### Title

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# Practice Variation in the Evaluation and Disposition of Febrile Infants ≤ 60 days of age

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## Abstract

**BACKGROUND:** Febrile infants commonly present to emergency departments (EDs) for evaluation.

**OBJECTIVE:** We describe the variation in diagnostic testing and hospitalization of febrile infants ≤ 60 days of age presenting to the EDs in the Pediatric Emergency Care Applied Research Network (PECARN).

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Conflict of Interest Disclosures:

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**METHODS:** We enrolled a convenience sample of non-critically-ill appearing febrile infants (temperatures ≥ 38.0 C/100.4 F) ≤ 60 days of age who were being evaluated with blood cultures in 26 PECARN EDs from 2008–2013. Patients were divided into younger (0–28 days) and older (29–60 days) cohorts for analysis. We evaluated diagnostic testing and hospitalization rates by infant age group using chi-square tests and by site using ANOVA.

**RESULTS:** 4778 patients were eligible for analysis, of whom 1517 (32%) were 0–28 days of age. Rates of lumbar puncture (LP) and hospitalization were high (>90%) among infants ≤ 28 days of age, with chest radiography (CXR) (35.5%) and viral testing (66.2%) less commonly obtained. Among infants 29–60 days old, LP (69.5%) and hospitalization (64.4%) rates were lower and declined with increasing age, with CXR (36.5%) use unchanged and viral testing (52.7%) slightly decreased. There was substantial variation between sites in the older cohort of infants, with LP and hospitalization rates ranging from 40–90%.

**CONCLUSIONS:** The evaluation and disposition of febrile infants 60 days of age or less is highly variable, particularly among infants 29–60 days of age. This variation demonstrates an opportunity to modify diagnostic and management strategies based on current epidemiology to safely decrease invasive testing and hospitalization.

### Keywords

Fever; Infant; Infectious Disease; Practice Variation; Guidelines

## Introduction:

Febrile infants ≤ 60 days of age commonly present to the emergency department (ED) for evaluation and management.(1) Recent studies have confirmed that 5–10% of febrile infants in this age group presenting to the ED will have serious bacterial infections (SBIs; defined here as urinary tract infections, bacterial meningitis or bacteremia) as the cause of their fever, with fewer than 2% having bacteremia. (2, 3) Due to the absence of any single or combination of clinical variables and/or laboratory tests that can detect presence of SBI with high degrees of sensitivity and specificity, several guidelines have been developed over the years to risk-stratify young febrile infants to determine who might be at low enough risk to safely forego invasive testing, empirical antibiotics and/or hospitalization.(4–7) These guidelines recommend obtaining screening tests including urinalysis for UTI, complete blood counts for bacteremia and cerebrospinal fluid analysis for bacterial meningitis along with respective cultures for definitive diagnosis of SBI. Most guidelines recommend a conservative approach i.e. complete evaluation for SBI along with empiric antibiotic use and hospitalization for febrile infants 28 days of age and younger. Other diagnostic modalities, including chest radiography and viral testing might also be incorporated into the fever evaluation. (8)

Despite the existence of these guidelines, there is substantial variation and lack of adherence to these traditional recommendations in the evaluation of these young febrile infants, due to the changing epidemiology of SBI in this population and the incorporation of newer biomarkers.(9–11) A recent retrospective analysis of Kaiser Permanente data demonstrated selective management strategies, noting nearly a quarter of infants between 7–28 days of age

presenting for fevers having no cultures obtained, noting the provider not believing the reported thermometer reading in most of these cases.(12) Although prior studies have revealed practice variation, many of those studies suffer from methodological issues as they were either retrospective in nature and/or have used varying study definitions for inclusion and SBI. Prospective, nationally representative multi-center data on the diagnostic evaluation and disposition of febrile infants ≤ 60 days of age in US EDs have not been reported.

We conducted a planned secondary analysis of a large prospective observational study of febrile infants ≤ 60 days of age who were evaluated for SBIs in the EDs of the Pediatric Emergency Care Applied Research Network (PECARN) to describe practice variation. (13) Our aim was to identify patient and hospital level variation in the evaluation of febrile infants with regards to performance of lumbar punctures (LPs), chest radiographs, viral testing, urine testing and patient disposition from the ED.

## Methods:

In the parent study, we enrolled a prospective convenience cohort of febrile infants ≤ 60 days of age who were evaluated for SBIs at 26 children's hospitals participating in PECARN from 2008 to 2013.(13) Only infants who had blood cultures obtained and whose parents consented for their child to have additional blood drawn for host response biomarkers (RNA biosignature by microarray analysis) were enrolled. (14) Enrollment included patient history and a physical examination of each patient including an assessment of clinical appearance using the Yale Observation Scale score (YOS).(15) We abstracted laboratory data and radiographic reports, if performed. Further diagnostic testing as well as patient disposition was at the discretion of the treating provider. Tests for viral infections ranged from individual seasonal viruses (such as respiratory syncytial virus or influenza) to comprehensive viral panels. (16) For our analysis, patients were considered to have had an LP performed if it was attempted, whether or not cerebrospinal fluid was actually obtained. Urine was considered to be obtained if either urinalysis or urine culture was obtained. We performed telephone follow-up for patients who were discharged without an LP to identify infants with missed meningitis.

### Selection of Participants

Infants ≤ 60 days of age with documented fevers (defined as rectal temperatures ≥38° C/ 100.4 F) were eligible. We excluded critically ill infants (i.e. those requiring emergent interventions such as endotracheal intubation, the use of vasoactive medications or cardiopulmonary resuscitation), infants who were born prematurely (≤36 weeks gestation), and those with congenital malformations or focal infections. Details of the parent study, which defined RNA biosignatures to distinguish febrile infants with bacterial versus viral infections have been published previously. (13) Because clinical data were collected only if the patient was enrolled in the parent PECARN study, those that did not have a blood culture and research blood specimen obtained for genomic analysis were ineligible for the current analysis. The parent study was approved by institutional review boards of all participating institutions.

### Data Analysis:

We reported patient demographics and basic clinical information using descriptive statistics with means and standard deviations (SD) or medians and inter-quartile ranges (IQR), as appropriate. We described the rates of diagnostic testing and hospital admission by week of age and by site. For the hospital-level analysis, we divided the study population into younger (0–28 days) and older (29–60 days) cohorts. We evaluated the frequency of diagnostic test performance and admission rates by patient age using chi-square tests and by ED site using one-way ANOVA. We also analyzed whether an abnormal white blood cell (WBC) count by existing guidelines (either below 5000 or above 15000 cells/mm3) had an effect on LP or hospitalization rates. Statistical analyses were performed using SAS software version 9.4 (Cary, NC).

## Results:

There were 7335 screened infants, of whom 5997 (81.8%) were enrolled in the parent study. Of these, 4778 (79.7% of enrolled) patients had research samples and clinical data collected, and therefore were eligible for this secondary analysis. Of the 4778 eligible patients, 1517 (32%) were 0–28 days old (Figure 1). There were no differences between the younger (0–28 days of age) and older (29–60 days of age) cohorts in their median presenting temperatures or Yale Observation (YOS) scores (Table 1). Diagnostic evaluation and patient disposition were stratified by age (Table 2). Rates of LP performance (69.5% vs 92.7%, $p<0.01$) and hospital admission (64.4% vs. 97.8%, $p<0.01$) were lower in the older cohort (Figures 2a, 2b). Furthermore, there was a decrease in the rates of LP performance and hospitalization frequency by increasing week of age in the older cohort. In contrast, viral testing (Figure 2c) showed a smaller but significant age-related effect, as the younger cohort had a higher rate of viral testing than the older cohort (66.2% vs 52.7%, $p<0.01$). The rates of chest radiographs (Figure 2d) did not vary with age. Urine samples were almost universally obtained in both age cohorts.

There was little difference among hospitals in LP performance rates (Figure 3a) or in hospitalization rates (Figure 3b) in the younger cohort. There was substantial variation, however, in the older cohort, as site LP rates varied between 40% and 90% across the participating institutions. Similarly, hospital admission rates were consistently high (>90%) among hospitals in the younger cohort, but ranged between 40% and 90% for the older cohort. For viral testing (Figure 3c) and chest radiographs (Figure 3d), testing rates varied widely between sites, between 20% and 90%, with similar variability in both the younger and older age cohorts. The site variation was significant for all four analyzed outcomes.

For infants ≤ 28 days of age, LP and admission rates were high (>90%) regardless of WBC counts. Table 3 shows the relationship between patient who received LPs and hospital admission. No patients discharged without an LP were determined to have bacterial meningitis using telephone follow up. For infants 29–60 days of age, LP (79.3% vs. 66.3%, risk difference 13.0%, 95% CI 9.6–16.4%) and hospitalization rates (82.0% vs. 58.8%, risk difference 23.2%, 95% CI 19.9–26.6%) were higher for infants with WBC counts > 15000 cells/mm3 or < 5000 cells/mm3 compared with infants with WBC counts of 5000 to 15000 cells/mm3. Regardless of WBC counts, there was wide variability between sites, with LP

rates ranging from approximately 35–90% in infants 29–60 days of age and WBC counts of 5000 to 15000 cells/mm3, and 50–100% in infants with WBC counts > 15,000 cells/mm3 or < 5000 cells/mm3. Rates of admission showed similarly wide variation between sites when stratified by WBC count.

C-reactive protein (CRP) levels were inconsistently obtained, with only 249 infants (5%) having CRP measured as part of their fever evaluation. Procalcitonin levels were rarely obtained, with only 2 infants having procalcitonin as part of their initial evaluation.

## Discussion:

In this secondary analysis of a large prospective observational study of febrile infants ≤ 60 days of age and younger, we demonstrated substantial practice variation in patient evaluation and disposition. Most of the variation was in the second month of life, with both LP performance and hospitalization rates decreasing consistently with increasing age and rates varying widely between hospitals.

Our prospectively collected data are consistent with prior retrospective studies that have demonstrated practice variation in the evaluation of young febrile infants in US hospitals. (9, 11, 12) There are a number of possible reasons why the evaluation and disposition of these patients demonstrates such wide variability; (a) low rates of bacteremia and meningitis with changing epidemiology of SBI,(17) (b) poor performance characteristics of historical screening biomarkers (complete blood counts, absolute neutrophil counts and band counts) (18), and (c) the availability of rapid turnaround multi-panel viral tests identify viral illness, although bacterial co-infections still do occur at a non-negligible rate. (16, 19, 20)

We observed a decrease in LP rates with increasing age for infants older than 28 days, with LP rates of less than 50% in the oldest age group (infants 57–60 days of age), despite guidelines recommending a universal approach for febrile infants between 29 and 60 days of age. (21, 22) Examining hospital-level variability revealed that clinicians performed LPs on essentially all enrolled infants less than 29 days of age. There was a wide range of LP performance rates between sites in the older cohort, which could reflect differences in disease prevalence between the age cohorts, differences in risk tolerance between clinicians and institutions, access to close outpatient follow-up or institutional culture and local guidelines.

Prior studies using administrative databases have demonstrated lower rates of LPs in the younger age group, which possibly reflects the inclusion of patients who presented with, and were coded as having ‘fever’ but were determined to not require laboratory workup. (9, 11) In one recent study, the most common reason cited for patients 7–28 days with fever who received no cultures was the provider not believing that the temperature was sufficient to initiate a laboratory workup, representing a patient population excluded from our current study. (12) Some newer guidelines use an age cutoff of 21 days to determine risk level, with infants 21 days and younger hospitalized, and those 22–90 days-old evaluated with laboratory tests and selectively discharged from the ED after a period of observation. (23) This evaluation strategy, however, was not published at the time of our data collection.

All published guidelines recommend urine testing in this age group, with no low risk criteria for urine sample omission, reflecting type of that UTIs are the most common type of SBI in this age group. (21, 24) In this analysis, urine was obtained at high rates across the two age cohorts, and did not show the same decrease with increasing age as was seen with LP rates. There has been an acknowledgement of the difference in risk of UTI/pyelonephritis versus invasive bacterial infections (i.e. bacteremia or meningitis). A recent multicenter retrospective study showed significant rates of concomitant bacteremia in patients with UTI, but low rates of bacterial meningitis, particularly in the 29–60 day age group, and suggested selective LP performance in patients greater than 28 days of age with UTIs. (25)

The decision to admit a febrile infant to the hospital has implications for exposure to parenteral antibiotics, hospital-acquired infections, costs of care, lost parental work days, and parental stress.(26) The rates of admission in our study followed a similar pattern to the rates of LPs, with patients 0–28 days old having consistently high rates of admission, with a relatively steady decrease in admission rate beyond 28 days old. The admission rate, like the LP performance rate, decreased with increasing age, and showed significant variation between sites.

The use of chest radiography in febrile infants without respiratory symptoms is controversial, with low rates of pathologic abnormalities detected.(27–29) About 1/3 of infants receiving chest radiographs across the age groups, but there was substantial variation in radiography use between hospitals.

Finally, we evaluated the use of viral testing in this cohort. Most guidelines for the evaluation of febrile infants do not include viral testing. There is little guidance on how to best incorporate the results of viral testing into decision-making regarding febrile infants evaluated in the ED and much new data are available and need to be considered how best to incorporate into evaluation strategies. One group of investigators demonstrated that infants with documented RSV infections were at substantially lower, but non-negligible, risk of SBIs than those without RSV;(20) the same group of investigators had similar results with influenza infections.(19) Serious bacterial co-infection in infants with documented viral infections has recently been re-examined in a large study performed by our group, with risks of SBI less common but non-negligible in viral-infected infants, especially those less than or equal to 28 days of age. (16) More than one-half of the infants in the current study had viral testing performed, with wide variation between study sites. Viral testing was more commonly performed in infants in the younger cohort. This may reflect an increased focus on identifying a causative agent for fever in younger infants, and the potential to scale back antibiotics or discharge home in cases of proven viral illness.

The variation in the evaluation of febrile infants in our study, both within infant age groups and between EDs, suggests that guidelines are not being adhered to by emergency providers in the PECARN network. The reasons for this are likely multifactorial. Older guidelines do not reflect the current epidemiology of SBIs, do not use more novel testing methods (e.g. procalcitonin), and do not accurately predict the risk of SBIs.(30–32) Clinical scoring systems or unstructured clinical suspicion have not been shown to be reliable in this population.(33) Improved diagnostic tests may improve diagnostic certainty, ultimately

decreasing the need for invasive testing, antibiotics and admission for infants who have self-limited viral illnesses. Newer molecular diagnostic techniques have shown early success and may play a large role in the not-distant future. (13, 34, 35) Improving the accuracy and decreasing the turn-around-times of screening tests for the evaluation of febrile infants could potentially standardize evaluations and decrease variation.

## Limitations:

Our study has several limitations. First, we enrolled a convenience sample of febrile infants who were being evaluated with blood cultures, based on the availability of study staff, and possibly could reflect a population at greater risk of SBIs. However, the patient sample size was large and the rates of SBI were reflective of those in the literature for this group of infants.(13) Therefore, our study population was likely generalizable to other cohorts of febrile infants in this age group. Focusing on patients who had, at a minimum, a blood culture obtained identifies patients for whom treating physicians had concerns for invasive SBIs. Critically ill-appearing infants were excluded from this study; however, those patients are unlikely to receive only partial evaluations for SBI or be discharged home from the ED. Furthermore, these critically ill-appearing infants do not represent a diagnostic conundrum that can be resolved by diagnostic testing alone. We did not have data on provider-level variation within an institution, or obtain details regarding clinical factors, such as the results of viral testing, which might have influenced providers' decisions to pursue various testing. We believe the impact of this potential limitation is mitigated by the large, prospective, geographically-diverse sample. It is also possible those some of the hospital variation in testing was due to external systemic factors such as availability of timely outpatient follow-up which might have affected treatment decisions. Finally, this study was conducted within a research network consisting mostly of academic pediatric EDs, which may or may not accurately reflect practice pertaining to febrile infants in general ED settings, where more than 80% of ED visits for US children occur. (36)

## Conclusions:

Substantial variation exists in the evaluation and disposition of febrile infants 60 days of age or younger in pediatric EDs within a national pediatric emergency research network, particularly among infants 29–60 days of age. This variation highlights an opportunity to update diagnostic and treatment strategies with better evidence-based tools and decision aids which incorporate the latest epidemiology of SBIs. This may assist with clinical decision-making, with a goal of safely decreasing invasive testing, antibiotic exposure and hospitalization.

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**Article Summary:**

**1.** Why is this topic important?

Young infants with fever commonly present to the Emergency Department for evaluation and management. Multiple guidelines exist, but guideline adherence has been variable in retrospective studies.

**2.** What does this study attempt to show?

This is the first US based multi-center report of prospectively collected data describing the practice variation in evaluation and disposition of febrile infants. The study describes variation in practice within the Pediatric Emergency Care Applied Research Network (PECARN).

**3.** What are the key findings?

Infants < 29 days had relatively little variation in lumbar puncture and admission rates. Infant 29–60 days had wide hospital level variation in the rates of both lumbar puncture and admission, with both rates decreasing with increased week of age. Use of chest radiography and viral testing also varied widely between hospitals.

**4.** How is patient care impacted?

Areas of practice variation represent opportunities for improvement in care. Newer guidelines with focus on current epidemiology and Updated biomarkers have the potential to safely decrease invasive testing and hospitalization.

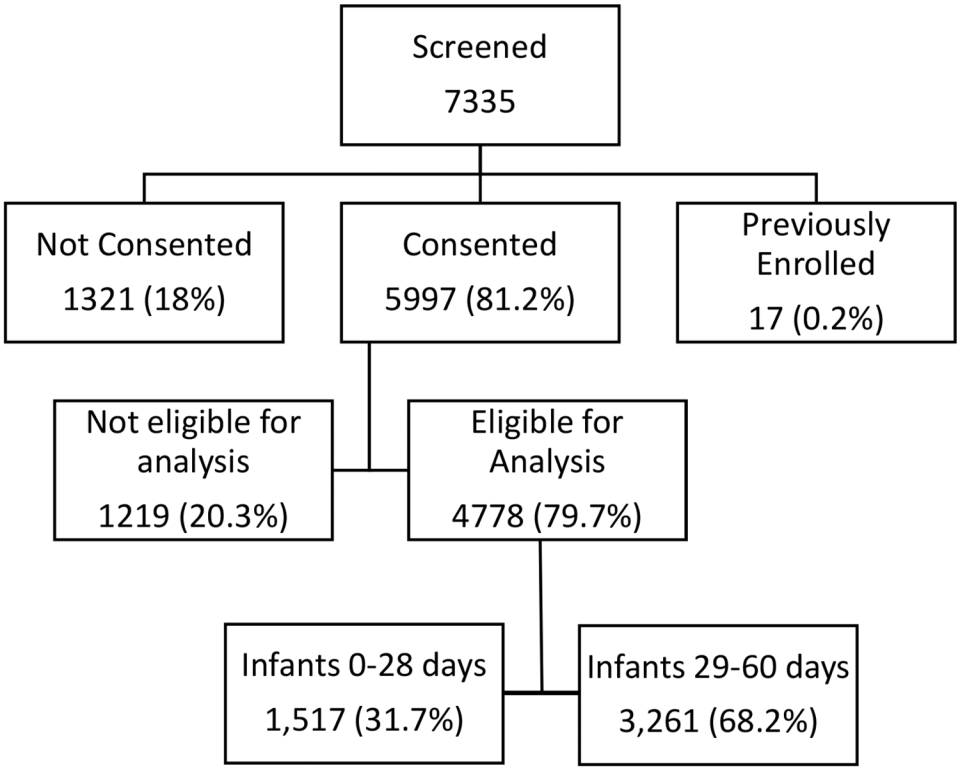


**Figure 1 –.**
Patient recruitment and enrollment

Figure 2a

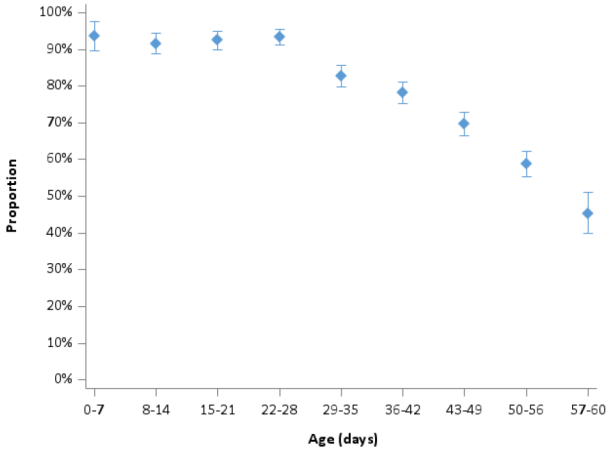


Figure 2b

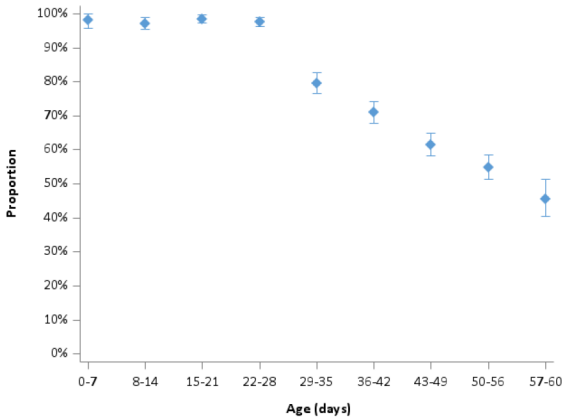


Figure 2c

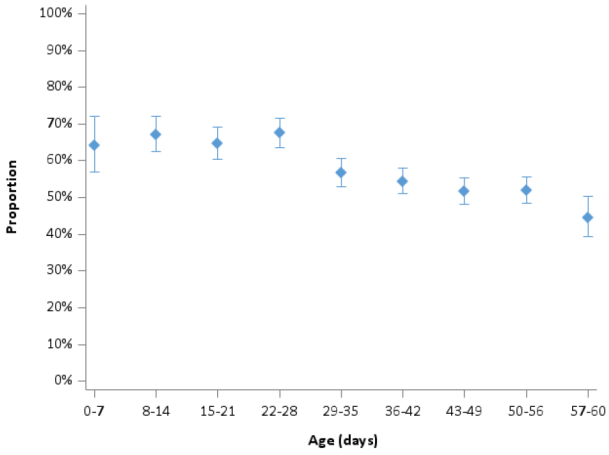


Figure 2d

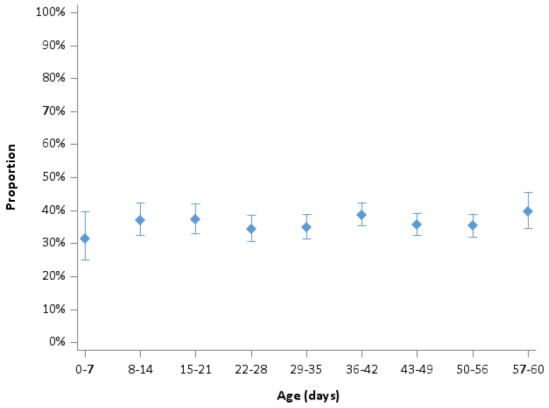


**Figure 2 –.**

Intervention rates by age of infant (with 95% CI). Rate of lumbar puncture (2a), admission (2b), viral testing (2c), and chest radiography (2d)

Figure 3a

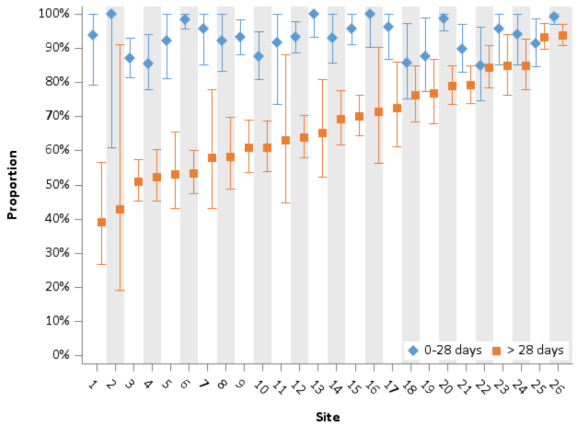


Figure 3b

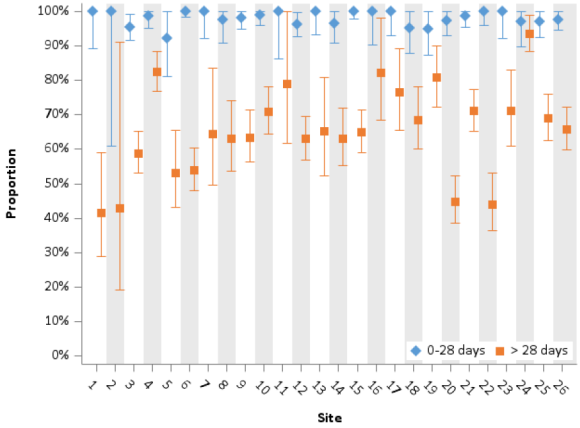


Figure 3c

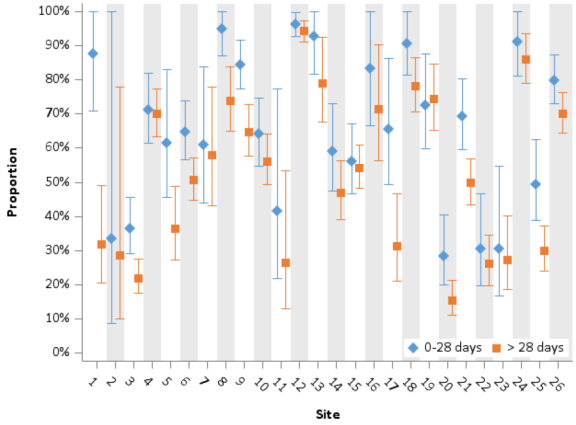


Figure 3d

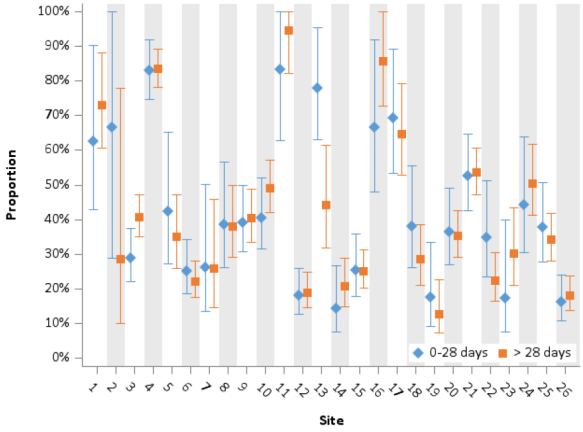


**Figure 3 –.**

Intervention rates by treating hospital (with 95% CI). Rate of lumbar puncture (3a), admission (3b), viral testing (3c), and chest radiography (3d)

**Table 1:**

Demographics and other baseline characteristics by age group

| | Age group | | Overall |
|---|---|---|---|
| | **0–28 days** | **29–60 days** | |
| **Total Patients [n (%)]** | 1,517 (31.7) | 3,261 (68.2) | N=4,778 |
| **Male Gender [n (%)]** | 865 (57.0) | 1,837 (56.3) | 2,702 (56.6) |
| **Race [n (%)]** | | | |
| **American Indian or Alaska Native** | 15 (1.0) | 54 (1.7) | 69 (1.4) |
| **Asian** | 44 (2.9) | 89 (2.7) | 133 (2.8) |
| **Black or African American** | 369 (24.3) | 786 (24.1) | 1,155 (24.2) |
| **Native Hawaiian or other Pacific islander** | 12 (0.8) | 12 (0.4) | 24 (0.5) |
| **White** | 866 (57.1) | 1,872 (57.4) | 2,738 (57.3) |
| **Other** | 98 (6.5) | 236 (7.2) | 334 (7.0) |
| **Stated as unknown** | 113 (7.4) | 212 (6.5) | 325 (6.8) |
| **Ethnicity [n (%)]** | | | |
| **Hispanic or Latino** | 429 (28.3) | 991 (30.4) | 1,420 (29.7) |
| **Not Hispanic or Latino** | 1,061 (69.9) | 2,203 (67.6) | 3,264 (68.3) |
| **Unknown** | 27 (1.8) | 67 (2.1) | 94 (2.0) |
| **Qualifying temperature (median $^{0}$C[IQR]$^{\#}$)** | 38.3 [38.2, 38.7] | 38.4 [38.2, 38.8] | 38.4 [38.2, 38.7] |
| **Yale Observation Scale Score (median [IQR]$^{\#}$)** | 6.0 [6.0, 8.0] | 6.0 [6.0, 8.0] | 6.0 [6.0, 8.0] |

$^{\#}$Interquartile Range

**Table 2:**

Diagnostic evaluation and disposition

| | Age group | | Overall N=4,778 |
|---|---|---|---|
| | **0–28 days n=1,517** | **29–60 days n=3,261** | |
| **Lumbar Puncture completed[#] n (% [95% CI])** | 1406 (92.7 [91.4–94.0]) | 2265 (69.5 [67.9–71.1]) | 3671 (76.8 [75.6–78.0]) |
| **Viral Testing Performed n (% [95% CI])** | 1004 (66.2 [63.8–68.6]) | 1718 (52.7 [51.0–54.4]) | 2722 (57.0 [55.6–58.4]) |
| **Chest Radiography n (% [95% CI])** | 539 (35.5 [33.2–38.0]) | 1191 (36.5 [34.9–38.2]) | 1730 (36.2 [34.9–37.6]) |
| **Admitted to hospital/transferred/died [*] n (% [95% CI])** | 1484 (97.8 [97.1–98.6]) | 2099 (64.4 [62.7–66.0]) | 3583 (75.0 [73.8–76.2]) |
| **Urine obtained n (% [95% CI])** | 1507 (99.3 [98.8–99.6]) | 3217 (98.7 [98.2–99.0]) | 4724 (98.9 [98.5–99.1]) |

[#]There were 24 total cases of confirmed bacterial meningitis, 19 of which were in the younger age cohort.

[*]A 34-day-old female died. Blood and CSF cultures were negative.

**Table 3:**

Patients with Lumbar Puncture and Hospital Admission

| | Admitted n (%) | Not Admitted n (%) |
|---|---|---|
| **Patients 0–28 days of age (n=1517)** | | |
| Lumbar Puncture | 1394 (92) | 12 (1) |
| No Lumbar Puncture | 90 (6) | 21 (1) |
| **Patients 29–60 days of age (n=3261)** | | |
| Lumbar Puncture | 1753 (54) | 512 (16) |
| No Lumbar Puncture | 346 (11) | 650 (20) |
| **All Patients (n=4778)** | | |
| Lumbar Puncture | 3147 (66) | 524 (11) |
| No Lumbar Puncture | 436 (9) | 671(14) |