal data set such as we report here.

We found that hospital LOS did not change for the fever group or the viral respiratory group. Most infants in the fever group had an LOS of ≤ 2 days, generally consistent with the “48 hours rule out sepsis” workup, but nearly one-third had an LOS ≥ 3 days, and 8% had an LOS for ≥ 4 days, which is well beyond when >99% of blood culture results become positive.³⁴ It is unclear why those infants with uncomplicated fever without an associated infection diagnosis had prolonged LOS. It may be that the patients had diagnoses or psychosocial family issues that were not captured with ICD-9-CM codes.

It is also possible that variations in coding practice at the hospital level classified a true 48-hour admission as 3 days.

We detected >350 complications of care in our cohort, and among those with a specified cause, nearly 80% were related to receipt of medication. We believe this to be a significant underestimate insofar as ours is a retrospective cohort study using administrative data, and systematic underdocumentation of adverse event-related ICD-9-CM codes is well described.^{35,36} Importantly, we found that infants with complications had a longer LOS. Authors of 2 previous small single-center studies of hospitalized young infants noted 20% to 29% of subjects developed a complication, and in 1 study, 60% were preventable.^{7,8} Moreover, a survey of parents of febrile infants hospitalized for sepsis evaluation revealed negative psychosocial consequences, including severe stress, disruption of breastfeeding, and continued perceptions that the child was ill despite no SBI found.³⁷ Infants hospitalized unnecessarily to “rule out sepsis” or who remain in the hospital for prolonged periods clearly present risks to the child and family of potentially severe complications and may create an economic burden as well.

We found that the likelihood of a complication of care increased with age, independent of the presence of an SI and concomitant chronic comorbidity. There are no other published data on this topic. Why this relationship is present is unclear, but for example, we speculate that perhaps older infants are less likely to be swaddled and therefore move their extremities more freely resulting in intravenous catheter dislodgement. As well, they may be more likely to receive empirical vancomycin because the likelihood of potential penicillin-resistant pneumococcal disease is greater in infants 60 to 90 days compared with those <60 days of age.³⁸ As well, these infants are therefore susceptible to potential nephrotoxicity associated with vancomycin and/or untoward events associated with monitoring drug levels. We did not have access to data to explicitly explore these hypotheses.

The initial decision to admit a febrile infant <90 days of age can be difficult and must

TABLE 4 Multivariate Logistic Regression Analysis of Complications, 2000–2012

Variable**	Odds Ratio (95% CI)
Diagnosis group	
Fever only	Reference
Viral respiratory infection	1.06 (0.77–1.46)
Age group, d	
1–30	Reference
31–60	1.37 (0.93–1.89)*
61–89	3.46 (2.39–5.02)**
Year	0.97 (0.92–1.02)
Critical clinical status	0.82 (0.55–1.21)
Chronic disease	1.89 (1.24–2.89)**
Girls	0.78 (0.58–1.04)
Insurance	
Public	Reference
Private	1.12 (0.81–1.54)
No insurance	1.12 (0.54–2.33)
Other	1.37 (0.52–3.65)
Race	
White	Reference
African American	1.36 (0.86–2.17)
Hispanic	0.96 (0.64–1.45)
Other	1.38 (0.88–2.18)
Missing	0.68 (0.41–1.15)
Hospital region	
West	Reference
Northeast	0.89 (0.59–1.35)
Midwest	1.06 (0.65–1.73)
South	1.25 (0.83–1.88)

Some categories may have missing values.

** $P < .01$; * $P < .05$.

balance the risks of missing an SBI with unnecessary admission and overtreatment. A report by the Agency for Healthcare Research and Quality did not provide conclusive guidance,² and no consensus exists on the appropriate management in the outpatient setting.^{6,39–41} Much data have been used to contribute to a summary estimate of 7% to 11% of febrile infants <90 days predicted to have an SBI.¹ Researchers of recent data from the Northern California Kaiser Permanente system note that among those with SBI, ~92% have UTI, 6% have bacteremia, and <0.5% have meningitis.⁹ Authors of previous work have provided the following useful information to guide clinicians toward

minimizing hospitalization and LOS: (1) febrile infants with a confirmed viral respiratory infection have a much lower likelihood of concomitant SBI,^{25,42,43} (2) evidence-based protocols minimize LOS,²⁴ and (3) in the outpatient private-practice setting, individualized clinical judgment compared with strict adherence to guidelines lessens the likelihood of admission without worsening outcomes.³⁰

We acknowledge the methodological limitations of ICD-9-CM code data; their robustness is also variable across pediatric age group and specific diagnoses.^{20,22,44} Most germane to our work is that of Aronson et al²¹, in which variability in the accuracy of such codes for “fever” was noted among hospitalized young infants by ascertainment method and by institution. Specifically, KID LOS data are not available in hours nor does KID allow for the consideration of “observation stays” of <24 hours. In addition, we could not determine provider reasoning or other qualitative information that might reveal discharge decision-making and its potential impact on LOS. We do not have data beyond 2012 because certain state data, compared with our study period, are not included in the 2015 KID and/or SID data release (KID is made available only every 3 years). Regardless, given the fairly constant data trends we observed over our long study period, we believe the likelihood of a meaningful change (in 2015) is low especially given that no new practice guideline has been published in the interim. Our data set does, however, include the largest study population on the topic, includes diverse hospital types from a well-dispersed geography, and a weighting method allowing for greater generalizability. We also identified predictors for the likelihood of prolonged hospital LOS, which has not been well described in this age group. Furthermore, our 13-year study period enabled an understanding of the potential impact of clinical factors germane to the management decision-making for these febrile infants.

We have shown that hospital LOS for young, otherwise uncomplicated febrile infants did not substantively change from 2000 to 2012,

despite decreasing risk for bacteremia and meningitis and maturation and acceptance of viral diagnostic testing. As well, important harms were identified. With these observations, we support the presumption that clinical integration of contemporaneous SBI epidemiology and more aggressive viral testing for inpatients have not been maximized in the inpatient setting. Targeted efforts used to raise awareness and implications of these issues in the care of inpatients, in concert with evidence-based guidelines for the approach to such infants in the emergency department setting may minimize LOS and complications associated with prolonged hospitalization. More data on the rationale behind the decision to admit and later discharge young febrile infants, prospective data collection on the incidence of complications related to procedures performed in the hospital, and the associated economic implications to hospital systems and families would be informative.

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