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Authors

Greenhow, Tara
Nguyen, Tran
Young, Beverly
et al.

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CA FIRST (California Febrile Infant Risk Stratification Tool) Algorithm Development in a Learning Health System

Tara L Greenhow, MD^{1,2}; Tran HP Nguyen, MD^{2,3}; Beverly R Young, MD^{2,3}; Madeline J Somers, MPH⁴; Jie Huang, PhD⁴; Amy Alabaster, MS, MPH⁴; David R Vinson, MD^{2,4}; Dustin G Mark, MD^{2,4}; Patrick J Van Winkle, MD^{5,6}; Adam L Sharp, MD, MSc^{6,7}; Mary E Reed, DrPH⁴; Judy Shan, BS⁸; Jennifer Y Zhang, BS⁴; Adina S Rauchwerger, MPH⁴; Dustin W Ballard, MD, MBE^{2,4}

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 TLG, 0000-0002-3480-7895

Abstract

INTRODUCTION: There is considerable variation in the approach to infants presenting to the emergency department (ED) with fever. The authors' primary aim was to develop a robust set of algorithms using community ED data to inform modifications of broader clinical guidance.

METHODS: The authors report the development of California Febrile Infant Risk Stratification Tool (CA FIRST) using key components of the Roseville Protocol (ROS) and American Academy of Pediatrics (AAP) Clinical Practice Guideline (CPG). Expanded guidance was derived using a retrospective analysis of a cohort of 3527 febrile infants aged 7–90 days presenting to any Kaiser Permanente Northern California ED between 2010 and 2019 who underwent a core febrile infant evaluation.

RESULTS: Melding ROS and AAP CPG algorithms in infants 7–60 days old, CA FIRST Algorithms had comparable performance characteristics to ROS and AAP CPG. CA FIRST enhancements included guidance on febrile infants 61–90 days old, high-risk infants, infants with bronchiolitis, and infants who received immunizations within the prior 48 hours. This retrospective analysis revealed that of 235 febrile infants 22–90 days old with respiratory syncytial virus and 221 who had fever in the 48 hours following vaccination, there were no cases of invasive bacterial infection.

DISCUSSION: CA FIRST is a set of 13 algorithms providing a thoughtful and flexible approach to the febrile infant while minimizing unnecessary interventions.

CONCLUSIONS: CA FIRST Algorithms empower clinicians to manage most febrile infants. Algorithms are being modified as new data become available, imparting useful and ever-current educational information within a learning health care system.

Corresponding Author

Tara L Greenhow, MD
tara.greenhow@kp.org

Author Affiliations

¹Division of Infectious Diseases, Department of Pediatrics, Kaiser Permanente Northern California, San Francisco, CA, USA

²The Permanente Medical Group, Oakland, CA, USA

³Department of Hospital Pediatrics, Kaiser Permanente Northern California, Roseville, CA, USA

⁴Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA

⁵Department of Pediatrics, Kaiser Permanente Southern California, Anaheim, CA, USA

⁶Kaiser Permanente Bernard J. Tyson School of Medicine, Health Systems Science Department, Pasadena, CA, USA

⁷Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA

⁸School of Medicine, University of California, San Francisco, CA, USA

Author Contributions

Tara L Greenhow, MD, conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript. Dustin W Ballard, MD, MBE, Tran HP Nguyen, MD, Beverly R Young, MD, and David R Vinson, MD, conceptualized and designed the study, collected data, and critically reviewed and revised the manuscript. Dustin G Mark, MD, Patrick J Van Winkle, MD, Mary E Reed, DrPH, and Adam L Sharp, MD, MSc, conceptualized and designed the study and critically reviewed and revised the manuscript. Madeline J Somers, MPH, Jie Huang, PhD, and Amy Alabaster, MS, MPH, conceptualized and designed the study, designed the data collection instruments, coordinated data collection, conducted the initial analyses, and reviewed and revised the manuscript. Judy Shan, BS, Jennifer Y Zhang, BS, and Adina S Rauchwerger, MPH, assisted in conceptualizing and designing the study, coordinated data collection, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Disclosures

Conflicts of Interest: None declared

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Introduction

Adverse outcomes may occur when a febrile young infant has an unrecognized and untreated invasive bacterial infection (IBI; bacteremia and bacterial meningitis).^{1,2} It is imperative that clinicians recognize and empirically treat infants at high risk for IBI while also minimizing unnecessary interventions for low-risk infants. In 2016 Kaiser Permanente Roseville Women and Children's Medical Center successfully piloted a protocol for the management of febrile infants first presented at the Clinical Pediatric Hospital Medicine Conference (San Diego, January 16–18, 2015). The Roseville Protocol³ (ROS) was based on the Rochester Protocol^{4,5} with two modifications: infants aged 7–28 days with temperature < 38.5°C were considered as high risk for IBI and underwent full evaluation to include blood, urine, and cerebrospinal fluid (CSF) cultures, and infants aged 29–60 days with positive urinalysis but low-risk laboratory results were discharged home on oral antibiotics without lumbar puncture (LP).³ Using retrospective analyses, these algorithms were validated with Kaiser Permanente Northern California infants with excellent outcomes. ROS was comparably sensitive and specific to existing Rochester,^{4,5} Philadelphia,⁶ and Boston⁷ protocols for IBIs in febrile infants 7–60 days old while allowing for fewer invasive procedures and hospitalizations in infants ≥ 29 days old.³

After 16 years of deliberation, the American Academy of Pediatrics (AAP) in August 2021

published a Clinical Practice Guideline (CPG) on the approach to the febrile infant 8–60 days old.⁸ This CPG differed from ROS in several ways, with the most notable differences in risk stratification and assessment. The AAP CPG denoted all febrile infants aged 8–21 days high risk, requiring them to undergo an LP, receive parenteral antibiotics (PAbx), and be admitted to the hospital. Compared to other published protocols,^{3–7} the AAP CPG used different definitions of high-risk inflammatory markers (IMs) and included the use of procalcitonin and C-reactive protein in infants 22–60 days old. Procalcitonin specifically is not widely available with rapid turnaround in community settings, which limits the benefit from the AAP CPG.⁹

The authors report the development of a robust set of algorithms that merged and expanded upon both the ROS and the AAP CPG, including several common clinical scenarios not addressed by either and additionally incorporating setting-specific risk estimates. The amalgamation of expanded guidance is titled the California Febrile Infant Risk Stratification Tool (CA FIRST).

Methods

This evidence-based initiative was approved by the Kaiser Permanente Northern California Institutional Review Board. Informed consent was waived.

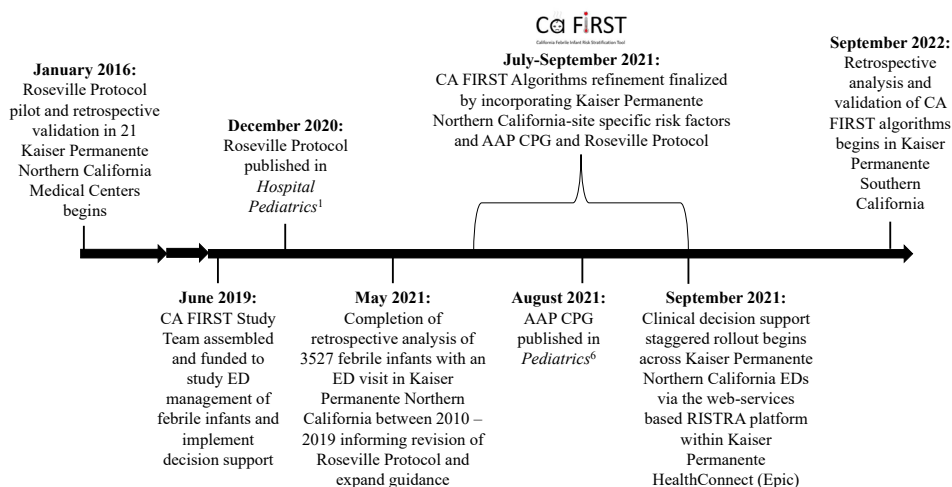


Figure 1: Timeline of CA FIRST. AAP = American Academy of Pediatrics; CA FIRST = California Febrile Infant Risk Stratification Tool; CPG = Clinical Practice Guideline; ED = emergency department; RISTRA = Risk STRAtification.

History	
Not previously well	Premature infants < 37 wk gestational age; infants younger than 14 d of age whose perinatal courses were complicated by maternal fever, infection, and/or antimicrobial use (excluding surgical prophylaxis or treatment of Group B <i>Streptococcus</i> colonization); infants 7–60 d old with increased herpes simplex virus risk; infants with documented or suspected immune compromise; infants whose neonatal course was complicated by surgery or infection; infants with congenital or chromosomal abnormalities; medically fragile infants requiring some form of technology or ongoing therapeutic intervention to sustain life.
Recent immunization	Received immunizations within the 48 h prior to onset of fever.
Clinical Findings	
Fever	“Retrospective” = any measured temperature $\geq 38^{\circ}\text{C}$ in a medical setting, either within 4 h of arrival to a Kaiser Permanente Northern California ED, or in clinic within the 12 h prior to arrival to the ED. “Prospective” = any measured temperature $\geq 38^{\circ}\text{C}$.
Ill appearance	One of the following documented in a physical examination or assessment: “cold,” “decreased mental status,” “difficult to arouse,” “floppy,” “hypotonic,” “ill-appearing,” “inconsolable,” “irritable,” “listless,” “toxic,” “nonresponsive,” “lethargic,” “poorly perfused,” “sick,” “shock.”
Laboratory results	
Abnormal urinalysis	< 5 WBCs per hpf, positive for leukocyte esterase, or positive for nitrites.
High-risk IMs	Abnormal WBC count (< 5000 cells/mm ³ , < 15,000 cells/mm ³), absolute band count < 1500 cells/mm ³ or, in infants 7–28 d old, fever < 38.5°C ⁵
Infections	
Apparent infection	Focal bacterial infections (eg, mastitis, omphalitis), clinical bronchiolitis with or without positive tests for respiratory syncytial virus, COVID-19, or high suspicion of herpes simplex virus infection (eg, vesicles, seizures).
Urinary tract infection	Isolation of a single urinary bacterial pathogen with colony count $\geq 50,000$ CFUs/mL.
Bacteremia	Isolation of a bacterial pathogen from blood. Commensal organisms typically found on the skin (eg, coagulase-negative <i>Staphylococcus</i>) were considered contaminants unless obtained from two or more cultures and treated by a clinician as a pathogen.
Bacterial meningitis	“Definite” with the isolation of a single bacterial pathogen from CSF or “probable” with sterile CSF with pleocytosis (CSF WBC ≥ 20 cells/hpf) obtained after antibiotics with diagnosis confirmed by a pediatric infectious disease specialist, according to criteria outlined by Schnadower 2011. ¹⁰ Infants who did not undergo LP were presumed not to have bacterial meningitis.

Table 1: Definitions of California Febrile Infant Risk Stratification Tool clinical findings, laboratory studies, and infections

CFU = colony forming unit; CSF = cerebral spinal fluid; ED = emergency department; hpf = high powered field; IM = inflammatory marker; LP = lumbar puncture; WBC = white blood cell.

In June 2019, a collaboration between emergency department (ED) physicians, pediatricians, pediatric infectious disease specialists, and data scientists in Kaiser Permanente Northern and Southern California was established. The CA FIRST Study Team was assembled and funded to study the ED management of febrile infants and implement electronic health record decision support to improve and standardize patient care (Figure 1). The authors’ overarching goal was to assimilate the best available evidence and the authors’ setting-specific data to create and validate a set of algorithms that expanded upon what was more broadly available. Building upon the prior validation of ROS within Kaiser Permanente Northern California, the CA FIRST Study Team performed a retrospective analysis of infants with a measured temperature $\leq 38.0^{\circ}\text{C}$ seen in the ED within an integrated health care system of 21 medical centers from 2010 to 2019 who had undergone a core febrile infant evaluation (urinalysis, complete blood count, and blood and

urine cultures), which was completed in May 2021. In July–September 2021, these algorithms, branded CA FIRST, were finalized by incorporating Kaiser Permanente Northern California site-specific risk factors, modifying ROS, and incorporating elements of AAP CPG. Definitions of CA FIRST clinical findings, laboratory studies, IMs, and infections are outlined in Table 1. CA FIRST Algorithms also provided targeted decision support for specific scenarios not addressed by ROS or AAP CPG. Specifically, neither of these protocols address the approach to febrile infants who 1) are 61–90 days old, 2) are high-risk/not previously well, 3) have bronchiolitis, or 4) received immunizations within the prior 48 hours. CA FIRST Algorithms recommending invasive interventions were created for high-risk infants, including additional guidance on ill-appearing infants. For those with signs of sepsis, the CA FIRST Study Team collaborated with pediatric Intensive Care Unit colleagues to provide comprehensive care via a separate algorithm.

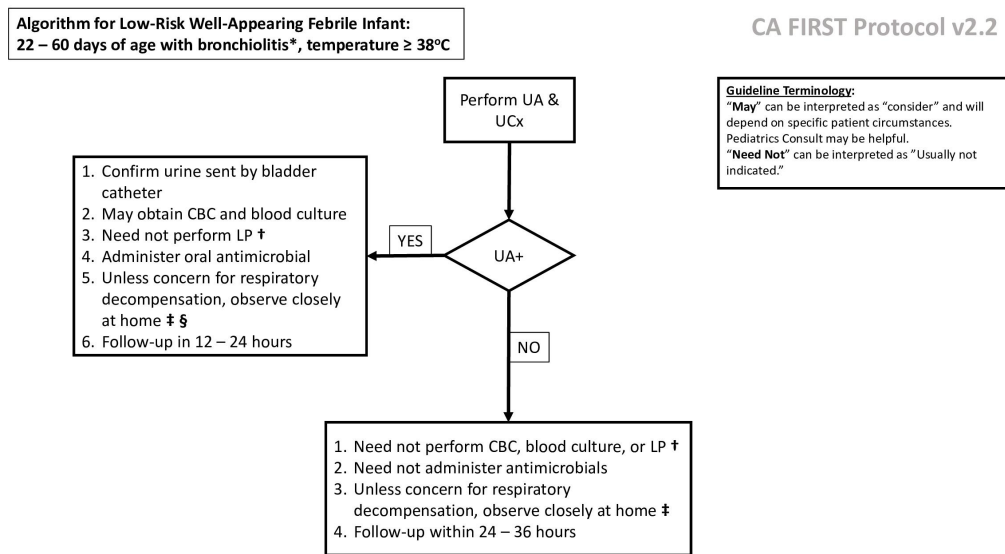


Figure 2: CA FIRST algorithm for low-risk, well appearing, febrile infants 22–60 days of age with bronchiolitis.

* The AAP guidance excludes infants with RSV and / or clinical bronchiolitis

† Bacterial meningitis is rare in RSV + bronchiolitis

‡ Clinicians may manage infants at home if ALL following criteria are met: 1) Verbal teaching and written instructions have been provided for monitoring throughout the period at home, 2) Follow-up plans for re-evaluation have been developed and are in place, 3) Plans have been developed and are in place in case of change in clinical status, including means of communication between family and providers and access to emergency medical care

§ If observed at home, then recommend prescription for oral antimicrobial to treat presumed UTI.

CBC = complete blood count; LP = lumbar puncture; RSV = respiratory syncytial virus; UA = urinalysis; UCx = urine culture; UTI = urinary tract infection

PUBLICATION AND DISSEMINATION WITHIN KAISER PERMANENTE

CA FIRST was vetted with internal and external experts, a process that included multiple presentations to pediatric infectious diseases, pediatric hospital medicine, and ED practitioners. In September 2021, clinical decision support staggered rollout began across Kaiser Permanente Northern California EDs via the web services-based Risk STRatification (RISTRA) platform within Kaiser Permanente HealthConnect (Epic-Care; Figure 1). In March 2022, CA FIRST Algorithms were published on the Kaiser Permanente Clinical Library (Figure 2, example of one of the 13 algorithms). In September 2022, retrospective analysis of a febrile infant cohort began in Kaiser Permanente Southern California to validate CA FIRST. Prospective data collection via the RISTRA platform is ongoing.

STATISTICAL ANALYSIS

Inclusion/exclusion criteria and performance characteristics (eg, sensitivity/specificity) were stratified by age groups. In terms of intensity of evaluation, CA FIRST and AAP CPG provided several conditional recommendations for further testing based on clinical discretion using either the terms “may” or “need not.” When clinical discretion allowed that an intervention “may” be performed, the data were analyzed twice—as if the most conservative choices were selected, and as if the least conservative choices were selected—and the results of both analyses were reported as a range. When clinical discretion allowed that an intervention “need not” be performed, the data were analyzed to include the least conservative option. Most conservative was defined as pursuing the most invasive interventions, and least conservative was defined as

CA FIRST Algorithms	Age (d)			
	7-21	22-28	29-60	61-90
Melded ROS and AAP CPG				N/A
Inclusion	Well appearance			
Exclusion	Not previously well; apparent infection			
			Recent immunization	
Expanded guidance				
Older infants	N/A			
Inclusion				
Exclusion	Well appearance Not previously well; apparent infection; recent immunization			
High-risk infants				
Inclusion	Ill appearance and/or not previously well			
Exclusion	Bronchiolitis; COVID-19			
			Recent immunization	
Infants with bronchiolitis				
Low-risk				
Inclusion	Bronchiolitis; well appearance			
Exclusion	Not previously well; apparent infection other than bronchiolitis			
High-risk	N/A			N/A
Inclusion		Bronchiolitis; well appearance; not previously well		
Exclusion		COVID-19		
			Recent immunization	
Recent immunizations	N/A			
Inclusion				
Exclusion	Recent immunization; well appearance Not previously well			

Table 2: Inclusion and exclusion criteria by age for California Febrile Infant Risk Stratification Tool Algorithms

AAP = American Academy of Pediatrics; CA FIRST = California Febrile Infant Risk Stratification Tool; CPG = Clinical Practice Guideline; N/A = not applicable; ROS = Roseville Protocol.

pursuing the fewest invasive interventions. Confidence intervals (CIs) were reported at 95%. All analyses were conducted in SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

CA FIRST was a revised ROS protocol incorporating key components of AAP CPG and expanding guidance beyond it. Thirteen algorithms were created to give management advice to clinicians in the evaluation of the vast majority of febrile infants (Table 2). CA FIRST incorporated the AAP CPG enhanced guidance regarding need for urinary catheterization, assessment of herpes simplex virus risk, recommendations for clinical decision making (eg, “may” or “need not”), and optimal timing of follow-up in infants discharged home from the hospital.

CA FIRST revised the ROS approach to the well-appearing, previously well infant aged 7–60 days without apparent infection or immunizations within the prior 48 hours. The sensitivity, specificity, and positive and negative predictive value of IBI and percentage of infants recommended to undergo invasive interventions for CA FIRST were comparable to published ROS and AAP CPG values^{3,8,9} (Table 3). (Performance characteristics of the AAP CPG were calculated using absolute neutrophil count < 5200/mm³ and temperature < 38.5°C as IMs.) CA FIRST performed fewer LPs and administered fewer PAbx in infants 7–60 days old compared to AAP CPG, but admitted more infants aged 7–28 days compared to ROS.

“Expanded guidance” was derived using a retrospective analysis of 3527 febrile infants ages 7–90 days between 2010 and 2019 with a core febrile infant evaluation.

Age (d)	N	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive value % (95% CI)	Negative predictive value % (95% CI)	Invasive interventions		
						LP	PAbx	Admit
7-21	292	95 (77-100)	27 (22-33)	10 (6-14)	99 (93-100)	75-100	75-100	100
22-28	180	100 (66-100)	32 (25-40)	7 (4-14)	100 (93-100)	70	47-70	100
29-60	940	90 (73-98)	56 (53-59)	6 (4-9)	99 (98-100)	0-29	15-29	0-29

Table 3: Performance characteristics and invasive interventions of California Febrile Infant Risk Stratification Tool

Admit = Admitted; CI = confidence interval; LP = lumbar puncture; PAbx = parenteral antibiotics.

INFANTS WITH HIGH-RISK UNDERLYING CONDITIONS OR ILL-APPEARING

Infants with high-risk underlying conditions were a diverse group with increased risk overall compared to those who were previously well. Infants with ill appearance were at the highest risk for IBI. Chance of IBI for ill-appearing infants aged 7-28 days, 29-60 days, and 61-90 days was 10%, 8%, and 7%, respectively. Risk for bacterial meningitis was 4%, 2%, and 4%, respectively.

LOW-RISK INFANTS

Febrile infants with bronchiolitis or those who received immunizations and developed fever within the following 48 hours were low risk. Among 235 infants 22-90 days old with respiratory syncytial virus, there were no cases of IBI. Fever in the 48 hours following vaccination was also a low-risk scenario with no cases of IBI in 221 infants (Table 4).

Discussion

Fever in a medical setting is common and occurs in 1.4% of infants ages 7-90 days.¹¹ CA FIRST is a reasonable approach to febrile infants that merged ROS and AAP CPG algorithms and imparted expanded guidance. It was created within a learning health care system, using pragmatic implementation of clinical decision support and evidence suggesting setting-specific risk differences in febrile infant outcomes. The development of this clinical guidance is an iterative process, with a flexible set of algorithms reviewed by key stakeholders within Kaiser Permanente Northern and Southern California.

Low-risk condition	Age (d)		Total
	22-60	61-90	
Bronchiolitis	0/119	0/116	0/235
Immunizations in prior 48 h	0/94	0/127	0/221

Table 4: Invasive bacterial infection in febrile infants 22-90 days old with bronchiolitis or immunization in the preceding 48 hours

In the authors' internal data, CA FIRST had comparable sensitivity, specificity, and positive and negative predictive values to both ROS and AAP CPG.^{3,9} It recommended fewer LPs and administered fewer PAbx in infants 7-60 days old compared to AAP CPG, but it admitted more infants 7-28 days old to the hospital compared to ROS.

Expanded guidance of febrile infants (eg, not previously well/high-risk, ages 61-90 days old, those with bronchiolitis or status post immunizations within prior 48 hours) was created to address content not present in either ROS or AAP CPG. Instead of excluding those infants from a febrile infant algorithm, the authors found it helpful for clinicians to feel empowered to manage these infants. CA FIRST Algorithms recommending invasive interventions were created for high-risk infants, including additional guidance on ill-appearing infants, to provide comprehensive care. Infants with bronchiolitis and those who had received immunizations and developed fever within the following 48 hours were low risk. Viral infections reduce the probability of bacteremia from 2.7% to 1%¹² and rates of IBI were even lower with bronchiolitis with no reported cases of meningitis.¹³⁻¹⁵ The authors recommend fewer LPs, PAbx, and hospital admissions in these low-risk infants, with the goal to minimize harm.

To best inform care, prospective, retrospective, and external algorithm validation studies are underway. As additional data, either through published studies or validation, become available, the RISTRA tool and Kaiser Permanente Clinical Library will be updated in an iterative process. Future areas of validation include febrile infants with COVID-19 and febrile preterm infants.

Conclusions

CA FIRST is a set of thoughtful algorithms that minimize unnecessary interventions and is appropriate for most febrile infants presenting for care to the ED. Algorithms are being modified as new data become

available, imparting useful and ever-current educational information to a variety of clinicians.

Acknowledgments

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