Outcomes Among Well-appearing Infants Initially Deferred Antibiotics for Fever

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ABSTRACT

Introduction: The 2021 American Academy of Pediatrics guideline on well-appearing febrile infants recommends deferral of lumbar puncture and/or initial antibiotics in certain patients 22 to 60 days old, along with shared decision-making with the patient's caregivers. This study sought to compare the incidence of invasive bacterial infection and/or need for escalation of care in febrile infants in this age group who did and did not receive initial empiric antibiotics before and after implementation of the guideline.

Methods: This was a single-center, retrospective cohort evaluation of admitted patients before and after guideline implementation. Well-appearing infants 22 to 60 days old who presented to the emergency department with fever and met guideline criteria were included. The primary outcome compares the incidence of invasive bacterial infections and escalation of care among patients who did and did not defer initial antibiotics. Secondary outcomes include rate of positive bacterial cultures, length of stay, and mortality. Patient demographics, antibiotic initiation, culture data, inflammatory markers, urinalysis, lumbar puncture and cerebrospinal fluid cell counts, readmission within 7 days of discharge, length of stay, and mortality within 30 days were collected and analyzed.

Results: Sixty-one patients were included: 21 in the pre-guideline group and 40 in the post-guideline group. There was no difference in the incidence of invasive bacterial infections or escalation of care between groups. There was no difference in rate of positive bacterial cultures, length of stay, or mortality. More patients in the pre-guideline group received a lumbar puncture compared to the post-guideline group.

Conclusions: Our results affirm guideline recommendations suggesting deferral of antibiotics in well-appearing infants meeting select criteria results in decreased antibiotic use and lumbar punctures without affecting the rate of invasive bacterial infections or need for escalation of care.

INTRODUCTION

Neonatal fever is common in the emergency department (ED) and a challenging presentation for infants less than 60 days old.[1] Clinical presentation cannot easily identify patients at high risk for invasive bacterial infection; fever is often the only clinical sign of an infection in these patients, which leads to many infants receiving lumbar punctures and empiric antibiotics.[2,3] Prompt initiation of antibiotics for infection leads to better outcomes.[1] Consensus recommendations support starting antibiotics within 1 hour of presentation for septic shock and 3 hours for all other infections.[1,4] However, unnecessary lumbar punctures, antibiotics, and hospital admissions are not without risks and can be costly, potentially harmful, and could lead to antimicrobial resistance and adverse effects.[5] Previous studies have developed criteria and algorithms for identifying patients at low risk for invasive bacterial infections.[1] Furthermore, advances in laboratory testing have led to more rapid identification of pathogens, and measurement of more specific inflammatory markers have improved the identification of infants at low risk for invasive bacterial infection.

Previously, a national guideline did not exist to guide treatment of febrile infants, and practice was largely based on expert opinion. In 2021, the American Academy of Pediatrics (AAP) released evidence-based guidelines to address evaluation and management of well-appearing, term infants 8 to 60 days old presenting with a fever and no evident source of infection.[5] The

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guideline recommends deferral of lumbar puncture and/or initial antibiotics in certain patients 22 to 60 days old, along with shared decision-making with the patient's caregivers. This study sought to evaluate the impact of implementing the guideline by comparing the incidence of invasive bacterial infection and/or need for escalation of care in febrile infants 22 to 60 days old before and after guideline implementation who did and not receive antibiotics, respectively.

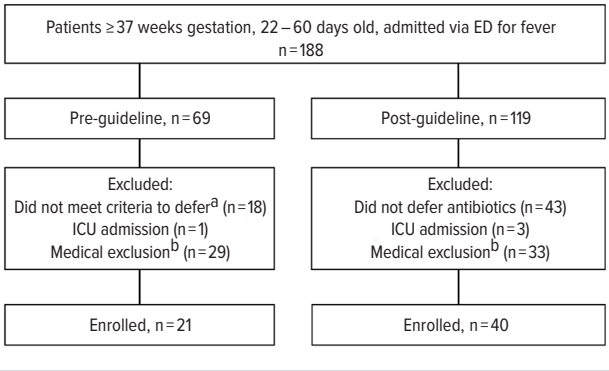
METHODS

This is a single-center, quasi-experimental study conducted at a 298-bed freestanding, academic children's hospital. Well-appearing patients 22 to 60 days old and at least 37 weeks gestation admitted through the ED for fever were included. An institutional guideline was created in 2021 that incorporated the AAP recommendations; well-appearing infants with no evident source of infection were candidates to be monitored without administration of antibiotics. We compared outcomes during a pre-guideline phase (January 1, 2020, through December 31, 2020) and a post-guideline phase (January 1, 2022, through December 31, 2022), with a washout period between when the guideline was being discussed and developed. Patients with confirmed or suspected herpes simplex virus infection, focal bacterial infection, clinical bronchiolitis, congenital or chromosomal abnormalities, or who were immunocompromised were excluded as outlined in the AAP guideline. Patients admitted to an intensive care unit (ICU) were excluded, as these patients were "ill-appearing" by guideline definition and did not qualify for antibiotic deferral. Infants who received antibiotics prior to admission also were excluded. Fever was defined as temperature ≥ 38 °C.

Patient demographics, laboratory, microbiologic, and clinical data were abstracted from the electronic health record. Patient demographics included age at admission, gestational age, and sex. Laboratory values collected included urinalysis, cerebrospinal fluid (CSF) analysis, and inflammatory markers (procalcitonin, C-reactive protein, absolute neutrophil count [ANC], and total white blood cell count). The urinalysis was considered positive if there were positive nitrites, leukocyte esterase, or greater than 5 white blood cells per high power field in the urine. Microbiologic data collected included blood, urine, and CSF cultures (if lumbar puncture was performed). Organisms considered contaminants by the medical team as documented in the electronic health record, such as coagulase negative *Staphylococci,* and urine cultures with less than 100 000 colony forming units were considered negative. Finally, antibiotic regimens, duration of therapy, length of hospital stay, readmission within 7 days of discharge with initiation of antibiotics for presumed or confirmed bacterial infection, and mortality within 30 days of admission also were reported through manual chart review.

Primary outcomes included (1) rate of invasive bacterial infections, defined as bacterial meningitis or bacteremia, and (2) need for escalation of care, defined as ICU admission, initiation of antibiotics after initial deferral, or readmission to the hospital or ED within 7 days of discharge for a bacterial infection. Secondary endpoints included rate of positive cultures, length of stay, and mortality within 30 days of discharge.

Figure. Consort Diagram



Abbreviations: ED, emergency department; ICU, intensive care unit.
[a]Criteria according to guidelines in accordance with the 2021 American Academy of Pediatric evaluation and management of well-appearing febrile infants 8–60 days old.
[b]Herpes simplex virus, focal bacterial infection, clinical bronchiolitis, congenital or chromosomal abnormalities, or immunocompromised.

The proportions of patients with various demographic or medical characteristics in the 2020 cohort versus the 2022 cohort were compared using chi-square tests or Fisher exact tests. Continuous/numeric variables (eg, age, antibiotic duration) were compared using *t* tests (not assuming equal variance). Statistical analysis was performed using IBM SPSS Statistics version 20.0 (IBM Corp, Armonk, New York). This study was reviewed by the Institutional Review Board and determined to be nonhuman subject research.

RESULTS

A total of 188 admitted patients from 22 to 60 days old were screened for inclusion; 21 met inclusion for deferral of antibiotics in the pre-guideline group and 40 in the post-guideline group (Figure). Baseline characteristics were similar between the groups (Table 1), except infants in the pre-guideline group were older than the post-guideline group (41 vs 33 days, $P = 0.031$).

Incidence of invasive bacterial infection was similar between the 2 groups (0 vs 1, $P = 1$) (Table 2). Likewise, need for escalation of care was similar ($P = 0.084$). Infants in the post-guideline group had fewer lumbar punctures performed compared to the pre-guideline group ($P < 0.001$). There were no deaths in either group. There was no difference in the number of positive cultures ($P = 0.541$). Length of stay was similar between groups ($P = 0.926$).

DISCUSSION

Our data suggest that deferring antibiotics in well-appearing febrile infants aged 22 to 60 days did not result in negative outcomes,

Table 1. Baseline Characteristics

	2020 Cohort (N = 21)	2022 Cohort (N = 40)	*P* value
Age (days), mean (SD)	40.76 (13.10)	33.13 (11.60)	0.031
22 – 28 days old, n (%)	8 (38.1)	23 (57.5)	0.150
29 – 60 days old, n (%)	13 (61.9)	17 (42.5)	
Gestational age (weeks), mean (SD)	38.38 (1.16)	38.58 (0.81)	0.500
Female, n (%)	10 (47.6)	15 (37.5)	0.445
Concomitant viral infection, n (%)	8 (38.1)	8 (20)	0.127
Maximum temperature, mean (SD)	38.26 (0.49)	38.35 (0.65)	0.576
White blood cell count, mean (SD)	9.94 (6.74)	9.49 (3.94)	0.781
Absolute neutrophil count, mean (SD)	4341.8 (4220.6)	3497.2 (2347.5)	0.403
Deferred initial antibiotics, n (%)	2 (9.5)	40 (100)	< 0.001

Table 2. Endpoints

	2020 Cohort (N = 21)	2022 Cohort (N = 40)	*P* value
Composite, escalation of care	0	7 (17.5)	0.084
ICU admission, n (%)	0	0	NA
ED or hospital within 7 days, n (%)	0	1 (2.5)	1.00
Initiation of antibiotics,[a] n (%)	0	6 (15.0)	1.00[b]
Lumbar puncture performed, n (%)	19 (90.5)	12 (30.0)	< 0.001
Invasive bacterial infection	0	1 (2.5)	1.00
Positive culture[c]	0	2	0.541
Blood, n (%)	0	0	NA
CSF or Biofire,[d] n (%) (n = 33)	0	1 (8.3)	0.364
Urine, n (%)	0	2 (5.0)	0.541
Length of stay (hours), mean (SD)	42.81 (11.99)	42.35 (26.68)	0.926
Mortality, n (%)	0	0	NA

Abbreviations: ICU, intensive care unit; ED, emergency department; CSF, cerebrospinal fluid.

[a]Among patients initially deferred antibiotics.

[b]Not applicable excluded.

[c]Contaminants excluded.

[d]Among patients with a lumbar puncture performed.

including invasive bacterial infections and need for escalation of care. Though not statistically significant, 6 patients in the post-guideline group had antibiotics initiated after initial deferral. One infant had an invasive bacterial infection with a positive CSF polymerase chain reaction (PCR) panel for *Haemophilus influenzae*, as well as a positive urine culture with *Escherichia coli*, which was subsequently treated with antibiotics. Another patient started antibiotics for an *Escherichia coli* urinary tract infection. Four patients who started antibiotics after initial deferral had no identified infection source and eventually stopped antibiotics within 48 hours. There was lack of documentation about the decision to start antibiotics in these patients; however, the AAP guideline includes shared decision-making with the patient's caretakers, so this may explain why antibiotics were initiated when they were initially deferred. Although there were no patients in the pre-guideline group who required escalation of care, most patients received antibiotics, which could explain why there were none admitted to the ICU or readmitted within 7 days.

Although patients were younger in the post-guideline cohort, the finding is not clinically relevant. The mean age for both populations falls within the 29- to 60-day-old algorithm per the guideline; therefore, both were assessed with the same criteria to defer initial antibiotics.

The use of inflammatory markers and urinalysis to determine risk stratification of febrile infants has been well described. Previous studies attempting to identify patients at highest risk of invasive bacterial infection were unsuccessful, but they were able to determine which patients were at low risk of infection.[5] Models such as the Boston, Philadelphia, and Rochester criteria as well as the step-by-step approach used clinical and laboratory data such as inflammatory markers and urinalysis to identify low risk patients; these risk stratifications have demonstrated high sensitivities and negative predictive values (>90%) with moderate specificity (20%-60%).[2,3,5] Urinary tract infection is the most common source of bacterial infection in patients with fever, and most will be identified by urinalysis.[2] Only 1 patient in the study who deferred initial antibiotics was identified as having an invasive bacterial infection, which supports the current risk stratification approach defined by the AAP guideline. At our institution, it is common practice for patients with a positive urinalysis in the ED to be started on antibiotics pending final identification and susceptibility results. Therefore, we excluded these patients because they did not defer initial antibiotics at admission.

Bacterial infection is a significant cause of infant morbidity and mortality and is preventable with timely initiation of antibiotics, but over half of patients without an invasive bacterial infection or urinary tract infection will receive unnecessary antibiotics.[1] The risks associated with antibiotics in infants include adverse drug reactions, intravenous line complications such as infection, disruption of the infant's gastrointestinal microbiome, and potential for antimicrobial resistance.[5] The risk-benefit discussion of initiating or deferring antibiotics must be assessed for each patient and further supports guideline recommendations.

There were more lumbar punctures performed in the pre-guideline group, but the ANC – an inflammatory marker used to determine if a patient qualifies for lumbar puncture and/or antibiotic deferral – was not different between groups. Lumbar punctures are invasive and painful procedures that can lead to complications, such as bleeding, infection, and respiratory compromise.[5,6] Our study supports the reduction in lumbar punctures performed based on inflammatory markers.

Although costs were not analyzed in this study, we suspect there was a cost savings due to the decreased number of lumbar punctures and antibiotics used, even with increased collection of procalcitonin. A previous study analyzed costs of incorporating procalcitonin in the evaluation of infants less than 60 days old and found an overall cost savings of about 10% when used to improve risk stratification practices.[7]

A strength of our study was inclusion of patients with COVID-19 and other positive viral PCRs as long as they did not have symptoms of bronchiolitis, which was determined by initiation of the bronchiolitis protocol and electronic heath record documentation. A study of 9841 febrile infants who tested positive for COVID-19 infection found the risk of bacterial co-infection to be low and were less likely to have a bacterial infection compared to those who tested negative for COVID-19.[8]

Limitations of this study include the retrospective design at a single center and including the timeframe of the COVID-19 pandemic. Patient volumes were lower during the COVID-19 pandemic and may have influenced the number of patients included in our study. Additionally, patients with suspected COVID-19 infection were placed in the hospital based on patient care and staffing needs, sometimes including ICU floors—even when not critically ill—thus excluding them from our data. Another limitation includes the small patient population; the estimated incidence of bacteremia and bacterial meningitis in infants is < 2% and < 0.5% respectively, so our study may not have been powered to detect a significant difference.[5] We did not include patients transferred from outside hospitals who otherwise may have qualified, as well as patients who were evaluated in the ED and discharged home; further studies would be needed to assess the impact on this patient population.

CONCLUSIONS

Our findings suggest that initial antibiotic deferral based on the 2021 AAP guideline criteria in well-appearing febrile infants is safe and the rate of invasive bacterial infection is low. Guideline implementation resulted in fewer lumbar punctures and antibiotic use without negatively affecting the incidence of invasive bacterial infections or escalation of care at our children's hospital. Future prospective, randomized controlled trials with a larger sample size are needed to fully investigate the impact of deferred antibiotics in this population.

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