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ORIGINAL RESEARCH

Pediatrics

Clinical management and outcomes for febrile infants 29–60 days evaluated in community emergency departments

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Abstract

Objective: Describe emergency department (ED) management and patient outcomes for febrile infants 29–60 days of age who received a lumbar puncture (LP), with focus on timing of antibiotics and type of physician performing LP.

Methods: Retrospective observational study of 35 California EDs from January 1, 2010 through December 31, 2019. Primary analysis was among patients with successful LP and primary outcome was hospital length of stay (LOS). Logistic regression analysis included variables associated with LOS of at least 2 days. Secondary outcomes were bacterial meningitis, hospital admission, length of antibiotics, and readmission.

Results: Among 2569 febrile infants (median age 39 days), 667 underwent successful LP and 633 received intravenous antibiotics. Most infants ($n = 559$, 88.3%) had their LP before intravenous antibiotic administration. Pediatricians performed 54% of LPs and emergency physicians 34%. Sixteen infants (0.6% of 2569) were diagnosed with bacterial meningitis, and none died. Five hundred and fifty-eight (88%) infants receiving an LP were hospitalized. Among patients receiving an LP and antibiotics ($n = 633$), 6.5% were readmitted within 30 days. Patients receiving antibiotics before LP had a longer

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length of antibiotics (+ 7.9 hours, 95% confidence interval [CI] 3.8–13.4). Primary analysis found no association between timing of antibiotics and LOS (odds ratio [OR] 0.67, 95% CI 0.34–1.30), but shorter LOS when emergency physicians performed the LP (OR 0.66, 95% CI 0.45–0.97).

Conclusions: Febrile infants in the ED had no deaths and few cases of bacterial meningitis. In community EDs, where a pediatrician is often not available, successful LP by emergency physician was associated with reduced inpatient LOS.

KEYWORDS
emergency medicine, fever, infant, lumbar puncture, meningitis, pediatrics

1 | INTRODUCTION

1.1 | Background

The indications for lumbar puncture (LP) in febrile infants 29–60 days of age presenting to the emergency department (ED) continue to evolve. In the past few years clinical guidelines have been published that address the risk factors and need for an LP in this age group,[1–3] including the American Academy of Pediatrics clinical practice guidelines.[4] These guidelines recognize that this age group is still at risk for meningitis, although at lower rates than previously thought.[2,3,5–7] For this reason, determining the need for LP in this age group has become more complex and the number of LPs being done is decreasing and as such physicians have less experience with the procedure. Studies have shown that emergency physicians' clinical experience and use of evidence-based research can influence whether they perform a LP[8] and that physicians with less experience are more likely to have traumatic or unsuccessful LPs.[9] This can be even more of an issue in community EDs, where very few emergency physicians are fellowship trained in pediatric emergency medicine. These circumstances highlight the need to understand associations with patient outcomes related to who performs the LP (emergency physician, pediatric hospitalist, other) and the timing of antibiotics (before or after LP) in this patient population.

1.2 | Importance

Emergency physicians have been trained to administer antibiotics for septic patients as soon as possible; however, the timing of antibiotic administration can be complicated when patients require a diagnostic LP.[10,11] Factors that can delay the acquisition of cerebral spinal fluid (CSF) include uncertainty about the need for a LP and unsuccessful attempts to obtain CSF. It has been shown that 18% to 35% of LPs in infants are unsuccessful or traumatic and that this can lead to unnecessary antibiotic use and hospitalization.[9,11] If antibiotics need to be given before the LP is performed, the antibiotics can sterilize the CSF making it less likely that bacteria will grow.[10,12,13] This can cause difficulty in confirming the diagnosis of meningitis, especially if there are other abnormalities in the CSF such as pleocytosis. The administration of antibiotics before an LP is completed may lead to increases in hospital admissions, antibiotic use, length of hospital stay (LOS), or need for additional procedures/tests.

1.3 | Goals of this investigation

The primary aim of this study is to evaluate if the timing of antibiotics before versus after successful LP, or the type of physician who performs the LP, is associated with hospital admission, LOS, length of antibiotic administration, readmission, or death. We also describe the general ED management of febrile infants 29–60 days of age and report the incidence of bacterial meningitis among these encounters.

2 | METHODS

2.1 | Study design and setting

A retrospective observational study was conducted among febrile infants (29–60 days old) evaluated in 35 Kaiser Permanente (KP) California EDs (14 Southern California and 21 Northern California) from January 1, 2010 through December 31, 2019. KP in California is an integrated health care delivery system serving nearly 10 million racially and socioeconomically diverse members who reflect the California population. Among the study EDs, there is variability in the annual volume (≈30k/year to nearly 100k/year), rural or urban setting, available inpatient pediatric services, residency affiliations, and geography. The integrated nature of the delivery system allows for more coordinated follow-up with outpatient care than a typical US ED, but in most other ways these EDs function similar to community EDs in the United States. Health care at KP is coordinated through an integrated electronic health record (EHR) that captures comprehensive information on the care received at KP California-owned and contracting facilities. KP California also obtains claims data on any out-of-network care that members receive.

There are approximately 1500 physicians who practice in our California KP EDs, the vast majority are general emergency physicians, less

The Bottom Line

This article is valuable in highlighting how the practice of managing the febrile neonate is challenging. Even with the American Academy of Pediatrics guidelines and with care in community hospitals, although not completely the same as academic centers, it can still be evidence based and effective. Infants 29–60 days of age presenting with fever to the emergency department had favorable clinical outcomes with no deaths and a low risk of meningitis, even among those who underwent lumbar puncture.

than 1% have pediatric fellowship training. The pediatric physicians referred to in this study are pediatricians and neonatologists that work in the KP hospitals and manage the pediatric and neonatal units. Over the study period more of the pediatric doctors were hospital based as their primary practice location and were functioning as pediatric hospitalists.

2.2 | Selection of participants

Participants in the study were infants 29–60 days old, born at a KP hospital who presented to a KP California ED with a documented fever in the ED (or within 12 hours before ED presentation) of greater than or equal to 38°C. We excluded from the study infants born at less than 37 weeks gestation; infants with any high-risk neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic, immunologic, metabolic, congenital or genetic, malignancy, or premature/neonatal comorbidity[14]; and patients hospitalized between birth and ED encounter. The study population used for our primary analysis was limited to those who had a successful LP performed within 24 hours of the ED registration.

2.3 | Main outcomes and measurements

The primary outcome was LOS, as measured in hours from ED registration to hospital discharge. Secondary outcomes included incidence of bacterial meningitis, bacteremia, urinary tract infection (UTI), 30-day mortality, receipt of successful LP (physician type), total intravenous antibiotics duration of treatment, hospitalization, and ED revisit or rehospitalization within 30 days of encounter. Bacterial meningitis was defined as (1) isolation of pathogenic bacteria from CSF, (2) bacteremia with CSF pleocytosis and treatment for presumed bacterial meningitis, or (3) antibiotics administered before LP, CSF pleocytosis, and treatment for presumed bacterial meningitis.[15] Bacteremia and UTI were defined by the presence of a positive culture with a single pathogenic organism. A CSF culture result was used to identify successful LP. Antibiotics were measured from first administration after ED registration to last before hospital discharge.

We evaluated the specialty of the physician who performed the LP based on the physician who ordered the CSF tests. LP time was defined as the time the sample was scanned into the EHR at the hospital laboratory. The LP was performed either in the ED or on the pediatric ward. LP was defined as "before" antibiotic administration if antibiotics were administered before or within the 2 hours after the LP. We chose this 2-hour window based on past evidence that evaluated how long it takes to sterilize CSF cultures[12] and also accounting for some time between when the CSF is collected and when it is processed and scanned into the EHR at the laboratory. We also performed a sensitivity analysis using 1 hour to identify potential differences in results from our analysis at 2 hours.

2.4 | Analysis

Logistic regression analysis was used to assess the association between longer LOS (LOS of 2 days or more) and the following variables: emergency physician performed LP (yes/no), LP before antibiotics (yes/no), age (in days), female sex, race (Asian/Pacific Islander, Black, Other or Unknown, White), Hispanic ethnicity (yes/ no), urinalysis (not tested, positive, negative), abnormal complete blood count WBCs (< 5 or $> 15 \times 1000$ cells per microliter)[16] compared to normal ($5\text{-}15 \times 1000$ cells per microliter) and not tested, and presence versus absence of bacteremia or meningitis (at least 1 culture positive vs both negative). LOS was dichotomized as either an inpatient stay of 2 days or more or an LOS less than 2 days. This cutoff was based on a traditional 48-hour rule-out for infants with bacterial cultures.[17,18] After identifying clinically relevant variables, stepwise selection (entry = 0.15, stay = 0.20) was used to identify the variables for the final model. LP within 2 hours of antibiotic administration was added, as well as race and ethnicity, to accomplish the primary outcome analysis and to account for any potential inequities that have been reported in the literature over the time period of the study.[19–21] For quantitative comparisons, all *P* values were 2 sided with alpha (type 1) error set to equal 0.05. All analyses and figures were conducted in SAS 9.4 (Cary, North Carolina). This study was approved by the Kaiser Permanente Southern and Northern California Institutional Review Boards.

3 | RESULTS

3.1 | Characteristics of study subjects

Across 35 study California EDs between 2010 and 2019, 2569 febrile infants 29–60 days of age met inclusion criteria. Among those, 667 (26.0%) underwent successful LP and 633 (94.9%, 633 of 667) of these were given intravenous antibiotics. For these 633 infants, the median age was 39 days (interquartile range: 33–47). Less than half of the infants were female (n = 252, 39.8%), and 43.6% were of Hispanic ethnicity. The average gestational age at birth was 39 weeks. Most infants (n = 559, 88.3%) had their LP before (or within 2 hours of) intravenous antibiotic administration, whereas 74 (11.7%) received an

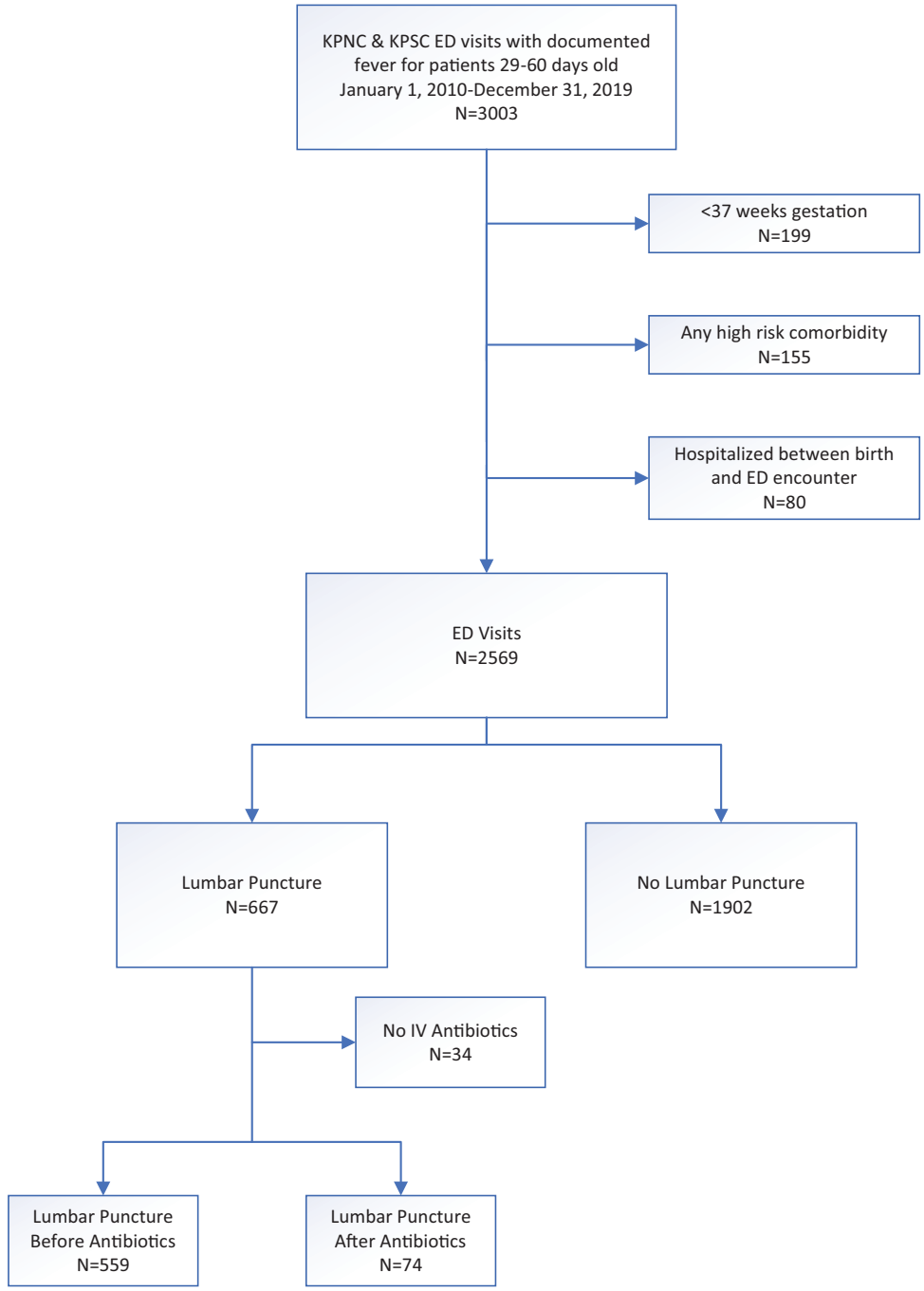

FIGURE 1 Flow diagram of the patient cohort used for analysis. Abbreviations: ED, emergency department; IV, intravenous; KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California

LP after intravenous antibiotics were administered (Figure 1). Patient characteristics were similar between these 2 groups (Table 1).

3.2 | Main results

Unadjusted median LOS was not significantly higher among infants with an LP after antibiotics compared to infants who had an LP before antibiotics (+4.8, 95% confidence interval [CI]: −1.0 to 15.7) (Table 2). Overall, 88% of patients were admitted to the hospital, with no difference in hospitalization between infants who received antibiotics before or after LP (+4.2, 95% CI: −4.6 to 9.6). Infants who underwent LP after antibiotics were more likely to have return visits to the ED (+6.4, 95% CI: 0.4–16) and readmission to the hospital (+7.3, 95% CI: 2.3–16.2) in the 30 days after discharge. Infants who had an LP after antibiotics were also more likely to be treated with intravenous antibiotics for a longer time (+7.9, 95% CI: 3.8–13.4). There were no deaths (0 of 2569).

TABLE 1 Demographic and clinical characteristics of febrile infants 29–60 days of age presenting to the ED, stratified by timing of the LP

	LP timing relative to IV antibiotics		
	Before	After	Total
	(*N* = 559)	(*N* = 74)	(*N* = 633)
Age at ED visit (days), mean (SD)	40.9 (8.8)	41.2 (8.6)	40.9 (8.7)
Female infant, *n* (%)	230 (41.1)	22 (29.7)	252 (39.8)
Infant race, *n* (%)			
Asian/Pacific Islander	94 (16.8)	9 (12.2)	103 (16.3)
Black	46 (8.2)	3 (4.1)	49 (7.7)
Other or unknown	88 (15.7)	18 (24.3)	106 (16.7)
White	331 (59.2)	44 (59.5)	375 (59.2)
Hispanic infant (Y), *n* (%)	242 (43.3)	34 (45.9)	276 (43.6)
Birth weight (g), mean (SD)	3418.4 (464.6)	3443.6 (459.9)	3421.4 (463.8)
Gestational age (weeks), mean (SD)	39.1 (1.1)	39.1 (1.2)	39.1 (1.1)
Maximum temperature, mean (SD)	101.7 (0.9)	101.7 (0.8)	101.7 (0.9)
CBC ANC, mean (SD)	5.2 (3.8)	5.4 (4.3)	5.2 (3.8)
CBC < 5 or > 15 × 1000/mcL, *n* (%)	200 (35.8)	31 (41.9)	231 (36.5)
Urinalysis leukocyte esterase (positive), *n* (%)	154 (29.9)	24 (34.3)	178 (30.4)
Urinalysis nitrite (positive), *n* (%)	32 (6.0)	6 (8.3)	38 (6.3)

Abbreviations: ANC, absolute neutrophil count; CBC, complete blood count; ED, emergency department; IV, intravenous; LP, lumbar puncture; mcl, cells per microliter.

TABLE 2 Clinical outcomes for febrile infants 29–60 days of age presenting to the ED, comparing those who received an LP before and after antibiotics

	LP before[a] antibiotics (*N* = 559)	LP after antibiotics (*N* = 74)
Mortality within 30-day of discharge	0 (0%)	0 (0%)
Admitted to IP/observation room	490 (87.7%)	68 (91.9%)
Hours of antibiotics, median (IQR)	47.1 (24.4, 57.9)	55.1 (45.5, 83.0)
Length of stay in hours, median (IQR)	61.3 (44.4, 71.5)	66.1 (51.1, 93.5)
Readmission		
ED visit within 30-day of discharge	32 (5.7%)	9 (12.2%)
Readmission: IP or observation	12 (2.1%)	7 (9.5%)
Culture result		
Bacterial meningitis	8 (1.4%)	2 (2.7%)
Bacteremia	30 (5.4%)	9 (12.2%)
UTI	117 (20.9%)	16 (21.6%)
UTI + bacteremia	14 (2.5%)	3 (4.1%)
Bacterial meningitis + bacteremia	6 (1.1%)	2 (2.7%)
Physician who ordered the lumbar puncture		
Emergency physician	217 (38.8%)	9 (12.2%)
Pediatric physician	301 (53.8%)	53 (71.6%)
Other	41 (7.3%)	12 (16.2%)

Abbreviations: ED, emergency department; IP, inpatient; IQR, intraquartile range; LP, lumbar puncture; UTI, urinary tract infection.
[a]within 2 hours of cerebral spinal fluid being received at the hospital laboratory.

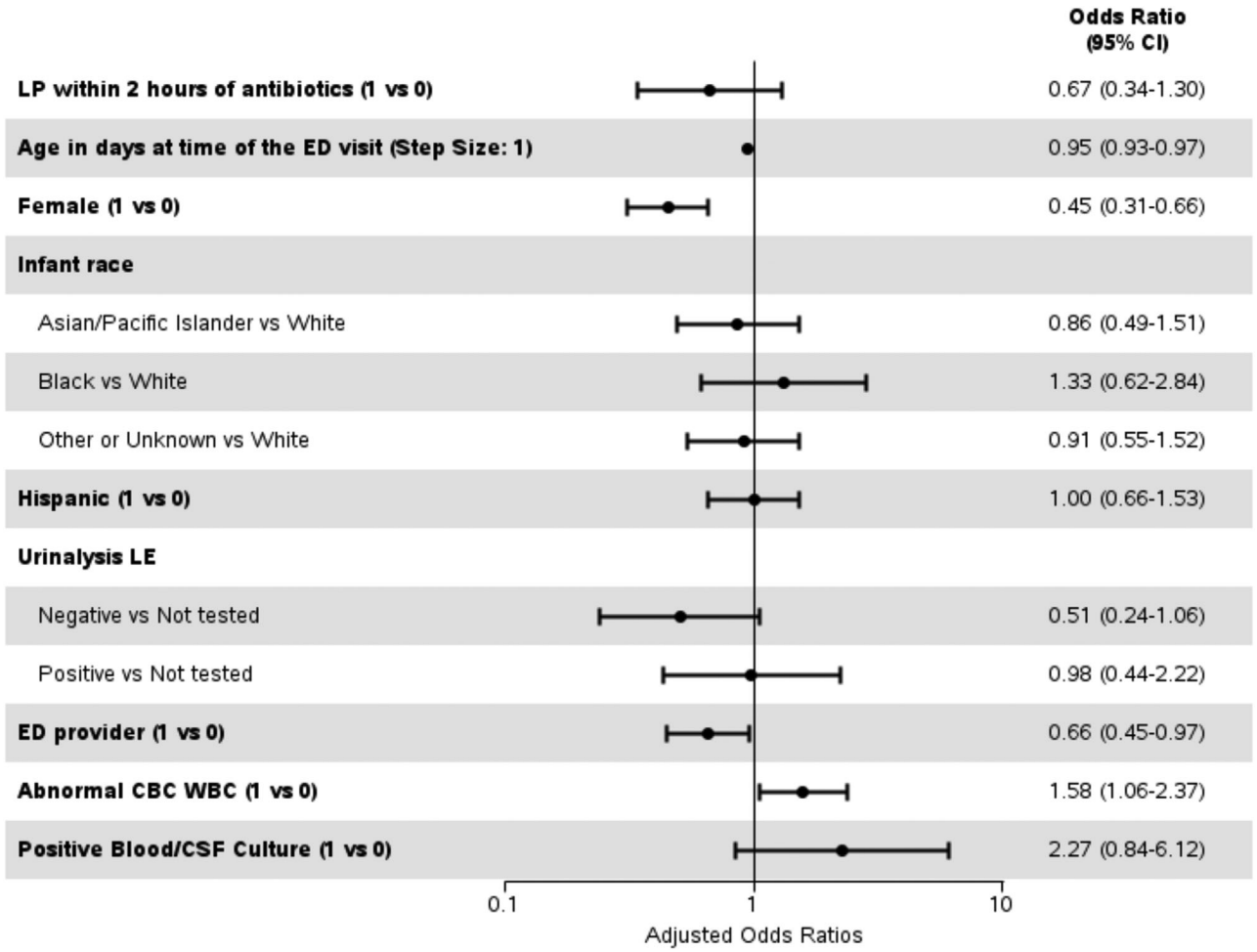

FIGURE 2 Odds of a length of stay ≥ 48 hours among infants with successful LP. Abbreviations: CBC, complete blood count; CI, confidence interval; CSF, cerebral spinal fluid; ED, emergency department; LE, leukocyte esterase; LP, lumbar puncture; WBC, white blood cell count

Overall, 16 infants (0.6% of 2569) were diagnosed with meningitis, 10 at initial visit (1.6%, 10 of 633), and 6 others in the following 72 hours (0.3%, 6 of 1902). No other infants were diagnosed with meningitis between 3 and 30 days after initial ED visit. For patients that had a LP with initial ED encounter, 8 (1.4% of 559) infants who had their LP completed before antibiotics were diagnosed with bacterial meningitis, whereas 2 (2.7% of 74) diagnosed with meningitis had their LP after antibiotics. Nine of the 10 patients diagnosed with meningitis had a positive CSF culture, 3 patients with *Escherichia coli* and 6 with *Streptococcus agalactiae* (Group B *Streptococcus*). The 1 patient diagnosed with culture negative but presumed meningitis was given antibiotics before the LP. Of the 10 infants with bacterial meningitis, 8 also had bacteremia. Among patients who did not have a LP at the initial ED encounter, there were 6 readmissions (0.3% of 1902) for meningitis within 30 days. Four of these patients had a blood culture done as part of the ED work up for fever and the blood culture became positive (eventually growing Group B *Streptococcus*); thus the patients were called back to the ED for LP and admission. One patient left against medical advice after the family refused LP and antibiotics at initial ED encounter and then returned because of positive blood culture (eventually growing Group B *Streptococcus*) and consented for LP and admission. The last patient was pretreated with oral amoxicillin for presumed acute otitis media and presented with clinical findings consistent with meningitis and was treated for presumed bacterial meningitis.

Overall, 35.7% of LPs were performed by emergency physicians, 55.9% by pediatricians, and 8.3% by others (primarily family medicine physicians and residents). Emergency physicians were more likely to perform LPs before antibiotics were given (38.8% of early LPs compared to 12.2% of late LPs), whereas most LPs performed after antibiotics were done by pediatric physicians (71.6%).

The logistic regression analysis (Figure 2) did not show a statistically significant association between LP before intravenous antibiotics and hospital LOS (adjusted odds ratio [aOR] 0.67, 95% CI 0.34–1.30). We also performed a sensitivity analysis using antibiotics given within 1 hour and those results were the same (Appendix Figure A1). The regression analysis did show a significant association between successful LP performed by an ED physician and a shorter LOS when

compared to pediatricians or other clinicians (aOR 0.66, 95/% CI 0.45–0.97). Older age at time of ED visit (aOR 0.95, 95% CI 0.93–0.97) and female sex (aOR 0.45, 95% CI 0.31–0.66) were also associated with a shorter LOS. A high-risk/abnormal WBC count (< 5 or > 15 × 1000 cells per microliter) was associated with a longer LOS compared to patients who had a normal WBC count or were not tested (aOR 1.58, 95% CI 1.06–2.37).

3.3 | Limitations

There are limitations to this study. It is an observational study and thus results are associations and not causal. We did not have data on whether the infants were well or ill appearing. For this reason, we did not comment on the need for the LP and focused on the timing compared to antibiotic administration. We did exclude high-risk and premature infants, and none of our patients died within 30 days and few were diagnosed with bacteremia or meningitis, representing an overall low risk of serious events among patients 29–60 days old presenting to study EDs with a fever. We were not able to capture LPs that were attempted but not completed. We did include LPs that were traumatic, as long as a culture was sent. The location, in addition to the type of physician performing an LP, may be associated with patient outcomes and LOS, but our data set does not have the location of the procedure to include this variable in our analyses. There were some relevant variables, such as C-reactive protein and procalcitonin, that were not obtained uniformly on the entire population, preventing inclusion in the analysis. Lastly, our study was performed in an integrated health care system and it is possible that results found here may not fully generalize to other patient populations or systems. Our findings are most relevant to community EDs and may be different from academic pediatric EDs. These results, however, should provide useful information and can be compared to future research in academic or other settings.

4 | DISCUSSION

Among 35 EDs in an integrated health care system from 2010–2019, 24.6% (633 of 2569) of febrile infants 29–60 days of age underwent LP and received intravenous antibiotics. These patients had favorable outcomes with no deaths, and few were diagnosed with meningitis. The analysis did not show an association between LP before antibiotics and decreased LOS. However, an LP before antibiotics was associated with fewer return ED visits and hospital readmissions within 30 days. The multivariate analysis also showed an association between successful LP by an emergency physician and decreased LOS. These results indicate that LPs performed before antibiotics were given were associated with improved clinical outcomes. In community EDs, where a pediatric physician is often not available, the ability of an emergency physician to perform the LP can contribute to this care. These results underscore the potential risks associated with late or unsuccessful LPs previously reported. It has been shown that challenges with the procedure can lead to unnecessary antibiotics use, hospitalization, and increased LOS,[9,11,13] and antibiotics before LP can create ambiguity regarding the diagnosis of meningitis based on elevated glucose and lowered protein levels.[10]

We found this 29- to 60-day-old group to be at low risk of meningitis (1.6% in LP group, 10 of 633; overall 0.6%, 16 of 2569) and death (0%). Other studies have also found similarly low rates. For infants 29–60 days of age, Bonilla et al. reported 1 meningitis case in 1378 infants (< 0.01%)[22] and Scarfone et al. reported 1 case in 1188 (< 0.01%).[7] This underscores the importance of having a clear understanding of the indication for LP in this age group, based on recent evidence and recommendations to inform management.[1–4] The balance between a complete diagnostic workup and the impact on the patient and health care usage needs to be assessed for this uncommon but potentially very serious diagnosis.

Aronson et al. interviewed pediatric and general emergency physicians to assess factors that influenced the decision to perform an LP on infants. Among the influences were the physician's clinical experience and the role of the pediatric clinician.[8] Nigrovic et al. also showed that less physician experience was associated with unsuccessful or traumatic LPs.[9] With the recent guidelines recommending less use of LP in the evaluation of febrile infants 29–60 days of age,[1–4] emergency physicians will likely have less experience in the procedure, which could lead to less use of LP when indicated and less success when attempted. This could exacerbate the use of pretreatment antibiotics before LP and the potential negative outcomes we observed in our study. This highlights the need for ongoing education regarding the evolving guidelines for the use of LP and the need for emergency physicians to remain confident in the ability to perform the procedure. It also highlights the importance of the collaboration with pediatricians, who can at times assist in the ED and will take over patient management on admission.

In summary, infants 29–60 days of age presenting with fever to the ED had favorable clinical outcomes with no deaths and very low risk of meningitis, even among those who underwent LP. The majority of these infants had their LP performed before receiving antibiotics and when emergency physicians performed the LP successfully, it was associated with a shorter LOS. Efforts to optimize when LPs are needed in this low-risk group and to perform the procedure early as part of the initial ED workup may improve care of febrile infants.

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CONFLICT OF INTERESTS

There are no conflicts of interest. None of the authors have any financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

AUTHOR CONTRIBUTION

All authors contributed to the study conception and design. Dustin W. Ballard, David R. Vinson, Tara L. Greenhow, Tran H. P. Nguyen, Beverly R. Young, Stacy Park, and Adam L. Sharp obtained research funding. Material preparation, data collection, and analysis were performed by Patrick J. Van Winkle, Samantha N. Lee, Qiaoling Chen, Aileen S. Baecker, Amy L. Alabaster, Jie Huang, and Adam L. Sharp. Patrick J. Van Winkle, Samantha N. Lee, Aileen S. Baecker and Adam L. Sharp drafted the manuscript, and all authors contributed substantially to its revision. All authors read and approved the final manuscript.

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APPENDIX

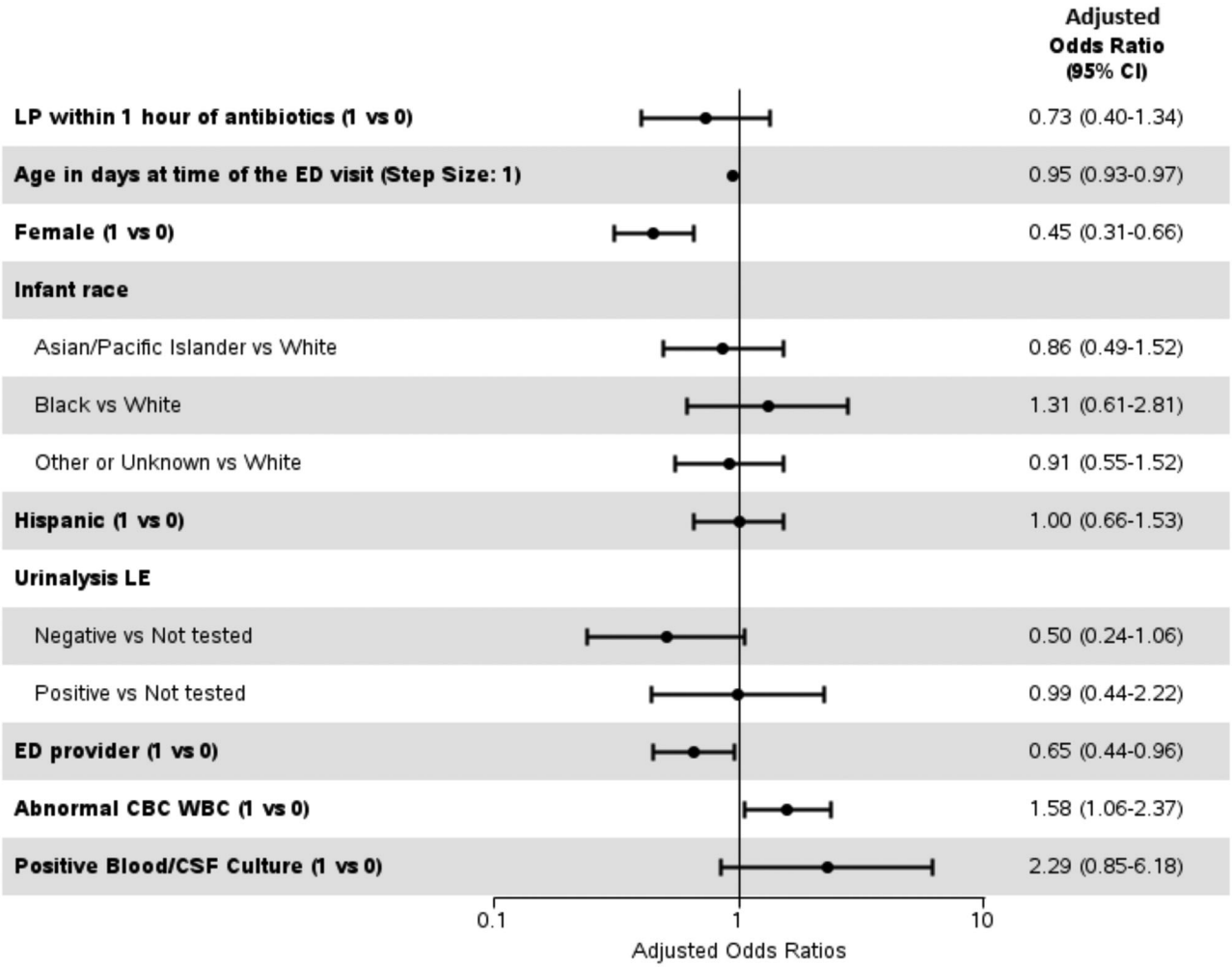

FIGURE A1 Odds of a length of stay ≥ 48 hours among patients with successful LP performed using 1 hour post-LP as the cutoff to define after antibiotics. Abbreviations: CBC, complete blood count; CSF, cerebral spinal fluid; ED, emergency department; LE, leukocyte esterase; LP, lumbar puncture; WBC, white blood cell count