Reducing Excessive Variability in Infant Sepsis Evaluation

Project REVISE

Change Package

(Quality Improvement Toolkit)

OVERVIEW OF Project REVISE CHANGE PACKAGE

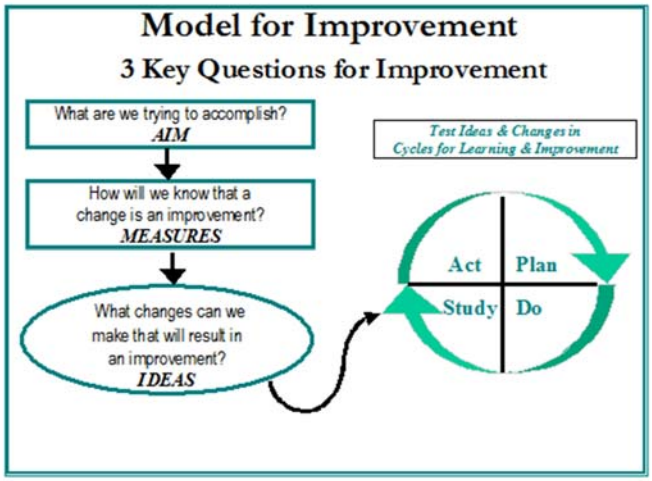
This Change Package (Quality Improvement Toolkit) is designed to provide your quality improvement team with ready-made material that your team can use to initiate improvement efforts as part of the Reducing Excessive Variability in Infant Sepsis Evaluation Project also known as Project REVISE. Over the course of the project, your team and the other teams in the collaborative will be encouraged to refine and repurpose the tools and resources in this change package/toolkit based on further review of the evidence and your own experiences testing and implementing the changes.

This Change Package is based on evidence-based research focused on diagnosis and treatment of infant fever and the local experience of the Project REVISE Expert Group members. The Expert Group has chosen a subset of recommendations from relevant literature for which we have set specific goals in order to offer a framework for your local project. Depending on the particular circumstances in your hospital, you may also need to implement other practices or modify your goals in order to successfully improve outcomes.

The aims and measures in this collection are not necessarily the *only* ones required to achieve the improved outcomes you are targeting. This project is not exhaustive, exclusive, or all-inclusive. Changes in practice will require testing and adaptation to your particular circumstances and context in order to achieve measured improvements in outcomes. As you test and implement new processes, you will monitor the results closely to ensure that you are obtaining the desired outcome, that no harm is being done, and that no unanticipated results or consequences emerge. In addition to the evidence-based measures, we have also provided some balancing measures to assess in order to help with the process of avoiding unanticipated consequences. Establishing sustainability efforts in order to promote continuous quality improvement (CQI) will be crucial for success as well.

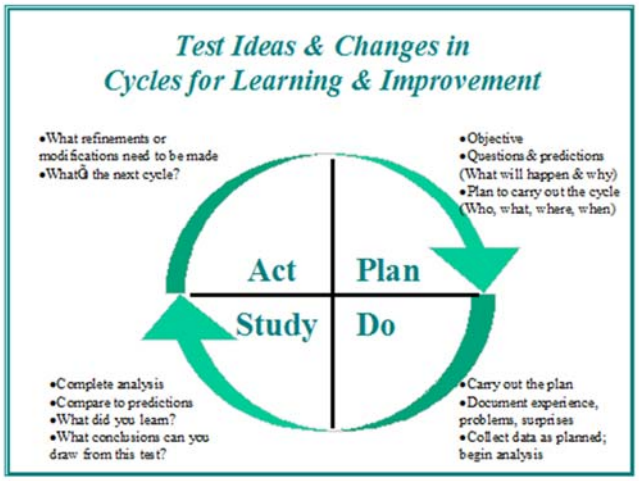
Model for Improvement

One theoretical basis for promoting change in healthcare is the Model for Improvement. We recommend the Model for Improvement[1] as a framework for your efforts. The three key questions of the Model for Improvement are:



Quality Improvement Elements

For Project REVISE, the following four items will be quality improvement elements which we will support: 1) clearly identified aims; 2) targeted measures; 3) planned changes; and 4) cycles of action - Plan-Do-Study-Act (PDSA)



Thank you for your participation in this important systemic change to improve the management of febrile infants in the hospital setting.

Project REVISE Expert Group

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[1] Langley, Nolan, Norman, and Lloyd P. Provost. *The Improvement Guide: A Practical Approach to Enhancing Organizational Performance*. New York: Jossey-Bass Inc., 1996

Reducing Excessive Variability in Infant Sepsis Evaluation – Project REVISE
Change Package Table of Contents

Project REVISE Sample Order Set: Febrile Infant 7 – 28 Days

SCOPE:

Inclusion Criteria:

- Otherwise healthy infants with documented or parent reported fever (Temp ≥38C or 100.4F)
- Age 7-60 days

Exclusion Criteria:

- Evidence of focal infection
- Significant chronic comorbid condition (e.g. congenital heart disease, neuromuscular disease, genetic/chromosomal abnormality, lung disease, etc.
- Severe ill-appearance or need for ICU care

Febrile Infant 7-28 Days Emergency Department Order Set

☒Initial Evaluation (all infants)

☒Vital Signs/Monitoring

Call provider if:

☒ HR: 80 – 205

☒RR: 30 – 60

☒SBP <60

☒Oxygen saturation <90%

☒Nutrition (check one):

☐Formula: _____ (type); _____ (ounces); every _____ (hours)

☐Breast Milk

☐Mother's tray (if mom breastfeeding)

☐NPO

☒Nursing (check all that apply)

☐ Lumbar puncture set up

☐ Suction by nurse prn

☐ IV placement

☐ Saline lock

☒Laboratory/Radiology Evaluation

☒Urinalysis and urine culture via catheter

☒CBC with differential/band count

☒Blood culture

☐C-reactive protein (if procalcitonin not available)

☐Serum procalcitonin

☐ If respiratory symptoms:

☐Rapid RSV

☐Rapid influenza

☐Respiratory viral panel

☐Chest X-ray

Additional evaluation (recommended for all high-risk infants and infants who will receive antibiotics):

☐Cerebrospinal fluid studies:

☐Cell count and differential

☐Protein

☐Glucose

☐Bacterial culture

☐Enterovirus PCR

☐Gram Stain (GS)

For Infants at Risk for HSV (see HSV checklist):

☐Basic metabolic panel/Chem 7
☐Hepatic Function Panel
☐HSV 1/2 CSF PCR
☐HSV 1/2 serum PCR
☐Viral surface culture for HSV Site: conjunctiva, eye
☐Viral surface culture for HSV Site: mouth
☐Viral surface culture for HSV Site: perianal
☐Viral surface culture for HSV Site: vesicle (if present)

Medications

☐ Ampicillin 50mg/kg, IV, one time only
☐ Cefotaxime 50mg/kg IV, one time only
☐ Gentamicin 4mg/kg IV, one time only
☐ Acyclovir 20mg/kg IV, one time only

Febrile Infant 7-28 Days Inpatient Order Set

☒Initial Evaluation (all infants)

☒Vital Signs/Monitoring
Call provider if:
☒ HR: 80 – 205
☒RR: 30 – 60
☒SBP <60
☒Oxygen saturation <90%

☒Nutrition (check one):
☐Formula: _____ (type); _____ (ounces); every _____ (hours)
☐Breast Milk
☐Mother's tray (if mom breastfeeding)
☐NPO

☒Nursing (check all that apply)
☐ Lumbar puncture set up
☐ Suction by nurse prn
☐ IV placement
☐ Saline lock

☐Laboratory/Radiology Evaluation
☐Urinalysis and urine culture via catheter
☐CBC with differential/band count
☐Blood culture
☐C-reactive protein (if procalcitonin not available)
☐Serum procalcitonin
☐ If respiratory symptoms:
☐Rapid RSV
☐Rapid influenza
☐Respiratory viral panel
☐Chest X-ray

Additional evaluation (recommended for all high-risk infants and infants who will receive antibiotics):

☐Cerebrospinal fluid studies:

- ☐Cell count and differential
- ☐Protein
- ☐Glucose
- ☐Bacterial culture
- ☐Enterovirus PCR

For Infants at Risk for HSV (see HSV checklist):

☐Basic metabolic panel/Chem 7
☐Hepatic Function Panel
☐HSV 1/2 CSF PCR
☐HSV 1/2 serum PCR
☐Viral surface culture for HSV Site: conjunctiva, eye
☐Viral surface culture for HSV Site: mouth
☐Viral surface culture for HSV Site: perianal
☐Viral surface culture for HSV Site: vesicle (if present)

Medications

☐ Ampicillin 50mg/kg, IV, q6H
☐ Cefotaxime 50mg/kg IV, q6H
☐ Gentamicin 4mg/kg IV, q24H
☐ Acyclovir 20mg/kg IV, q8H

Project REVISE Sample Order Set: Febrile Infant 29 – 60 Days

SCOPE:

Inclusion Criteria:

- Otherwise healthy infants with documented or parent reported fever (Temp ≥38C or 100.4F)
- Age 7-60 days

Exclusion Criteria:

- Evidence of focal infection
- Significant chronic comorbid condition (e.g. congenital heart disease, neuromuscular disease, genetic/chromosomal abnormality, lung disease, etc.
- Severe ill-appearance or need for ICU care

Febrile Infant 29-60 Days Emergency Department Order Set

☒Initial Evaluation (all infants)

☒Vital Signs/Monitoring

Call provider if:

☒ HR: 80 – 205

☒RR: 30 – 60

☒SBP <70

☒Oxygen saturation <90%

☒Nutrition (check one):

☐Formula: _____ (type); _____ ounces; every _____ hours

☐Breast Milk

☐Mother's tray (if mom breastfeeding)

☐NPO

☒Nursing (check all that apply)

☐ Lumbar puncture set up

☐ Suction by nurse prn

☐ IV placement

☐ Saline lock

☒Laboratory/Radiology Evaluation

☒Urinalysis and urine culture via catheter

☒CBC with differential/band count

☒Blood culture

☐C-reactive protein (if procalcitonin not available)

☐Serum procalcitonin (if available)

☐ IF respiratory symptoms:

☐Rapid RSV

☐Rapid influenza

☐Respiratory viral panel

☐Chest X-ray

Additional evaluation (recommended for all high-risk infants and infants who will receive antibiotics):

☐Cerebrospinal fluid studies:

- ☐Cell count and differential
- ☐Protein
- ☐Glucose
- ☐Bacterial culture
- ☐Enterovirus PCR
- ☐Gram Stain (GS)

For Infants at Risk for HSV (see HSV checklist for infants 29-60 days old):

☐Basic metabolic panel/Chem 7
☐Hepatic Function Panel
☐HSV 1/2 CSF PCR
☐HSV 1/2 serum PCR
☐Viral surface culture for HSV Site: vesicle (if present)

Medications

☐ Ampicillin 50mg/kg, IV, one time only
☐ Cefotaxime 50mg/kg IV, one time only
☐ Ceftriaxone 50mg/kg IV, one time only
☐ Gentamicin 4mg/kg IV, one time only
☐ Acyclovir 20mg/kg IV, one time only

Febrile Infant 29-60 Days Inpatient Order Set

☒Initial Evaluation (all infants)

- ☒Vital Signs/Monitoring

  Call provider if:

  - ☒ HR: 80 – 205
  - ☒RR: 30 – 60
  - ☒SBP <70
  - ☒Oxygen saturation <90%
- ☒Nutrition (check one):
  - ☐Formula: _____ (type); _____ ounces; every _____ hours
  - ☐Breast Milk
  - ☐Mother's tray (if mom breastfeeding)
  - ☐NPO
- ☒Nursing (check all that apply):
  - ☐ Lumbar puncture set up
  - ☐ Suction by nurse prn
  - ☐ IV placement
  - ☐ Saline lock
- ☐Laboratory/Radiology Evaluation:
  - ☐Urinalysis and urine culture via catheter
  - ☐CBC with differential/band count
  - ☐Blood culture
  - ☐C-reactive protein (if procalcitonin not available)
  - ☐Serum procalcitonin
  - ☐ If respiratory symptoms:

☐Rapid RSV
☐Rapid influenza
☐Respiratory viral panel
☐Chest X-ray

Additional evaluation (recommended for all high-risk infants and infants who will receive antibiotics):

☐Cerebrospinal fluid studies:
- ☐Cell count and differential
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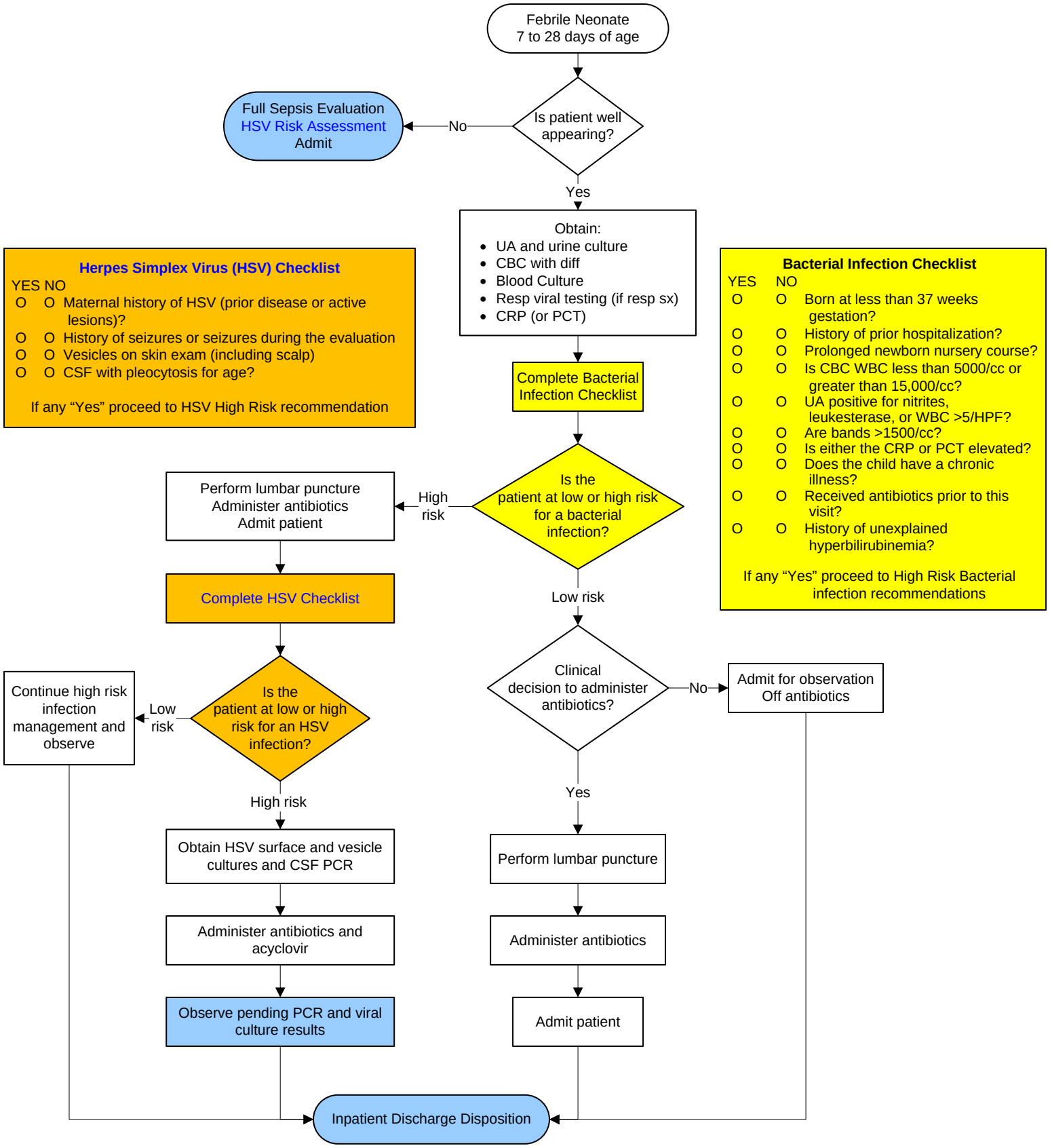
- ☐Glucose
- ☐Bacterial culture
- ☐Enterovirus PCR

For Infants at Risk for HSV (see HSV checklist):

☐Basic metabolic panel/Chem 7
☐Hepatic Function Panel
☐HSV 1/2 CSF PCR
☐HSV 1/2 serum PCR
☐Viral surface culture for HSV Site: vesicle (if present)

Medications:

☐ Ampicillin 50mg/kg, IV, q6H
☐ Cefotaxime 50mg/kg IV, q6H
☐ Ceftriaxone 50mg/kg IV, q12H
☐ Gentamicin 4mg/kg IV, q24H
☐ Acyclovir 20mg/kg IV, q8H



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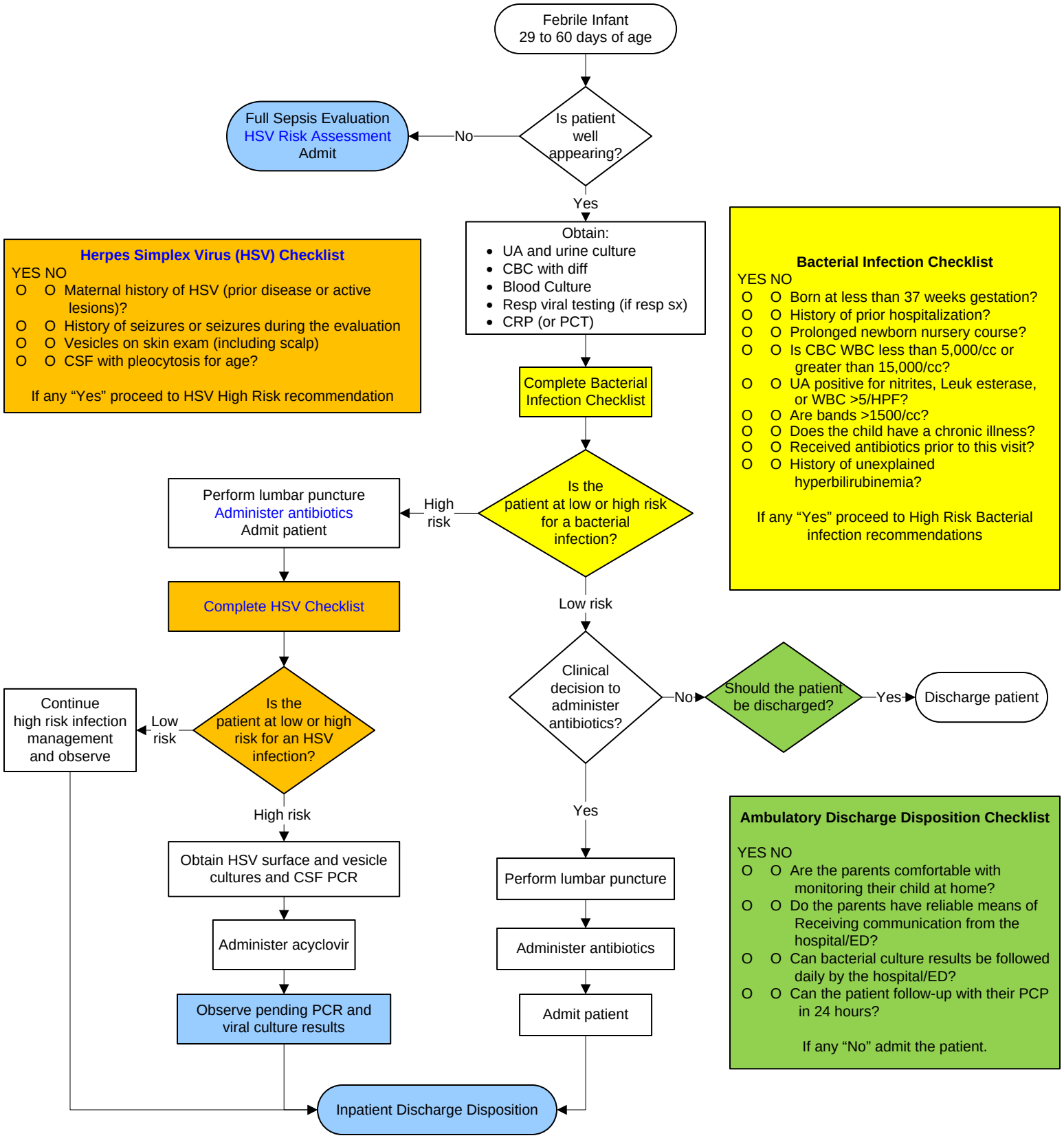

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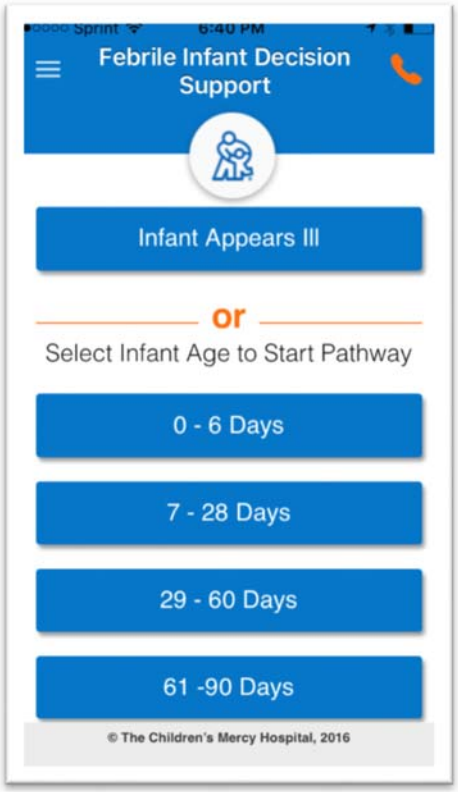
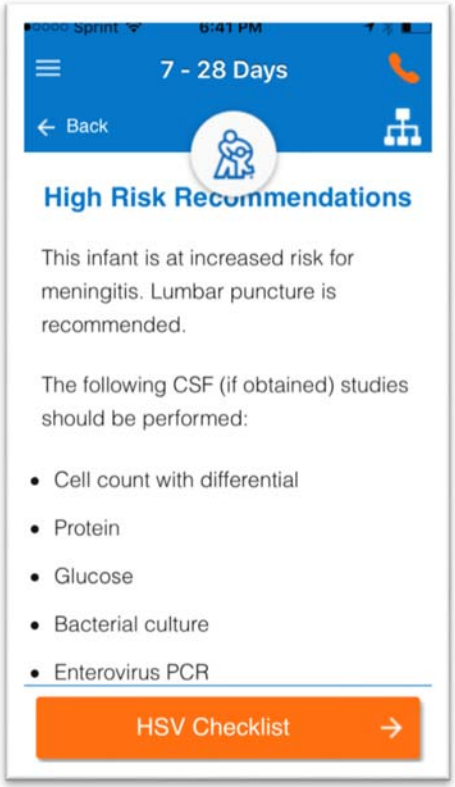
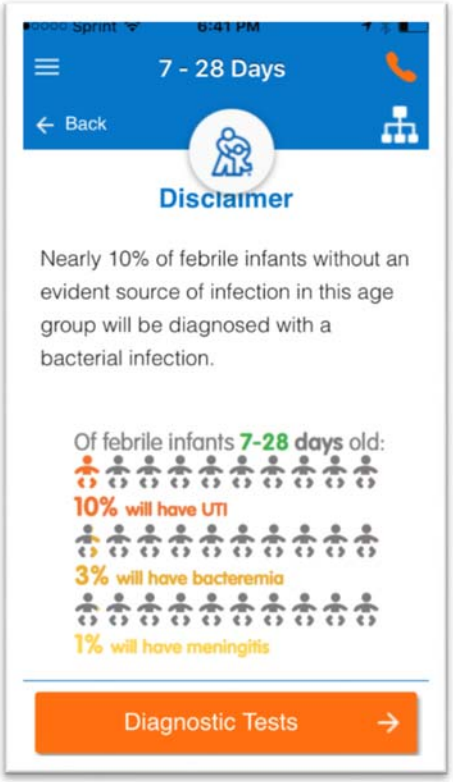
Children's Mercy Fever App

Instructions on how to download the app and use it in practice will be provided during the next live learning session webinar – December 8, 2016. Screenshots of the app are provided below.







Reducing Excessive Variability in Infant Sepsis Evaluation (revise) Quality Improvement Project

Informational Webinar
September 6, 2016
10am PT/11am MT/12pm CT/1pm ET

SLIDES SHARED WITH PERMISSION FROM EBIONDI, KROBERTS, LSCHROEDER "REVISE: INFORMATIONAL WEBINAR" ORIGINALLY PRESENTED 09/06/16 TO THE VIP NETWORK PROJECT REVISE QI PROJECT TEAMS

Agenda

Agenda Item	Presenter
Welcome and introductions	AAP Staff
❑ Background	Roberts
❑ About the VIP Network ❑ Project Aim ❑ Method for setting metrics ❑ Review of metrics ❑ Project Timeline ❑ What to Expect ❑ Change Package ❑ Expert Mentors	Biondi
❑ Team Composition ❑ Site Selection & After Selection ❑ Benefits of participation	Schroeder
❑ Immediate next steps ❑ Contact Information	AAP Staff

Welcome & Introductions: Today's Speakers

Eric Biondi, MD, FAAP
Project Leader
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Kenneth Roberts, MD, FAAP
REVISE Project Advisor

Lisa Schroeder, MD, FAAP
Expert Group Member
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Background

Fever in infants is very common resulting in trips to the hospital and/or emergency room

The clinical management of fever in infants has been a topic of much ambiguity for decades

Despite available research, fever management remains extremely variable from hospital to hospital

This collaborative improvement project seeks to build a national QI collaborative designed to improve and standardize care for febrile infants between the ages of 7 to 60 days

About the Value in Inpatient Pediatrics (VIP) Network

An informal group of pediatric hospitalists

Most research conducted in free-standing children's hospitals attached to academic medical centers; 70% of children are cared for in NON-children's hospitals - these 70% deserve the same access to collaborative data and quality of care afforded in children's hospitals

- Build an inclusive pediatric inpatient collaboration for clinicians in order to provide all hospitalized children the most efficient, safe, and evidence based healthcare
- Begin with addressing overtreatment in pediatrics
- Do so through peer group benchmarking sharing common experiences
- Power of the VIP Network lies in creating *Improvement*
- *Collaboratives* focused on identifying best practices and disseminating knowledge

Project Aim

Provide multi-disciplinary teams with quality improvement education and tools specific to management of children with fever to increase compliance with the evidence-based research and thereby decrease overuse of non-evidence-based therapies and tests.

Determining Project Metrics: Meet the REVISE Expert Group


Eric Biondi, MD, FAAP


Matthew Garber, MD, FAAP


Lisa Schroeder, MD, FAAP


Russell McCulloh, MD, FAAP


Julia Arana, MD, FAAP


Matt Hall, PhD


Jeff Bennett, MD, FAAP


Beth Natt, MD, FAAP


Benj Barsotti, MD, FAAP


Alan Schroeder, MD, FAAP


Jennifer Light, MD, FAAP

Thank you to Kenneth Roberts, MD, FAAP and Robert Pantell, MD, FAAP who served as project advisors!

Inclusion and Exclusion Criteria

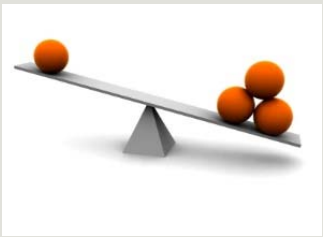
Inclusion Criteria	Exclusion Criteria
• Age 7 through 60 days • Evaluated in site ED or transferred to site inpatient unit from an outpatient setting • Evaluated for fever without a source • Discharged from site ED or inpatient unit	• Infant was not well-appearing on presentation • Co-morbid conditions predisposing to severe or recurrent bacterial illness, including genetic, congenital, chromosomal, neuromuscular, or neurodevelopmental abnormalities. • Transfer to or from site inpatient hospital from another inpatient setting

Project Metrics

- Reduce length of hospitalization for infants who are hospitalized to <30 hours for infants who are low risk and <42 hours for infants who are not low risk (80% target allows for infants who are ultimately diagnosed with bacterial infection as well as extenuating circumstances e.g. parent couldn't pick up until after work)
- Increase the proportion of hospitalized infants who are hospitalized appropriately (90% target)
- Increase the proportion of infants who have a urinalysis (UA) performed via any method of collection on the first day of encounter (95% target)
- Decrease the proportion of infants who get a chest x-ray (CXR) within 24 hours of presentation without documented respiratory symptoms (90% target)
- Increase use of recommended empiric antibiotic regimens within 24 hours of presentation (90% target allows for infants who have labs suggestive of resistant infections)

Balancing Measure

Missed serious bacterial infection: Decrease proportion of patients diagnosed within 7 days of treat and release or discharge with UTI, bacteremia or meningitis (<2%)



Overall Project Timeline (Tentative)

Application Process:	Pre-work Period:	Action/Intervention Period:	
• Form core improvement team and determine roles of each member • Attend informational webinar (optional) • Complete and submit project application by mid to late September	• Gain hospital leadership buy-in to project participation • Obtain local IRB approval (if necessary) • Sign Consent Form • Remit payment for participation as outlined in consent form • Participate in orientation webinar • Watch data entry webinar offered by QIDA (required for Group Administrator) • Submit 12-month retrospective baseline data in QIDA (representing September 2015 – August 2016 charts) • Complete Pre-project survey • Participate in 1-2 webinars (QI Basics and Introduction to the Change Package)	• Participate in up to 10 periodic learning session webinars • Collect monthly data for 12 months between December 2016 – November 2017 • Test changes using PDSA cycles • Provide feedback on tools	**Wrap-up & Data Analysis (February – March 2018)**
September	**October - December**	**January 2017 – January 2018**	

What to Expect: Baseline Data Collection

Complete Pre-Project Survey → Participate in a Project & QI orientation, and Change Package Learning Session Webinars → Group Administrator will view an on-demand webinar detailing the data entry process in QIDA (QIDA Webinar for Group Administrators)

Baseline Data

- Minimum 24 – Maximum 240 charts
- 12 months of retrospective data, in 1 month increments representing September 2015 – August 2016
- Group Administrator will enter data, but collection is responsibility of the whole team

What to Expect: 12-month Action Period

(18-month complete project with 6 months pre/post work)

Learn the Model for Improvement and implement Plan, Do, Study, Act (PDSA) cycles

Make appropriate changes in the structure of how inpatient fever care is delivered to patients

Regularly collect and submit data to monitor changes

What to Expect: 12-month Action Period

(18-month complete project with 6 months pre/post work)

Data Collection

- 12 months of data collection entered in monthly increments during the action period
- 100% of eligible chart or minimum of 2 and maximum of 20 charts monthly
- Time period: December 2016 – November 2017

Webinars

- Opportunity to participate in up to 10 live and/or pre-recorded learning session webinars

Surveys

- Complete 1 pre survey after acceptance into the project.
- Complete 1 post survey at the end of the project

Expert Mentors

- The mentors will be assigned based on various factors including QI knowledge, specific areas of interest for intervention, hospital type, etc.
- Communicate with your mentor throughout the project via email or phone.

Collaboration

- Share lessons learned and problems solved with other participating hospitals through a project-dedicated e-mail listserv

ABP MOC Part 4 Credit (If Approved)

Physicians in the hospital who are not on the core improvement team, but who are actively participating in the project, can receive credit if they meet the required criteria outlined by the project

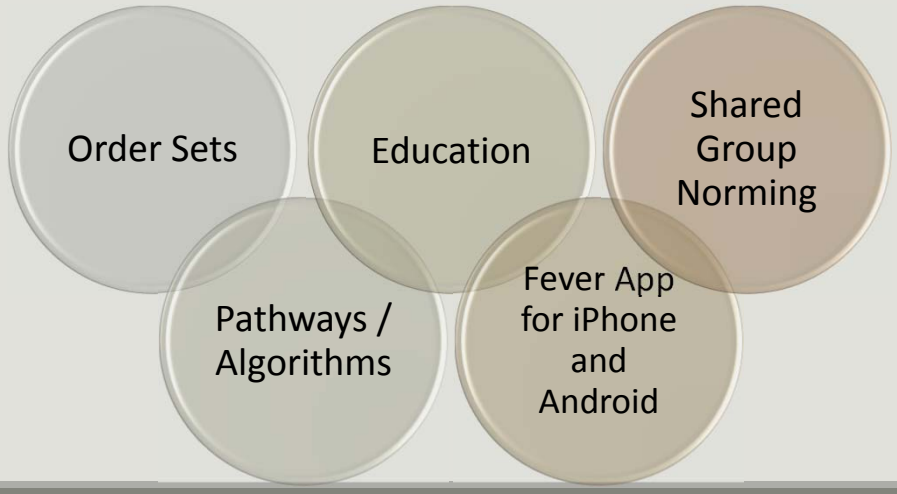
ED Physicians will also be eligible for credit

Lead hospitalist on core improvement team must attest for these physicians. The project requires co-leadership by an ED physician but only one leader serves as the local leader for ABP MOC.

VIP Network/QuIIN project leader will attest for the lead physicians

Additional details will be provided if approval is granted

Change Package Resources & Tools



Expert Mentors

Each site will be matched with at least one more site and be assigned an expert mentor based on various criteria such as individual and collective goals/interests.

They will provide project mentorship, suggest ideas for implementation, and assist with any issues that arise via periodic e-mail exchanges and as needed by phone.

Team Composition

Core team of 3 participants as "Quality Improvement Project Participants"

- Project **must** be co-led by one hospitalist and one emergency department physician
- May have one additional non-core team members that participate at site (preferably non-physician)

Responsibilities of the core team

- Obtain buy-in from hospital leadership
- Obtain IRB approval (or data sharing/use/transfer agreement) at local site if needed
- Attend webinars
- Receive and provide direct communication with project leaders and AAP staff via project-specific listserv
- Disseminate learnings from project to non-core team members at site
- Data collection/entry
- If appropriate, participate in the VIP business meeting in at the 2017 annual Pediatric Hospital Medicine (PHM) Conference

Hospital Site Selection Criteria

- ❑ All applications received will be reviewed by the review team
- ❑ **Up to 100 pediatric hospital teams** will be selected, representing geographically diverse locations, sizes, and hospital types
- ❑ An emphasis will be placed on sites that identify a **multi-disciplinary** core improvement team including having a hospitalist and ED physician lead the project
- ❑ Applicants are expected to have identified a team and obtain the commitment of the senior leadership to support this project
- ❑ Priority will be given to those applications that are submitted by the **specified deadline in the recruitment announcement**. Due to the anticipated popularity of this project recruitment will be open until the specified deadline or until 100 eligible teams have been identified – whichever occurs first.

After Selection

All core improvement team members will be asked to sign a consent form and the physician leader will be asked to join the Quality Improvement Innovation Networks (QuIIN), a program of the American Academy of Pediatrics (AAP).

Joining QuIIN is free and easy and requires completion of a simple membership application available at http://quiin.aap.org.

Benefits of Participation

Be a part of a nationally recognized project

Test strategies management of fever in infants age 7 – 60 days

Work with colleagues from around the country in a quality improvement learning collaborative

Learn from national experts with content expertise throughout a 12-month action period, and receive ongoing support for improvement

Receive American Board of Pediatrics Part 4 Maintenance of Certification credit if you meet the minimum criteria (Physicians only) (pending approval)

Immediate Next Steps

Identify team leads (hospitalist and emergency department physician)

Identify 1 additional core team member (multi-disciplinary)

Obtain local leadership buy-in

Determine if local IRB approval is required

Complete recruitment application in Survey Monkey by specified deadline (or sooner) as noted in the recruitment materials.

Project Contacts

Eric Biondi, MD, FAAP
Project Leader
Eric_Biondi@URMC.Rochester.edu

Faiza Wasif, MPH
QuIIN Project Manager
fwasif@aap.org

Reducing Excessive Variability in Infant Sepsis Evaluation (revise) Quality Improvement Project

Live Webinar #1: Orientation Webinar
October 31, 2016
3pm ET/2pm CT/1pm MT/12pm PT

Agenda

Agenda Item	Presenter
Welcome and introductions	Faiza Wasif, MPH
Project Overview	Eric Biondi, MD, FAAP
Inclusion/Exclusion Criteria	
Metric Evidence	
Overview of Chart Review Tool	
Brief Introduction to QIDA	
Brief Introduction to the Change Package	Russell McCulloh, MD, FAAP Benj Barsotti, MD, FAAP
Questions & Answers	Eric Biondi, MD, FAAP

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Welcome & Introductions: Today's Speakers

Eric Biondi, MD, FAAP
Project Leader

Russell McCulloh, MD, FAAP
REVISE Expert Group

Benj Barsotti, MD, FAAP
Expert Group Member

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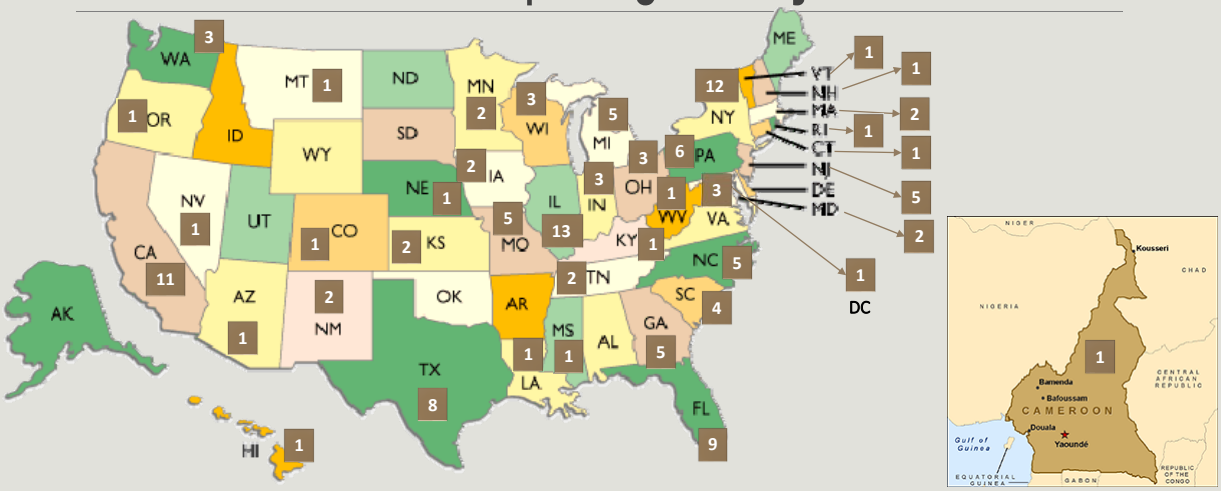
133 Teams Participating in Project REVISE



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How will we manage this large collaborative?


Listserv


Mentors


Email/Phone


Meet Deadlines

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Background


Fever in infants is very common resulting in trips to the hospital and/or emergency room


The clinical management of fever in infants has been a topic of much ambiguity for decades

Despite available research, fever management remains extremely variable from hospital to hospital


This collaborative improvement project seeks to build a national QI collaborative designed to improve and standardize care for febrile infants between the ages of 7 to 60 days

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Project Aim

Provide multi-disciplinary teams with quality improvement education and tools specific to management of children with fever to increase compliance with the evidence-based research and thereby decrease overuse of non-evidence-based therapies and tests.

Overall Project Timeline (Tentative)

Pre-work Period:	**Action/Intervention Period:**	**Wrap-up & Data Analysis (February – March 2018)**
• Gain hospital leadership buy-in to project participation • Obtain local IRB approval (if necessary) • Remit payment for participation as outlined in consent form • Watch data entry webinar offered by QIDA (required for Group Administrator) • Submit 12-month retrospective baseline data in QIDA (representing September 2015 – August 2016 charts) • Complete Pre-project survey • Participate in 1-2 webinars (QI Basics and Introduction to the Change Package)	• Participate in up to 10 periodic learning session webinars • Collect monthly data for 12 months between December 2016 – November 2017 • Test changes using PDSA cycles • Provide feedback on tools	
October - December	**January 2017 – January 2018**	

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Inclusions and Exclusions

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Age 7 through 60 days • Evaluated in site ED or transferred to site inpatient unit from an outpatient setting • Evaluated for fever without a source • Discharged from site ED or inpatient unit	• Infant was not well-appearing on presentation • Co-morbid conditions predisposing to severe or recurrent bacterial illness, including genetic, congenital, chromosomal, neuromuscular, or neurodevelopmental abnormalities. • Transfer to or from site inpatient hospital from another inpatient setting

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Methodology for Finding Charts

There is no validated way to identify these infants via discharge code, so the process will involve manual review to identify infants who were likely to have undergone an evaluation fever in your ED or who were transferred to your inpatient unit after/while undergoing such an evaluation from an outside institution.

First, obtain a list of all infants evaluated in your ED or admitted to your inpatient unit between the ages of 7 – 60 days of age. *It might be helpful to apply additional filters depending on your institution (e.g. admissions only to certain specialties to limit the number of unnecessary charts). With this list, you should also request all discharge (and/or treat and release) diagnoses for the patient.*

Next, exclude any infants who did not have a diagnosis suggestive of the need for a well-appearing, febrile infant workup (e.g. diagnoses such as UTI, fever, viral illness, sepsis, etc. therefore require further manual review, but pyloric stenosis, rash, etc would not require further screening as these infants would be excluded from the chart review)

Then, exclude any infants with a discharge diagnosis (in any position) of bronchiolitis

Finally, manually review the remaining charts and include any who presented as febrile, well-appearing infants without a clear source of infection. Exclude any:

- Without either a report of fever at home or documented fever in the ED.
- Infants who are non-well appearing based on words such as "toxic", "ill-appearing", "lethargic", "sick-appearing"
- With a focal infection (we are only attempting to evaluate well-appearing, febrile infants undergoing an evaluation for fever without a clear source)
- With any co-morbid conditions predisposing the infant to severe or recurrent bacterial illness

The remaining charts should be entered into QIDA.

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Metric Evidence

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Determining Project Metrics: Meet the REVISE Expert Group


Eric Biondi, MD, FAAP


Matthew Garber, MD, FAAP


Lisa Schroeder, MD, FAAP


Russell McCulloh, MD, FAAP


Julia Arana, MD, FAAP


Matt Hall, PhD


Jeff Bennett, MD, FAAP


Beth Natt, MD, FAAP


Benj Barsotti, MD, FAAP


Alan Schroeder, MD, FAAP


Todd Wiley, MD, FAAP

Thank you to Kenneth Roberts, MD, FAAP and Robert Pantell, MD, FAAP who served as project advisors!

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Metric 1: Increase proportion of appropriately hospitalized infants

Author (year)	Criteria Age of Infants	Early management detail	n/N (delayed SBI diagnosis/total infant at low risk)	Complications
Bonadio, WA (1993)[10]	Combined clinical and laboratory (Milwaukee protocol) 28–56 d	Discharged after injection of ceftriaxon (50mg/kg)	1/143 (0.7%) Bacteremia	None occurred
Bressan, S (2010)[47]	Well appearing + repeated lab test > 12 hrs of fever neonates	All infants were hospitalized upon admission.	5/62 (8.1%) 3 bacteremia; 2 meningitis	No data
Brik, R (1997)[58]	Combined clinical and laboratory (Philadelphia protocol) 0 - 30 d	Low risk infants were treated as outpatient treatment without antibiotics	9/296 (3.04%) 1 bacteremia; 7 UTI	No data
Chiu C (1997)[57]	Combined clinical and laboratory (Rochester criteria) neonates	All low risk infants were hospitalized and closely monitored without antibiotics; 44.3% of infants were reclassified as high risk on 2nd or 3rd day and were given antibiotics	1/131 (0.8%) UTI	7 day course antibiotics Recovered with no complications
Jaskiewicz, J (1994)[23] Combined clinical and laboratory	Combined clinical and laboratory criteria (Rochester criteria) 0 - 60 d	203 (39.7%) of infants were treated without antibiotics (this included 4/5 infants with SBI) Remaining infants were treated with IM ceftriaxone and discharged home	5/437 (1.1%) 2 bacteremia; 3 UTI	None occurred
Kaplan, R (2000)[25]	Combined clinical and laboratory criteria (Boston criteria) 28 - 90 d	NR	3/1146 (0.3%)	None occurred
McCarthy, CA (1990)[70]	Combined clinical and laboratory 11–59 d	Discharged after injection of ceftriaxon (50mg/kg)	1/86 (1.2%)	No data
Pantell, R (2005)[5] The PROS study (office setting)	Laboratory (75%) and clinical criteria (PROS practitioner guidelines) 0 - 90 d	1264 (64%) were treated as outpatients; initially treated 57% of infants with antibiotics unclear how many of these infants had SBI;	2/1975 (0.1 %)	None occurred
Wasserman, G (1990)[67]	Combined clinical and laboratory criteria 0 - 30 d	All infants were hospitalized, 222 (high risk) were treated with antibiotics and 221 (low risk) received no antibiotics	5/221 (2.3%) 3 infants < 2 weeks of age with Bacteremia or bacterial meningitis 2 infants > 2 weeks of age	None occurred

Febrile Infants. Content last reviewed October 2014. Agency for Healthcare Research and Quality, Rockville, MD.
http://www.ahrq.gov/research/findings/evidence-based-reports/er205-abstract.html

Metric 1: Increase proportion of appropriately hospitalized infants

TWO COMPONENTS TO THIS METRIC, MUST FUFILL ALL OF THEM TO GET CREDIT

WORKUP (meant to mimic risk stratification criteria) *MUST* INCLUDE:

- ❑ Urinalysis
- ❑ Inflammatory Marker (e.g. CBC, CRP, Procalcitonin)

APPROPRIATE PATIENTS TO ADMIT (meant to mimic risk stratification criteria):

- ❑ Less than 30 days at time of presentation
- ❑ Abnormal urinalysis
- ❑ Abnormal inflammatory marker (e.g. CBC, CRP, Procalcitonin)
- ❑ Past medical history or social concern suggestive of need for hospitalization

TARGET: 90%

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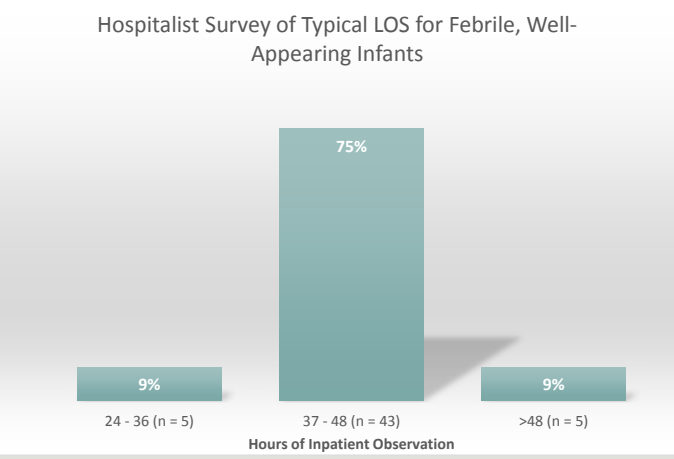
Metric 2: Increase the proportion of hospitalized infants who are discharged in an appropriate time frame for their risk category (low risk <30 hours and non-low risk <42 hours)



Biondi E, et al. Peds in Review. 2013;34(3)

Metric 2: Increase the proportion of hospitalized infants who are discharged in an appropriate time frame for their risk category (low risk <30 hours and non-low risk <42 hours)

	Base and Training Periods, N = 4524, n (%)	Implementation Period, N = 2467, n (%)	Absolute Difference in Propositions
Infants admitted within 72 h post ED discharge	92/1904 (5)	45/927 (5)	0.02% (−1.7% to 1.7%, 1.000)
Readmission within 72 h after discharge inpatient or observation unit	21/2620 (0.8)	10/1540 (0.6)	−0.2% (−0.7% to 0.4%, .710)
Missed SBI after admission	0	0	NA

Byington C, et al. Costs and infant outcomes after implementation of a care process model for febrile infants. *Pediatrics*. 2012;130(1)

Metric 2: Increase the proportion of hospitalized infants who are discharged in an appropriate time frame for their risk category (low risk <30 hours and non-low risk <42 hours)

12. Was the infant admitted to your hospital (includes through the ED or as a direct admission from an outside ED, urgent care or other outpatient setting)?

◎ Yes ◎ No

12A. How many hours was the hospitalization (inclusive of ED visit it it occurred at your institution) from the time of first recorded vital sign to time of placement of the discharge order?

hours

TARGET: 80%

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Metric 3: Increase the proportion of infants who have a urinalysis (UA) performed via any method of collection within 24 hours of presentation

METRIC 3: URINALYSIS UTILIZATION

18. Was a urinalysis performed within 24 hours before or after arrival to the ED or, if a direct admission to your hospital, within 24 hours before or after arrival on the inpatient unit?

○ Yes ○ No

TARGET: >95%

Metric 4: Decrease proportion of infants receiving a CXR within 24 hours of presentation without documented respiratory symptoms

- Crain EF et al. Is a chest radiograph necessary in the evaluation of every febrile infant less than 8 weeks of age. *Pediatrics* 1991;88:821-824.
  Conclusion: In the absence of resp signs, febrile infants are unlikely to have an abnormal chest radiograph
- Bramson RT et al. The futility of the chest radiograph in the febrile infant without respiratory symptoms. *Pediatrics* 1993 Oct;92(4):524-526.
  Conclusion: Chest radiographs should be obtained only febrile infants who have clinical indications of pulmonary disease.
- Mintegi s et al. Occult pneumonia in infants with high fever without source: a prospective multicenter study. Pediatr Emerg Care 2010 Jul; 26(7): 470-474.
  Conclusion: Chest radiographies do not play a role in the routine evaluation of the infant with FWS.
- Hernandez DA and Nguyen Y. Fever in infants <3 months old: What is the standard? Pediatr Emerg Med Reports 2011 Jan; 16(1).
  Conclusion: Radiographs should be done only in infants who present with respiratory symptoms, abnormal pulse oximetry, hyperpyrexia, or marked leukocytosis
- Baraff LJ. Editorial: Clinical Policy for Children Younger Than Three: Update to ACEP Guidelines. 2013
  Conclusion: There is no need for chest radiograph if there are no signs or symptoms of pulmonary infection.

Metric 4: Decrease proportion of infants receiving a CXR within 24 hours of presentation without documented respiratory symptoms

METRIC 4: CHEST X-RAY UTILIZATION WITHIN 24 HOURS OF INITIAL ENCOUNTER

19. Did the patient have documented respiratory symptoms within 24 hours arrival to the ED or, if a direct transfer to your hospital, within 24 hours before or after arrival on the inpatient unit?

○ Yes ○ No

20. Did the patient receive a chest x-ray within 24 hours PRIOR TO presentation at your institution (e.g. an infant who arrives to your ED after having a chest x-ray done at an urgent care clinic)?

○ Yes ○ No

21. Did the patient receive a chest x-ray within 24 hours after arrival to the ED or, if a direct admission to your hospital, arrival on the inpatient unit?

○ Yes ○ No

TARGET: <10%

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Metric 5: Increase proportion of infants who receive only recommended empiric antibiotic regimens within 24 hours of presentation

Bacterial Pathogens Identified From Infants With Bacteremia

Pathogen	*n* (%)	Male (%)	Median Age in Days (Range)	Concurrent UTI (%)	Concurrent Meningitis (%)
All Species	181 (100)	91 (50)	34 (3–90)	86/174 (49)	20/152 (13)
E coli	76 (42)	44 (58)	31 (5–87)	69/75 (92)[a]	5/63 (8)
GBS	41 (23)	18 (44)	36 (11–88)	4/39 (10)	10/37 (27)
S pneumoniae	10 (6)	3 (30)	65 (10–81)	0/9 (0)	1/4 (25)
S aureus	9 (5)	3 (33)	35 (20–58)	1/8 (13)[b]	0/8 (0)
Klebsiella sp.	8 (4)	5 (63)	30 (11–90)	6/8 (75)	0/7 (0)
Viridans *streptococci*	8 (4)	5 (63)	34 (7–78)	1/8 (13)	0/7 (0)
Enterococcus sp.	7 (4)	2 (29)	33 (6–71)	1/7 (14)	1/6 (17)
γ-heme Strep.	4 (2)	1 (25)	32 (23–85)	0/3 (0)	0/3 (0)
Salmonella sp.	3 (2)	1 (33)	31 (25–40)	1/3 (33)[c]	0/3 (0)
S pyogenes	3 (2)	2 (67)	42 (11–74)	0/3 (0)	0/3 (0)
Pseudomonas sp.	2 (1)	1 (50)	25 (11–39)	1/1 (100)	0/1 (0)
Moraxella sp.	2 (1)	2 (100)	86 (84–88)	0/1 (0)	0/2 (0)
Neisseria sp.	2 (1)	0 (0)	54 (33–74)	0/2 (0)	1/1 (100)
CoNS	1 (1)	1 (100)	24 (24)	0/1 (0)	1/1 (100)
Citrobacter sp	1 (1)	1 (100)	21 (21)	1/1 (100)	0/1 (100)
B cereus	1 (1)	1 (100)	28 (28)	0/1 (0)	0/1 (0)
Pantoea sp.	1 (1)	0 (100)	15 (15)	0/1 (0)	1/1 (100)[a]
H influenzae	1 (1)	1 (100)	3 (3)	0/0	0/1 (0)
Enterobacter sp.	1 (1)	1 (100)	24 (24)	0/1 (0)	0/1 (0)

Biondi E, et al. Epidemiology of bacteremia in febrile infants in the U.S. Pediatrics. 2013;132(6).

Metric 5: Increase proportion of infants who receive only recommended empiric antibiotic regimens within 24 hours of presentation

EMPIRIC ANTIBIOTICS WITHIN 24 HOURS OF INITIAL ENCOUNTER

22. Please select the answer that best describes ALL the antibiotics the patient received within 24 hours after arrival to your ED or, if a direct admission to your hospital , arrival on your inpatient unit? The answer should not include arrivals.

- ○ No antibiotics were administered
- ○ Monotherapy or combination therapy with ampicillin, amikacin, gentamicin, or a 3rd generation cephalosporin
- ○ Any other antibiotic or combination of antibiotics

TARGET: >90%

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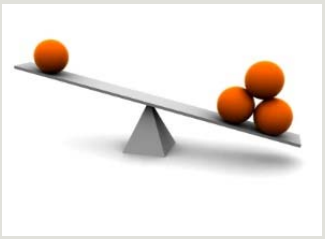
Balancing Measure

Missed serious bacterial infection: Decrease proportion of patients diagnosed within 7 days of treat and release or discharge with UTI, bacteremia or meningitis (<2%)



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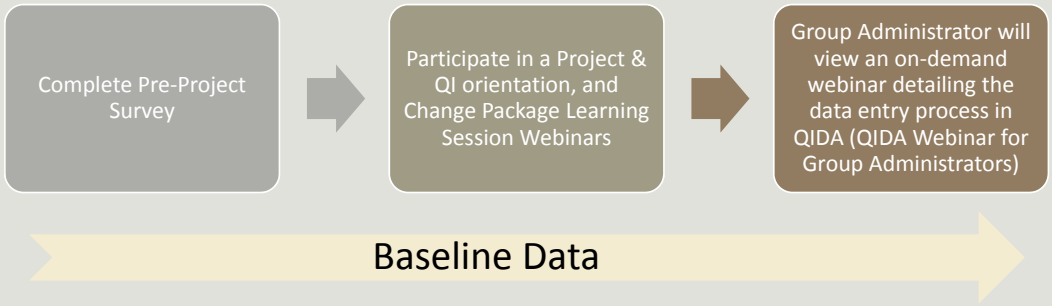
Quick Review of Baseline Data Collection and Intervention Phase/Action Period

What to Expect: Baseline Data Collection



- Minimum 24 – Maximum 240 charts
- 12 months of retrospective data, in 1 month increments representing September 2015 – August 2016
- Group Administrator will enter data, but collection is responsibility of the whole team

What to Expect: 12-month Action Period

(18-month complete project with 6 months pre/post work)

Data Collection

- 12 months of data collection entered in monthly increments during the action period
- 100% of eligible chart or minimum of 2 and maximum of 20 charts monthly
- Time period: December 2016 – November 2017

Webinars

- Opportunity to participate in up to 10 live and/or pre-recorded learning session webinars

Surveys

- Complete 1 pre survey after acceptance into the project.
- Complete 1 post survey at the end of the project

Expert Mentors

- The mentors will be assigned based on various factors including QI knowledge, specific areas of interest for intervention, hospital type, etc.
- Communicate with your mentor throughout the project via email or phone.

Collaboration

- Share lessons learned and problems solved with other participating hospitals through a project-dedicated e-mail listserv

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Brief Introduction to the Quality Improvement Data Aggregator (QIDA)

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ABOUT QIDA

- Web-based data aggregation system
- Secure login for all project participants
- Clinician enter chart data securely by patient or in aggregate
- Analyzes data via real time run charts
- Collaboration between project team members
- View project specific resources (workspace) and QIDA system documents

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ACCESSING QIDA

- To access QIDA, go to the following link: **http://qidata.aap.org/revise**
- For AAP members, you will use your AAP log-in and password to access the site
- For non-AAP members, an AAP log-in has been created for you and that information will be e-mailed to you next week

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GROUP ADMINISTRATOR'S QIDA WEBINAR

- **QIDA Orientation Webinar** (Open to all team members, **required for Group Administrators**)
- **20 minute pre-recorded webinar**
- Available now at **http://youtu.be/BgNSSJc84ak**

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Brief Introduction to the Project REVISE Change Package

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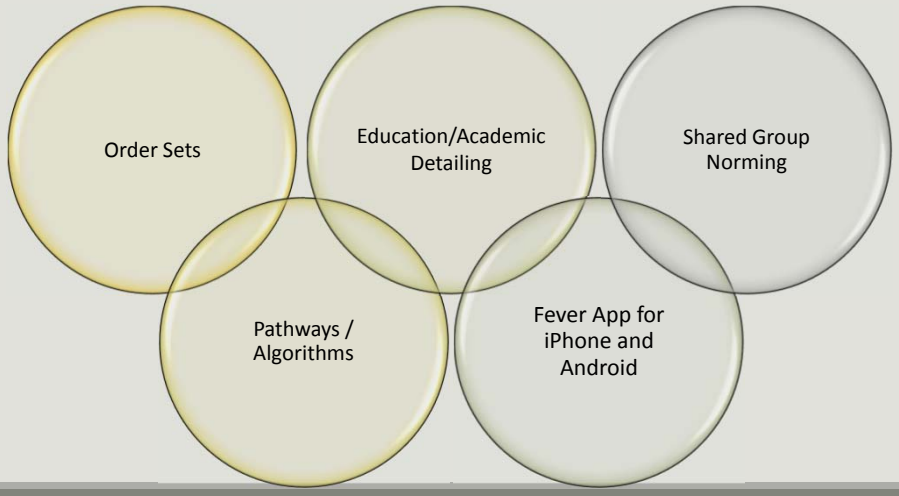
Change Package Resources & Tools



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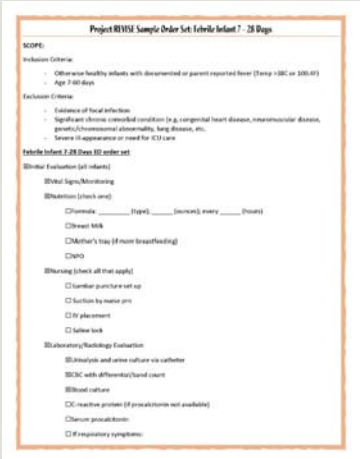
Order sets


Project REVISE Sample Order Set: Febrile Infant 7 - 28 Days

SCOPE:

Inclusion Criteria:

- Otherwise healthy infants with documented or parent reported fever (Temp >38C or 100.4F)
- Age 7-60 days

Exclusion Criteria:

- Evidence of focal infection
- Significant chronic comorbid condition (e.g. congenital heart disease, neuromuscular disease, genetic/chromosomal abnormality, lung disease, etc.
- Severe ill-appearance or need for ICU care

Febrile Infant 7-28 Days ED order set

☐Initial Evaluation (all infants)

☐Vital Signs/Monitoring

☐Nutrition (check one):

☐Formula: _____ (type); _____ (ounces); every _____ (hours)

☐Breast Milk

☐Mother's tray (if mom breastfeeding)

☐NPO

☐Nursing (check all that apply)

☐ Lumbar puncture set up

☐ Suction by nurse prn

☐ IV placement

☐ Saline lock

☐Laboratory/Radiology Evaluation

☐UAnalysis and urine culture via catheter

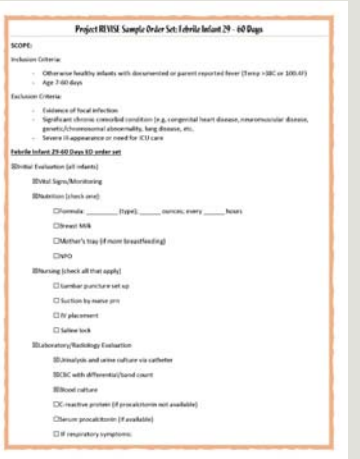
☐CBC with differential/band count

☐Blood culture

☐C-reactive protein (if procalcitonin not available)

☐Serum procalcitonin

☐ If respiratory symptoms:


Project REVISE Sample Order Set: Febrile Infant 29 - 60 Days

SCOPE:

Inclusion Criteria:

- Otherwise healthy infants with documented or parent reported fever (Temp >38C or 100.4F)
- Age 7-60 days

Exclusion Criteria:

- Evidence of focal infection
- Significant chronic comorbid condition (e.g. congenital heart disease, neuromuscular disease, genetic/chromosomal abnormality, lung disease, etc.
- Severe ill-appearance or need for ICU care

Febrile Infant 29-60 Days ED order set

☐Initial Evaluation (all infants)

☐Vital Signs/Monitoring

☐Nutrition (check one):

☐Formula: _____ (type); _____ ounces; every _____ hours

☐Breast Milk

☐Mother's tray (if mom breastfeeding)

☐NPO

☐Nursing (check all that apply)

☐ Lumbar puncture set up

☐ Suction by nurse prn

☐ IV placement

☐ Saline lock

☐Laboratory/Radiology Evaluation

☐UAnalysis and urine culture via catheter

☐CBC with differential/band count

☐Blood culture

☐C-reactive protein (if procalcitonin not available)

☐Serum procalcitonin (if available)

☐ If respiratory symptoms:

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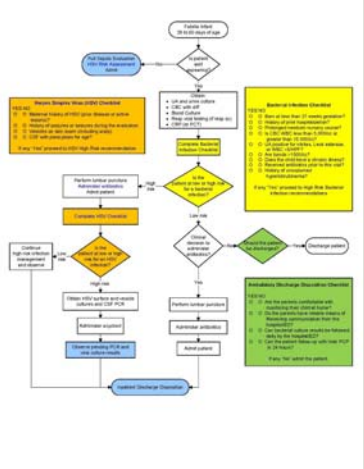
Algorithms



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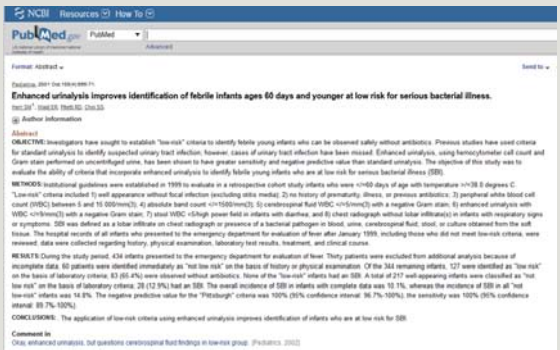
Academic Detailing

Webinars

Relevant Publications



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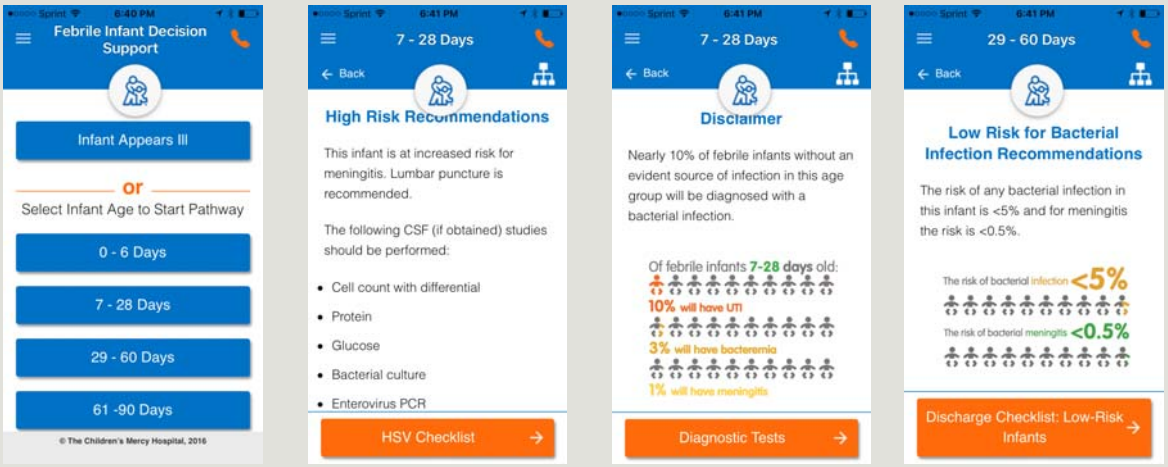
Fever App



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Overview of Chart Review Tool

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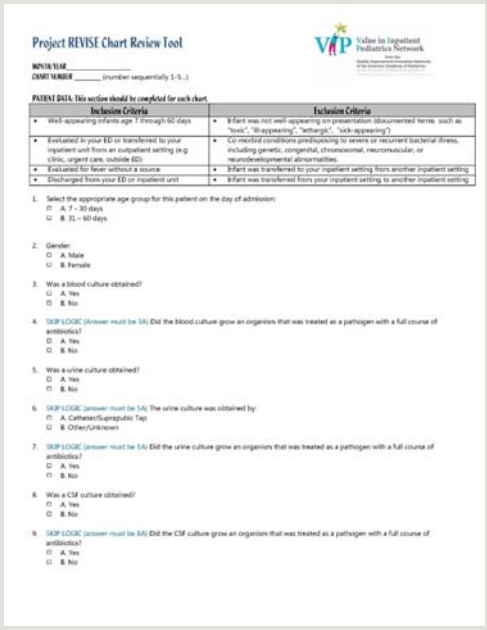


Project REVISE Chart Review Tool

Value in Inpatient Pediatrics Network

MONTH/YEAR _____
CHART NUMBER _____ (number sequentially 1-5...)

PATIENT DATA: This section should be completed for each chart.

Inclusion Criteria	Exclusion Criteria
• Well-appearing infants age 7 through 60 days	• Infant was not well-appearing on presentation (documented terms such as "toxic", "ill-appearing", "lethargic", "sick-appearing")
• Evaluated in your ED or transferred to your inpatient unit from an outpatient setting (e.g. clinic, urgent care, outside ED)	• Co-morbid conditions predisposing to severe or recurrent bacterial illness, including genetic, congenital, chromosomal, neuromuscular, or neurodevelopmental abnormalities.
• Evaluated for fever without a source	• Infant was transferred to your inpatient setting from another inpatient setting
• Discharged from your ED or inpatient unit	• Infant was transferred from your inpatient setting to another inpatient setting

1. Select the appropriate age group for this patient on the day of admission:
   - ☐ A. 7 – 30 days
   - ☐ B. 31 – 60 days

2. Gender:
   - ☐ A. Male
   - ☐ B. Female

3. Was a blood culture obtained?
   - ☐ A. Yes
   - ☐ B. No

4. SKIP LOGIC (Answer must be 3A) Did the blood culture grow an organism that was treated as a pathogen with a full course of antibiotics?
   - ☐ A. Yes
   - ☐ B. No

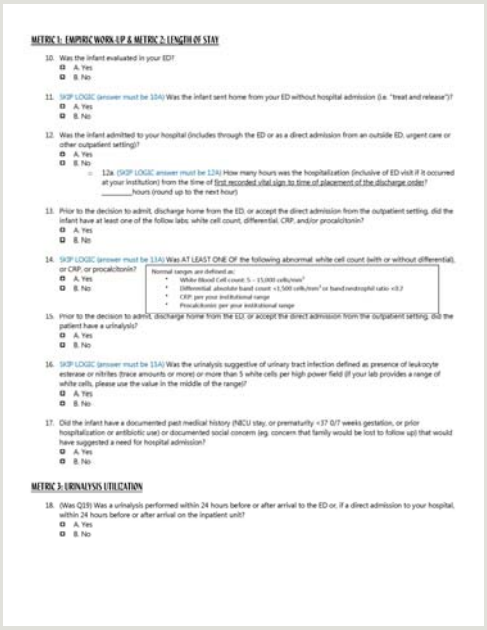
5. Was a urine culture obtained?
   - ☐ A. Yes
   - ☐ B. No

6. SKIP LOGIC (answer must be 5A) The urine culture was obtained by:
   - ☐ A. Catheter/Suprapubic Tap
   - ☐ B. Other/Unknown

7. SKIP LOGIC (answer must be 5A) Did the urine culture grow an organism that was treated as a pathogen with a full course of antibiotics?
   - ☐ A. Yes
   - ☐ B. No

8. Was a CSF culture obtained?
   - ☐ A. Yes
   - ☐ B. No

9. SKIP LOGIC (answer must be 8A) Did the CSF culture grow an organism that was treated as a pathogen with a full course of antibiotics?
   - ☐ A. Yes
   - ☐ B. No



METRIC 1: EMPIRIC WORK-UP & METRIC 2: LENGTH OF STAY

10. Was the infant evaluated in your ED?
    - ☐ A. Yes
    - ☐ B. No

11. SKIP LOGIC (answer must be 10A) Was the infant sent home from your ED without hospital admission (i.e. "treat and release")?
    - ☐ A. Yes
    - ☐ B. No

12. Was the infant admitted to your hospital (includes through the ED or as a direct admission from an outside ED, urgent care or other outpatient setting)?
    - ☐ A. Yes
    - ☐ B. No
      - 12a. (SKIP LOGIC answer must be 12A) How many hours was the hospitalization (inclusive of ED visit if it occurred at your institution) from the time of first recorded vital sign to time of placement of the discharge order? _____hours (round up to the next hour)

13. Prior to the decision to admit, discharge home from the ED, or accept the direct admission from the outpatient setting, did the infant have at least one of the follow labs: white cell count, differential, CRP, and/or procalcitonin?
    - ☐ A. Yes
    - ☐ B. No

14. SKIP LOGIC (answer must be 13A) Was AT LEAST ONE OF the following abnormal: white cell count (with or without differential), or CRP, or procalcitonin?
    - ☐ A. Yes
    - ☐ B. No

    Normal ranges are defined as:
    - White Blood Cell count: 5 – 15,000 cells/mm³
    - Differential: absolute band count <1,500 cells/mm³ or band:neutrophil ratio <0.2
    - CRP: per your institutional range
    - Procalcitonin: per your institutional range

15. Prior to the decision to admit, discharge home from the ED, or accept the direct admission from the outpatient setting, did the patient have a urinalysis?
    - ☐ A. Yes
    - ☐ B. No

16. SKIP LOGIC (answer must be 15A) Was the urinalysis suggestive of urinary tract infection defined as presence of leukocyte esterase or nitrites (trace amounts or more) or more than 5 white cells per high power field (if your lab provides a range of white cells, please use the value in the middle of the range)?
    - ☐ A. Yes
    - ☐ B. No

17. Did the infant have a documented past medical history (NICU stay, or prematurity <37 0/7 weeks gestation, or prior hospitalization or antibiotic use) or documented social concern (eg. concern that family would be lost to follow up) that would have suggested a need for hospital admission?
    - ☐ A. Yes
    - ☐ B. No

METRIC 3: URINALYSIS UTILIZATION

18. (Was Q15) Was a urinalysis performed within 24 hours before or after arrival to the ED or, if a direct admission to your hospital, within 24 hours before or after arrival on the inpatient unit?
    - ☐ A. Yes
    - ☐ B. No

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Project Reminders

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Immediate Next steps

October 28, 2016	Consent Form due – **submit ASAP if deadline was missed**!
November 7 – 11, 2016	Receive invoice from AAP to remit $750.00 payment for participation (90 days to submit)
November 30, 2016	Pre-project survey due in Survey Monkey (link to be provided)
	Data cycles open in QIDA
	Optional webinar #3: Focus on community hospitals
December 8, 2016	Required Live Webinar #2: Introduction to REVISE Change Package & Collaborating Across the Continuum
December 30, 2016	Cycles 1 – 3 of baseline data due in QIDA
January 20, 2017	Submit MOC Local Leader Acknowledgement form and list of participants seeking MOC Part 4 credit (*If application is approved*)
January 31, 2017	First cycle of intervention data due in QIDA
February 28, 2017	Second cycle of intervention data due in QIDA
March 24, 2017	Last day to remit $750.00 payment for participation

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Questions

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Reducing Excessive Variability in Infant Sepsis Evaluation – Project REVISE

PURPOSE

The management of fever in infants has been a topic of much ambiguity for decades. The American Academy of Pediatrics (AAP) Value in Inpatient Pediatrics (VIP) Network, an established inpatient pediatric quality improvement (QI) network, seeks to build a national QI collaborative designed to improve and standardize care for febrile infants between the ages of 7 – 60 days. This QI effort will provide inpatient and emergency physicians with education about evidence-based best practice, strategies for implementation, and tools to bring about sustainable change.

PROJECT AIMS

The specific aim of the project is to:

- Decrease admissions for infants presenting to emergency departments (EDs) with fever who are at low risk of bacterial infection
- Decrease variation in care of febrile infants presenting to the ED and/or hospital
- Decrease length of stay for infants admitted to the hospital with fever
- Decrease use of unnecessary chest x-rays in the care of febrile infants

PATIENT CHART CRITERIA

In general, the patient population for this project are well-appearing infants age 7 – 60 days identified with a fever.

Inclusion Criteria	Exclusion Criteria
Well-appearing infants age 7 through 60 days Evaluated in site ED or transferred to site inpatient unit from an outpatient setting Evaluated for fever (T≥38.0 C) without a source Discharged from site ED or inpatient unit	Infant was not well-appearing on presentation Co-morbid conditions predisposing to severe or recurrent bacterial illness, including genetic, congenital, chromosomal, neuromuscular, or neurodevelopmental abnormalities. Transfer to or from site hospital (except transfer from an outpatient setting as noted above)

PARTICIPATING TEAMS

133 hospital teams from across the US and internationally are participating in this quality improvement collaborative.

PROJECT TIMELINE

The project will engage teams between October 2016 – March 2017. Data collection will occur as follows:

- Baseline (monthly, retrospectively representing data from September 2015 – August 2016): Minimum of 24 or maximum of 240 charts representing 12 months
- Intervention/Action Phase: 12 months of the action/intervention period data divided into monthly increments between December 2016 – November 2017 with a minimum of 2 charts or a maximum of 20 charts per month

DATA COLLECTION

Teams will enter the non-PHI chart data into a secure web-based system – the AAP Quality Improvement Data Aggregator (QIDA). Only registered team members will have access to the system via a password protected process.

INTERVENTION STRATGIES AND RESOURCES

Tools to facilitate improvement – including regular learning session webinars, a change package of resources, and project mentors – will be provided to participating teams. A dedicated project listserv is used to facilitate communication between sites. Real-time, regular reports will be generated to monitor improvement during the project.

VIP Value in Inpatient Pediatrics Network
from the Quality Improvement Innovation Networks of the American Academy of Pediatrics

Performance of Low-Risk Criteria in the Evaluation of Young Infants With Fever: Review of the Literature

WHAT'S KNOWN ON THIS SUBJECT: Fever in neonates is common. The rate of SBIs in young infants may be as high as 12%. Low-risk criteria have been developed to aid in management decisions for well-appearing, febrile young infants.

WHAT THIS STUDY ADDS: Although the total risk of SBI in febrile young infants in this review was 10.9%, low-risk criteria allowed 30% of these patients to be treated safely without empiric antibiotic therapy.

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KEY WORDS
fever, infant, bacteremia, meningitis, urinary tract infection

ABBREVIATIONS
SBI—serious bacterial illness
CI—confidence interval
RR—relative risk
UTI—urinary tract infection

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FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

abstract

FREE

OBJECTIVE: The goal was to determine the performance of low-risk criteria for serious bacterial illnesses (SBIs) in febrile infants in prospective studies in which empiric antibiotic treatment was withheld, compared with studies (prospective and retrospective) in which empiric antibiotic treatment was administered.

METHODS: A search of the English-language literature was undertaken by using a PubMed database and reference lists of relevant studies of fever, low-risk criteria, and SBIs. Studies of infants >90 days of age, infants with specific infections, or infants with additional risk factors for infection were excluded. Publications were categorized as retrospective, prospective with empiric antibiotic treatment for all patients, or prospective with antibiotics withheld. The relative risk of SBI in high-risk versus low-risk patients was determined for pooled data in each category. The rates of SBIs in low-risk patients in each category were compared.

RESULTS: Twenty-one studies met the inclusion criteria. In prospective studies in which patients were cared for without empiric antibiotic treatment, 6 patients assigned to the low-risk category had SBIs; all recovered uneventfully. The rate of SBIs in these low-risk patients was 0.67%. The relative risk of SBIs in high-risk versus low-risk patients in these studies was 30.56 (95% confidence interval: 7.0–68.13). The rate of SBIs in low-risk patients in all studies was 2.23%. The rate of SBIs in low-risk patients in the prospective studies without empiric antibiotic treatment was significantly different from the rate in all other studies (0.67% vs 2.71%; $P = .01$).

CONCLUSIONS: Low-risk criteria perform well in prospective studies in which empiric antibiotic treatment is withheld. These criteria allow ~30% of young febrile infants to be observed without antibiotic treatment, thus avoiding unnecessary hospitalization, nosocomial infection, injudicious use of antibiotics, and adverse effects of antibiotics. *Pediatrics* 2010;125:228–233

Fever in very young infants is a common and important problem. Neonates have unique vulnerabilities to infection because of their immature immune systems and incomplete barriers to invasion. The rate of serious bacterial illnesses (SBIs) in young febrile infants has been reported to be between 8.5% and 12%.[1–3]

Before 1985, it was recommended that all febrile infants (<60 days of age) be hospitalized and treated with parenteral antibiotic therapy after a full sepsis evaluation, because various criteria used to identify "high-risk" infants were insufficiently sensitive to identify all infants with SBIs.[4–6] However, the approach of hospitalizing and treating all febrile young infants with empiric antibiotic therapy had the disadvantages of unnecessary hospitalizations, nosocomial infections, injudicious use of antibiotics, emergence of resistant bacteria, and adverse effects of antibiotics.[7,8]

During the late 1980s and early 1990s, investigators changed strategies and attempted to identify febrile infants who were at low risk for SBIs and might be treated with close observation (inpatient or outpatient) without antibiotic treatment.[3,9–16] After the development of various low-risk criteria, several groups undertook studies to validate the criteria in their own populations.[17–27] The designs of those studies alternated between retrospective and prospective, with variable approaches to empiric use of ceftriaxone. We hypothesized that prospective studies that implemented a strategy of observation without antibiotic treatment for low-risk infants, thereby relying on meticulous evaluation and careful decision-making, would show significantly better performance of low-risk criteria than would studies that continued to treat all patients (prospectively or retrospectively), regardless of risk stratification.

METHODS

We searched the English-language literature for original articles studying low-risk criteria for SBIs in febrile infants between 0 and 90 days of age. A National Library of Medicine PubMed database search for articles was performed by using combinations of the following search terms: "low risk criteria," "criteria," or "risk"; "serious bacterial illness," "serious bacterial infection," "bacterial infection," or "bacteremia"; and "fever" or "fever without source".Studies were limited to humans, infants, and publication after 1985.

The search criteria identified 740 articles. Bibliographic references from the relevant studies (original research and review articles) were reviewed for additional citations. Articles were excluded on the basis of abstracts if they focused on infants >90 days of age, patients with underlying conditions (such as patients with sickle cell disease, neutropenia, malignancy, central vascular catheters, or other immunocompromised states), or patients with a single focus of bacterial infection (eg, urinary tract infection [UTI] or meningitis). Sixty-three publications were reviewed carefully for inclusion criteria, definition of SBIs, and evaluations performed for study patients. The components of the low-risk criteria used in each study were reviewed and compared with the original Rochester Criteria[9] (Tables 1 and 2). Studies with overlapping subjects were excluded.

Articles were grouped according to type of study, and total patients were aggregated. The categories of studies were prospective without antibiotic treatment of low-risk infants, prospective with antibiotic treatment of low-risk infants, and retrospective.

Portions of studies using different management plans for low-risk infants were classified accordingly. Data were extracted from the tables and text of each study and included the number of low-risk infants, the number of high-risk infants, the number of SBIs in each group, types of SBIs, and the outcomes of low-risk infants with SBIs. The random-effects method described by DerSimonian and Laird[28] was used to estimate overall relative risks (RRs) and corresponding 95% confidence intervals (CIs). This method accounts for the heterogeneity of studies through a statistical parameter representing interstudy variation.

Heterogeneity between studies was assessed by using the Q statistic, as well as graphic techniques. The β-binomial model for overdispersed data[29] was used to estimate pooled rates of SBIs for low- and high-risk patients. Comparison of pooled rates between groups was performed by using a likelihood ratio test. Linear regression analysis was used to evaluate the trend in the proportions of infants designated as being at low risk over time.

TABLE 1 Rochester Criteria for Infants at Low Risk of SBIs[9,27]

1. Previously healthy term infant without perinatal complications and with no previous antibiotic treatment
2. Normal physical examination findings (including no otitis media)
3. White blood cell count: 5000–15 000 cells per mm^3
4. Band count: <1500 cells per mm^3
5. Urinalysis: <10 white blood cells per high-power field in centrifuged catheterized specimen
No comment about stool

Reference 9 established the original Rochester criteria. Reference 27 used identical laboratory criteria and slightly different inclusion criteria.

RESULTS

Twenty-one studies met inclusion criteria; 14 were prospective studies (Tables 3 and 4) and 7 were retrospective (Table 5).[3,9–27,30] Among the prospective studies, 9 treated low-risk patients empirically with antibiotics, 4 monitored low-risk patients without antibiotic treatment, and 1 used both strategies.

TABLE 2 Variations of Rochester Criteria

Type of Low-Risk Criteria	Differences From Original Rochester Criteria	References
Rochester 2	If diarrhea, ≤5–10 WBCs per high-power field in stool	10, 17, 18, 20, 30
Modified Rochester	Normal inflammatory markers (C-reactive protein levels or ESR)	13, 19, 21
Milwaukee	CSF: <10 WBCs per mm^3; WBC count: <15 000 cells per mm^3 (no band criteria); urinalysis: ≤5–10 WBCs per high-power field, no bacteria; urine dipstick: negative LE/nitrite	14
Philadelphia	Infant observation score[33]: <10; WBC count: <15 000 cells per mm^3 (no band criteria); urinalysis: <10 WBCs per high-power field, few or no bacteria; CSF: <8 WBCs per mm^3, no bacteria, nonbloody	11
Philadelphia 2	WBC count: <15 000 cells per mm^3; band/neutrophil ratio: <0.2; CSF: <8 WBCs per mm^3, no bacteria, nonbloody	20, 22–25
Boston	WBC count: <20 000 cells per mm^3 (no band criteria); CSF: <10 WBCs per mm^3; urinalysis: <10 WBCs per high-power field, no LE	12, 24
Pittsburgh	Enhanced urinalysis: ≤9 WBCs per mm^3, negative Gram stain results; CSF: ≤5 WBCs per mm^3, negative Gram stain results (if <6 wk)	26
Impression of sepsis	"Not ill" or negative clinical impression of sepsis (history, physical examination, ESR of <30 mm/h, WBC count of <15 000 cells per mm^3)	3, 15, 16

WBC indicates white blood cell; ESR, erythrocyte sedimentation rate; CSF, cerebrospinal fluid; LE, leukocyte esterase. The infant observation score includes 5 observations, that is, quality of cry, reaction to parent stimulation and state variation, color, hydration, and response to social overtures, each scored on a scale of 1 to 5.[31]

The type of low-risk criteria was categorized, with 10 studies using variations of the Rochester criteria, 6 studies using Philadelphia criteria (2 comparing Rochester criteria with Philadelphia criteria), 2 studies using Boston criteria, 1 study using Pittsburgh criteria, 1 study using Milwaukee criteria, and 3 studies using "clinical impression of sepsis" or "not ill" descriptions (Tables 1 and 2). Studies were performed between 1979 and 1999. One study[12] included only children in the low-risk category, without a high-risk comparison group. Fever was defined as a temperature of >38.2°C in 1 study,[11] >38.1°C in 3 studies,[15,20,27] and >38.0°C in the rest of the studies.

SBIs included bacteremia, meningitis, bacterial diarrhea, pneumonia, and UTIs.[31] The defining characteristics for each type of infection varied slightly between the studies, most notably in the definition of UTI. Two studies accepted bagged urine specimens for culture, resulting in 8 diagnoses of UTIs in low-risk patients.[13,19] Ten studies diagnosed UTIs in patients with catheterized urine cultures with <50 000 colony-forming units of a single organism per milliliter.[11,12,14,17,18,20–23,25] Four studies provided no microbiologic definition of UTI or description of urine collection methods.[3,15,16,30] Another variation was the inclusion of pneumonia as a SBI without microbiologic documentation. All infants studied were between 0 and 90 days of age. Six studies included only infants in the first month of life, and 4 studies excluded infants in the first month of life. The majority of studies were limited to the first 2 months of life, with 6 studies extending to 3 months.

A summary of the prospective studies in which patients underwent observation alone is shown in Table 3.[10,11,18,19,22] A total of 1858 patients were included, and 870 were classified as being at low risk. Six patients with SBIs were missed, including 2 patients with bacteremia and 4 patients with UTIs. The first child with bacteremia received parenteral antibiotic treatment within 24 hours after presentation and recovered uneventfully.[11] The identity of the organism was not noted. The second child had a blood culture positive for *Yersinia enterocolitica* and fared well after treatment.[18] The authors noted that a confirmatory culture was not performed before initiation of treatment. Three urine specimens obtained with sterile technique yielded either group B streptococcus or *Escherichia coli*.[18] Those patients fared well with treatment. One urine specimen collected by bag yielded *E coli*.[19]

TABLE 3 Prospective Studies of Performance of Low-Risk Criteria for SBIs in Young Infants in Which Antibiotics Were Withheld From Low-Risk Patients

Year and Reference	Criteria Type	Age, d	No. of Patients	No. of High-Risk Patients	Cases of SBI in High-Risk Patients	Rate of SBIs in High-Risk Patients, %	No. of Low-Risk Patients	Cases of SBI in Low-Risk Patients	Rate of SBIs in Low-Risk Patients, %
1988[10]	Rochester 2	0–56	236	88	21	23.9	148	0	0.00
1993[11]	Philadelphia	29–56	747	460	64	13.9	287	1	0.35
1994[18]	Rochester 2	0–60	203				203	4	1.97
1997[19]	Modified Rochester	4–28	250	119	40	33.6	131	1	0.76
1999[22]	Philadelphia 2	29–60	422	321	43	13.4	101	0	0.00
Total			1858	988	168	20.6	870	6	0.67

TABLE 4 Prospective Studies of Performance of Low-Risk Criteria for SBIs in Young Infants With Empiric Use of Antibiotics for All Patients

Year and Reference	Criteria Type	Age, d	No. of Patients	No. of High-Risk Patients	Cases of SBI in High-Risk Patients	Rate of SBIs in High-Risk Patients, %	No. of Low-Risk Patients	Cases of SBI in Low-Risk Patients	Rate of SBIs in Low-Risk Patients, %
1985[9]	Rochester	0–90	233	89	22	24.7	144	1	0.69
1987[16]	Impression of sepsis	0–56	97	36	5	13.9	61	2	3.28
1988[15]	Impression of sepsis	0–14	35	11	4	36.4	24	2	8.33
1992[12]	Boston	28–89	503				503	27	5.37
1993[14]	Milwaukee	28–56	534	391	23	5.9	143	1	0.70
1994[18]	Rochester 2	0–60	802	494	61	12.3	308	1	0.32
1994[13]	Modified Rochester	0–31	254	120	37	30.8	134	8	5.97
2004[30]	Rochester 2	0–90	1378	922	118	12.8	456	12	2.63
2005[20]	Rochester 2 and Philadelphia 2	0–56	259	186	63	33.9	73	2	2.74
2007[21]	Modified Rochester	Neonate	386	220	107	48.6	166	1	0.60
Total			4481	2469	440	23.8	2012	57	2.71

TABLE 5 Retrospective Studies of Performance of Low-Risk Criteria for SBIs in Young Infants

Year and Reference	Criteria Type	Age, d	No. of Patients	No. of High-Risk Patients	Cases of SBI in High-Risk Patients	Rate of SBIs in High-Risk Patients, %	No. of Low-Risk Patients	Cases of SBI in Low-Risk Patients	Rate of SBIs in Low-Risk Patients, %
1986[27]	Rochester	0–90	117	47	4	8.5	70	3	4.29
1990[3]	Impression of sepsis	0–91	443	222	48	21.6	221	5	2.26
1997[17]	Rochester 2	0–29	119	71	19	26.8	48	3	6.25
1997[25]	Philadelphia 2	3–90	492	196	52	26.5	296	8	2.70
1999[23]	Philadelphia 2	3–28	254	145	27	18.6	109	5	4.59
2000[24]	Boston and Philadelphia 2	1–28	372	141	37	26.2	231	8	3.46
2001[26]	Pittsburgh	0–60	404	277	41	14.8	127	0	0.00
Total			2201	1099	228	19.8	1102	32	2.70

TABLE 6 Comparison of Performance of Low-Risk Criteria for SBIs in Young Infants, According to Study Design

Type of Study	Total No. of Patients	No. of Patients With SBIs	No. of High-Risk Patients	Pooled Rate of SBIs in High-Risk Patients, Estimate (95% CI), %[a]	No. of Low-Risk Patients	Pooled Rate of SBIs in Low-Risk Patients, Estimate (95% CI), %[a]	RR of SBI in High-Risk vs Low-Risk Patients (95% CI)
Prospective, no antibiotic treatment	1858	174	988	20.6 (9.4–31.8)	870	0.67 (−0.04–1.30)	30.56 (7.0–68.13)
Prospective, empiric antibiotic treatment	4481	497	2469	23.8 (13.4–34.1)	2012	2.71 (0.93–4.50)	8.75 (2.29–15.21)
Retrospective	2201	260	1099	19.8 (14.5–25.1)	1102	2.70 (0.40–5.02)	6.93 (3.10–10.75)
Retrospective and prospective, empiric antibiotic treatment	6682	757	3568	22.3 (15.8–28.3)	3114	2.71 (1.4–4.0)	7.74 (3.82–11.67)

[a] Estimated by using the β-binomial model for overdispersed data.[29]

In the rest of the studies summarized in Tables 4 and 5 (prospective studies in which patients received empiric antibiotic treatment and retrospective studies), 89 low-risk infants (2.71%) were diagnosed as having SBIs. This total included 2 cases of meningitis (1 with UTI and 1 with bacteremia), 22 cases of bacteremia (1 with gastroenteritis and 1 with osteomyelitis), 39 cases of UTI, and 14 cases of gastroenteritis. Twelve cases of SBI did not have a source identified.

Table 6 shows a comparison of the performance of the low-risk criteria for SBIs in young infants according to study design. The overall validity of the low-risk criteria in pooled studies was assessed by calculating the RR for SBI in high-risk versus low-risk infants. The RR reached statistical significance in all 3 categories of studies. In prospective studies with no empiric antibiotic treatment, the RR was 30.56 (95% CI: 7.0–68.13). In prospective studies with empiric antibiotic treatment, the RR was 8.75 (95% CI: 2.29–15.21). In retrospective studies, the RR was 6.93 (95% CI: 3.10–10.75). Of importance, there was a statistically significant difference in the rates of SBIs in low-risk patients in the prospective studies with no empiric antibiotic treatment, compared with all other studies (*P* for difference = .010). When prospective studies with no empiric antibiotic treatment were compared with all other studies, no significant difference in the rate of SBIs in high-

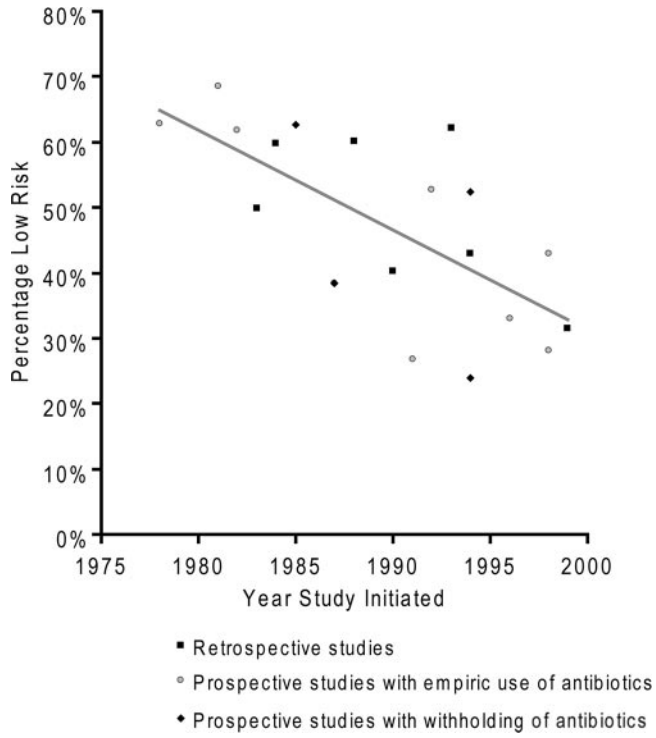

FIGURE 1
Proportions of infants assigned to the low-risk category according to year of study initiation, with a statistically significant trend toward assignment of fewer infants to the low-risk category over time ($P = .001$).

risk patients was found (RR: 1.10; $P = .75$).

An analysis examining the proportion of infants designated as low risk in all studies showed a significant trend toward assigning fewer infants to the low-risk category over time ($\rho = -0.67$; $P = .001$). The slope parameter of the linear regression model of the proportions of infants designated as low risk by time (year) was −0.015 ($P < .001$). Early studies placed ~60% of children in the low-risk category. By the middle 1990s, only 30% of children were considered at low risk, as illustrated in Fig 1.

DISCUSSION

The impetus for this study was the apparent discrepancy in the rate of SBIs among low-risk febrile infants reported in the literature. Previous studies reported a range of rates of SBIs in low-risk infants of 0% to 8.3%.[10,15,22,26] This can be explained, in part, by the different sets of criteria used by various investigators (Table 2).[3,9–26,30] We showed that the rates of SBIs in low-risk patients in both retrospective studies and prospective studies using empiric antibiotic treatment were the same (2.7%) and were significantly different from the rate of SBIs in low-risk patients in prospective studies in which antibiotics were withheld (0.67%). We hypothesized that the low-risk criteria would function best when used in prospective studies in which low-risk patients underwent observation alone. Without reliance on empiric antibiotic treatment, it would be essential to capture all infants at risk of early deterioration in the high-risk group. Careful sample collection, as well as meticulous physical examination, excluded infants with SBIs from the low-risk group.

For physicians to rely on clinical algorithms, they must be convinced that patients will not be placed in jeopardy. The clinical predictability provided by low-risk criteria will be deemed satisfactory if the children identified as being at low risk either do not have a SBI or remain in stable condition until the SBI is recognized. In prospective trials that treated low-risk infants with observation alone, the low-risk criteria "missed" SBIs in 6 patients (bacteremia in 2 patients and UTIs in 4 patients). One of the cases involved a positive urine culture from a bagged specimen, which may represent a contaminant. These patients were treated with appropriate antibiotics when the cultures yielded positive results, and all recovered uneventfully. Therefore, careful application of these low-risk criteria was very effective in identifying children from whom empiric antibiotic therapy could be withheld.

Overall, data from 8540 infants were analyzed in this study. The total number of SBIs was 931, that is, 10.9%, consistent with rates commonly reported in the literature. With the use of low-risk criteria, ~30% of febrile infants can be identified as being at low risk for SBIs and can be treated with observation alone. These patients can be spared the negative effects that may be associated with empiric use of antibiotics, including cost, adverse effects of medications, development of resistant organisms, and psychosocial stresses on family dynamics. The criteria must be applied carefully to avoid misassignment of infants. Special attention should be given to the physical examination and medical history.

This study represents a comprehensive review of the literature that has evaluated the effectiveness of low-risk criteria in the identification of infants unlikely to have SBIs over the previous

23 years. The major weakness of this analysis is that the studies demonstrated minor variations in the low-risk criteria used and the age groups included. Although these small differences in demographic characteristics prohibit a "clean" comparison of all of the studies, we conclude that the observed difference in the performance of low-risk criteria was a function of the study design. When low-risk criteria are applied prospectively after careful evaluation, clinicians should be confident in withholding empiric antibiotic treatment.

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Performance of Low-Risk Criteria in the Evaluation of Young Infants With Fever: Review of the Literature

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Febrile Infants at Low Risk for Serious Bacterial Infection—An Appraisal of the Rochester Criteria and Implications for Management

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ABSTRACT. *Objective.* **Prospective studies were conducted to test the hypothesis that infants *unlikely* to have serious bacterial infections (SBI) can be accurately identified by low risk criteria.**

Methods. **Febrile infants (rectal T ≥ 38°C) ≤60 days of age were considered at low risk for SBI if they met the following criteria: 1) appear well; 2) were previously healthy; 3) have no focal infection; 4) have WBC count 5.0–15.0 × 10^9 cells/L (5000–15 000/mm^3), band form count ≤ 1.5 × 10^9 cells/L (≤1500/mm^3), ≤10 WBC per high power field on microscopic examination of spun urine sediment, and ≤5 WBC per high power field on microscopic examination of a stool smear (if diarrhea). The recommended evaluation included the culture of specimens of blood, cerebrospinal fluid, and urine for bacteria. Outcomes were determined. The negative predictive values of the low risk criteria for SBI and bacteremia were calculated.**

Results. **Of 1057 eligible infants, 931 were well appearing, and, of these, 437 met the remaining low risk criteria. Five low risk infants had SBI including two infants with bacteremia.**

The negative predictive value of the low risk criteria was 98.9% (95% confidence interval, 97.2% to 99.6%) for SBI, and 99.5% (95% confidence interval, 98.2% to 99.9%) for bacteremia.

Conclusions. **These data confirm the ability of the low risk criteria to identify infants *unlikely* to have SBI. Infants who meet the low risk criteria can be carefully observed without administering antimicrobial agents.** ***Pediatrics* 1994;94:390–396; *febrile infants, bacteremia, low risk criteria, serious bacterial infection.***

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These data were presented in part before the Society for Pediatric Research in Washington, DC in May, 1989 (McCarthy et al) and the Ambulatory Pediatric Association in Baltimore, Maryland in May, 1992 (Jaskiewicz et al).

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ABBREVIATIONS. SBI, serious bacterial infection; CSF, cerebrospinal fluid; UTI, urinary tract infection.

Strategies to identify infants less than 2 to 3 months of age with serious bacterial infection (SBI) lack sufficient sensitivity to be clinically useful.[1–10] Therefore, the conservative management of febrile infants ≤60 days of age includes a complete evaluation for sepsis (blood, urine, and cerebrospinal fluid specimens for culture), hospitalization, and parenteral antimicrobial therapy for a minimum of 48 hours.[11] Despite such recommendations, practice varies widely.[12–15] Our group has attempted to use low risk criteria to determine whether infants *unlikely* to have SBI can be identified with sufficient accuracy to consider less aggressive management for these infants.

The low risk criteria evolved from studies designed to test the hypothesis that well appearing febrile infants who meet defined history, physical examination, and laboratory criteria are unlikely to have SBI.[16–18] These low risk criteria are known as the Rochester criteria for the evaluation of febrile infants (rectal T ≥ 38°C) ≤60 days of age (Table 1).

The purpose of the present analysis was twofold. First, we determined the ability of the Rochester criteria to identify infants unlikely to have SBI and, particularly, bacteremia, based on the negative predictive value of the criteria when applied to a large number of prospectively evaluated febrile infants. Second, we used these data to determine if refinements of the Rochester criteria should be studied further.

METHODS

The present analysis includes data collected during three prospective studies (Table 2). For each study, only infants ≤60 days of age who had a documented rectal temperature ≥38°C at home or at the time of medical evaluation were eligible for inclusion in the study. Written informed consent was obtained for all infants enrolled in a study in which an intervention (eg, antimicrobial therapy) was tested, and these studies were approved by all appropriate human investigation committees.

Patient Populations (Table 2)

Study 1

From July 1, 1987 to June 30, 1992 consecutive febrile infants seen in the Emergency Department or Pediatric Clinic at Strong Memorial Hospital in Rochester, NY were prospectively evaluated. Eighty-six infants participated in a previously published intervention study[19] and are included in the present analysis.

TABLE 1. The Rochester Criteria

1) Infant appears generally well
2) Infant has been previously healthy
   - born at term (≥37 weeks gestation)
   - did not receive perinatal antimicrobial therapy
   - was not treated for unexplained hyperbilirubinemia
   - had not received and was not receiving antimicrobial agents
   - had not been previously hospitalized
   - had no chronic or underlying illness
   - was not hospitalized longer than mother
3) No evidence of skin, soft tissue, bone, joint, or ear infection
4) Laboratory values:
   - peripheral blood WBC count 5.0 to 15.0 × 10^9 cells/L (5000 to 15 000/mm^3)
   - absolute band form count ≤1.5 × 10^9 cells/L (≤1500/mm^3)
   - ≤10 WBC per high power field (×40) on microscopic examination of a spun urine sediment
   - ≤5 WBC per high power field (×40) on microscopic examination of a stool smear (only for infants with diarrhea)

Seventeen of these infants were enrolled at Rochester General Hospital.[19]

Study 2

From July 1, 1984 to November 30, 1984, consecutive febrile infants evaluated for suspected sepsis and hospitalized at Strong Memorial Hospital in Rochester, NY were prospectively evaluated.

Study 3

During 1985 through 1988 participants in the Febrile Infant Collaborative Study Group prospectively identified febrile infants at low risk for SBI by the Rochester criteria. In a multicenter interventional study, these infants were randomly assigned to hospitalization for observation only or hospitalization and parenteral antimicrobial therapy.

Data Collection

Data obtained on all infants included: age, sex, race, global assessment (judged to be well or ill appearing, by house officer or attending physician assessment without reference to specific criteria and without reliability testing), past medical history, physical examination, and laboratory evaluation as detailed in Table 1. Examination of a stool smear in infants with diarrhea was not done in Study 2 (Table 2). Specimens of blood, CSF, and urine (obtained by bladder tap or catheterization) for culture for bacterial pathogens were obtained. Urine specimens from selected low risk infants observed without antimicrobial therapy during 1989 through 1992 were not cultured because of physician preference. Additional specimens for culture were obtained at the discretion of the examining physician. Chest roentgenograms were performed when clinically indicated (tachypnea, cough, focal abnormality on physical examination of lungs). Urinalyses and stool smear examinations were performed by examining physicians. Skin, soft tissue, and ear infections were diagnosed by physical examination.

Specimens for culture were evaluated using standard techniques in the diagnostic microbiology laboratories of the participating centers. Commensal bacteria isolated from blood or CSF specimens were considered contaminants (eg, *Staphlococcus epidermidis*, α- or γ-hemolytic streptococci (excluding enterococcus, *Streptococcus pneumoniae*, and group D streptococci), diptheroid sp., bacillus sp.). Serious bacterial infections were defined as bacteremia, meningitis, osteomyelitis, suppurative arthritis, soft tissue infections (cellulitis, abscess, mastitis, omphalitis), urinary tract infection, gastroenteritis, and pneumonia. Soft tissue infections were defined by physical examination with or without isolation of a bacterial pathogen. UTI was defined as the isolation of >10^4 colony forming units per milliliter of urine of a single pathogen. Urine specimens with more than one isolate were considered to be contaminated. Bacterial pneumonia was defined as a focal infiltrate on chest roentgenogram in association with a bacterial pathogen isolated from the blood or the presence of capsular polysaccharide in the urine detected by counterimmunoelectrophoresis.

All evaluations were performed and data recorded by the house officer and/or supervising attending physician in the emergency department or pediatric clinic where the infant was seen. An investigator verified age, temperature, and completeness of data collection for each infant by chart review. All infants in each study for whom complete data were available were classified as low risk or not low risk by the Rochester criteria in Table 1 (excluding stool smear examination for infants in Study 2, Table 2). Since well appearing infants who do not meet at least one of the low risk criteria are excluded from the low risk group, such infants were included in the analysis in the not low risk group even when all classifying data were not available. Treatment decisions were made on an individual basis by the evaluating physician, except when the infant was enrolled in a protocol mandating treatment versus no treatment (Study 1[19] and Study 3 (Table 2)).

Statistical Methods

Chi square analysis was used for comparisons of sex, age, and race between low risk and not low risk infants and for comparisons of the proportion of SBI in low risk and not low risk groups between studies. The difference in the proportion of SBI among low risk infants in each of the three studies (Table 2) was not statistically significant, therefore data from low risk infants in each study were combined. Since only low risk infants were included in Study 3, these data were not used to calculate the negative predictive value of the low risk criteria. The differences in the proportion of SBI among low risk infants and among not low risk infants between Studies 1 and 2 were not statistically significant. Therefore, data from Studies 1 and 2 were combined for complete analysis and calculation of the negative predictive value of the criteria.

The operating characteristics of the low risk criteria and the criteria components were calculated by the following: sensitivity, the rate of a positive test in infants with disease; specificity, the rate of a negative test in infants without disease; and negative predictive value, the rate of no disease in infants who test negative. The 95% confidence intervals of each test's operating characteristics were calculated using the method of Fleiss.[20]

RESULTS

From 1984 to 1992, 1057 febrile infants ≤ 60 days of age were identified as eligible for analysis (Studies 1 and 2 (Table 2) and Fig 1). Infants with insufficient data to determine risk (N = 54) and ill appearing infants (N = 72) were excluded from further analysis. Of 931 evaluable, well appearing infants, 437 met all low risk criteria and 494 did not (Fig 1). An additional 74 low risk infants (Study 3 (Table 2)) identified by the Rochester criteria were included in discussion of the low risk group only, bringing the total number of low risk infants to 511 (Fig 1).

Table 3 shows the distribution of the low risk and not low risk infants by age. There were no differences in sex, race, or age between low risk and not low risk infants. SBI was documented in 66 (7.1%) of 931 study infants and bacteremia in 13 (1.4%). The distribution of SBI and bacteremia by age and risk group is shown in Fig 2.

Specimens cultured for bacterial pathogens and isolation rates from the study infants are shown in Table 4. Sixty-six infants had SBI. No bacterial pathogens were isolated from seven infants with skin or soft tissue infections and from one infant with pneumonia. The same pathogen was isolated from blood and urine in three infants and from urine and soft tissue in one infant.

TABLE 2. Studies Included in Present Analysis

Study	Years	Total	Low Risk (SBI/Bacteremia)	Not Low Risk	Ill Appearing,* Insufficient Data
1 McCarthy CA and Jaskiewicz JA, et al‡	1987 through 1992	978	381 (5/2)	472	125
2 Dagan R	1984	79	56 (0/0)	22	1
Total 1		**1057**	**437 (5/2)**	**494**	**126**
3 Febrile Infant Collaborative Study Group	1985 through 1988	74	74 (0/0)		
Total 2			**511 (5/2)**		

* Not included in analysis.
‡ Reference 19.

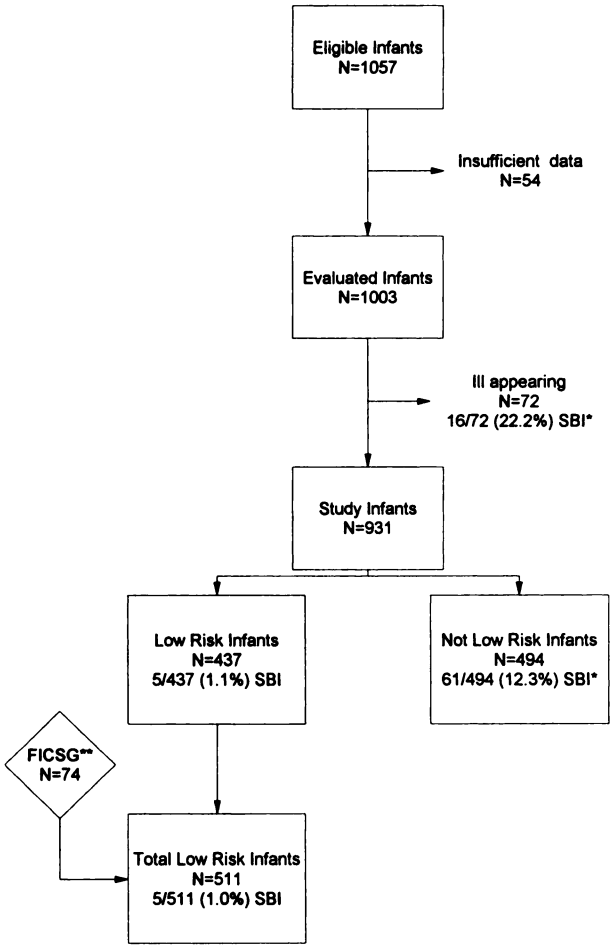

Fig 1. Algorithm to identify low risk febrile infants. *Difference from low risk group: $P < .05$. **Febrile Infant Collaborative Study Group.

TABLE 3. Age Distribution by Risk Group

Age (days)	Total (n = 1005)		Low Risk (n = 511)*		Not Low Risk (n = 494)	
	n	(%)	n	(%)	n	(%)
0 to 14	142	(14.1)	73	(14.3)	69	(13.9)
15 to 30	294	(29.2)	154	(30.1)	140	(28.2)
31 to 45	303	(30.2)	157	(30.7)	146	(29.7)
46 to 60	266	(26.5)	127	(24.9)	139	(28.2)

* Includes 74 low risk infants from Study 3 (Table 2).

Low Risk Infants

SBI occurred in five (1.0%) of 511 low risk infants. Three infants, age 25, 41, and 54 days, had UTI caused by Group B streptococcus, *E. coli*, and *E. coli*, respectively. None of the three infants were initially treated with antimicrobial agents, but all were treated as soon as cultures became positive and all did well. One 34-day-old infant was hospitalized for observation and did not receive empiric antimicrobial therapy. When *Yersinia enterocolitica* was isolated from a blood specimen on the second hospital day, antimicrobial therapy was begun and the infant did well. A repeat blood specimen for culture was not obtained before antimicrobial therapy was begun. One 29-day-old infant, enrolled in a study of outpatient management of selected low risk infants,[19] was treated with intramuscular ceftriaxone at the time of evaluation. At the 24-hour follow-up, the infant was afebrile and appeared well, but the blood culture was positive for *Neisseria meningitidis*. The infant was hospitalized and received a total of 7 days of once daily intramuscular ceftriaxone and did well. At the time of hospitalization two doses of ceftriaxone had already been given, therefore a repeat blood culture was not obtained.

Of 511 low risk infants, 308 (60.3%) were initially treated with antimicrobial agents and 203 (39.7%) were not. Eighty-six low risk infants were enrolled in a study of outpatient management of febrile infants and all received intramuscular ceftriaxone (Study 1 (Table 2)). Seventy-four low risk infants were randomized to receive either parenteral antimicrobial agents following hospitalization (N = 41) or hospitalization and observation alone (N = 33) (Study 3 (Table 2)). The remaining low risk infants were given antimicrobial therapy at the discretion of the evaluating physician.

Negative Predictive Value of the Rochester Criteria

Five of 437 low risk infants in Studies 1 and 2 (Table 2) had SBI and two had bacteremia. The statistical analysis did not include the 74 infants from Study 3 (Table 2). Based on these data, the negative predictive value of the Rochester criteria is 98.9% with a 95% confidence interval of 97.2% to 99.6% for any SBI, and 99.5% with a 95% confidence interval of 98.2% to 99.9% for bacteremia.

Not Low Risk Infants

SBI occurred in 61 (12.3%) of 494 infants who did not meet the low risk criteria, including UTI (31 infants), skin or soft tissue infection (18), bacteremia (11), gastroenteritis (4), and pneumonia (1, lobar infiltrate and urine positive for *S. pneumoniae* antigen

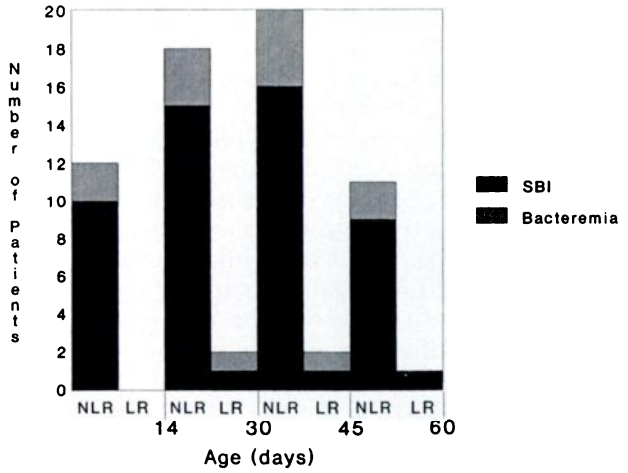

Fig 2. Distribution of SBI and bacteremia in 1005* febrile infants. LR, low risk; NLR, not low risk *includes 74 low risk infants from study 3, Table 2.

by counterimmunoelectrophoresis). Three infants with UTI also had bacteremia, and one infant with UTI had mastitis. (Complete data are available from K.R.P. upon request.)

Evaluation of the Components of the Rochester Criteria

Global Assessment

Infants who were not well appearing were managed expectantly and not included for data analysis. Of 72 ill appearing infants who had outcomes ascertained, the 16 SBIs included eight UTI, three meningitis, two bacteremia, two mastitis, and one gastroenteritis.

Medical History

Of the 494 infants excluded from the low risk group, 181 (36.6%) were not previously healthy by history. Fourteen (7.7%) of these infants had SBI, including five (2.8%) infants with bacteremia. A history of not being previously healthy was the only reason for excluding 92 infants from the low risk group. One infant with only a history of phototherapy for unexplained hyperbilirubinemia had Group B streptococcus bacteremia. One infant with a history of both prior hospitalization and prior antimicrobial therapy had *E. coli* UTI. Twenty-one infants excluded from the low risk group by history did not have urinalyses performed. Of these infants, one who had only a history of prematurity had *Salmonella* bacteremia. Only two infants had a history of chronic illness and neither had SBI. No infant excluded solely because of perinatal antimicrobial therapy (N = 7), hospitalization longer than the mother (N = 1), or both (N = 16) had SBI.

Physical Examination

Skin, soft tissue, or ear infection was observed in 97 (20.0%) of the 494 infants excluded from the low risk group. Seventy-nine infants had otitis media, and in 36 otitis media was the only reason for exclusion from the low risk group. None of the 79 infants with otitis media had bacteremia or meningitis. Four infants with otitis media had *E. coli* UTI. One of these infants was also excluded from the low risk group by history, and three had abnormal laboratory assessments.

TABLE 4. Isolation Rates of Bacterial Pathogens in 931 Study Infants

Specimen	Patients		Bacterial Pathogen Isolated		Bacterial Contaminant Isolated	
	n	(%)	n	(%)	n	(%)
Blood	922	(99.0)	13	(1.4)	48	(5.2)
CSF*	902	(97.0)	0	(0.0)	47	(5.2)
Urine	694	(74.5)	34	(4.9)	108	(15.6)
Stool	63	(6.8)	4	(6.3)	0	(0.0)
Other	131	(14.1)	11	(8.4)	0	(0.0)

* CSF, cerebrospinal fluid.

Eighteen infants had skin or soft tissue infection, including cellulitis (9), omphalitis (3), mastitis (2), abscess (3), and paronychia (1). Specimens from these sites were obtained from 11 infants and all yielded pathogens. Isolates included *Staphylococcus aureus* (6), *E. coli* (3), Group B streptococcus (1), and *Neisseria sp.* (1). Seven infants with skin or soft tissue infection were excluded from the low risk group on that basis alone. No infant with skin or soft tissue infection had bacteremia or meningitis. No study infant had a bone or joint infection.

Laboratory Assessment

Of the 494 infants excluded from the low risk group, 325 (65.8%) had at least one abnormal laboratory test. One or more abnormal laboratory test was the only reason for excluding 226 infants from the low risk group. Specificity, sensitivity, and negative predictive value for each test was calculated. No individual test or combination of tests had a sensitivity of ≥75%. The band form count was $\leq 1.5 \times 10^9$ cells/L ($\leq 1500/mm^3$), and the urine WBC count was ≤10 for most infants without SBI, having specificities of 96% and 98%, respectively.

Urinalysis

Urinalyses were obtained from 907 (90.2%) of 1005 infants. Urine specimens from 42 (4.6%) of 909 infants had >10 white blood cells per high power field on microscopic examination of spun sediment. Twenty infants with >10 WBC on urinalysis had UTI (17 *E. coli*, 1 Group B streptococcus, and 2 *Enterobacter cloacae*), 2 had *E. coli* UTI and bacteremia, and 1 had *S. aureus* bacteremia. Results of urinalyses were recorded in 32 of 34 infants with UTI. Of these, 11 specimens had ≤10 WBC per high power field. Eight of these infants were excluded from the low risk group by other criteria, and three met all low risk criteria.

Urinalyses were not recorded for 98 infants excluded from the low risk group by one or more of the other criteria. Eleven of these infants had SBI; three of them were bacteremic.

Stool Smear

Four infants with diarrhea had >5 WBC per high power field on microscopic examination of a stool

smear. Cultures of stool specimens from two of these infants revealed no pathogens, no stool specimen was sent for culture from the third infant, and both *Salmonella sp.* and *Yersinia enterocolitica* were isolated from a stool specimen from the fourth infant. *Salmonella enteritidis* was isolated from stool specimens from three additional infants. Stool smear results were not recorded for two infants, and one had a normal stool smear. All four infants with bacterial gastroenteritis had either an abnormal peripheral blood WBC count, band form count, or both.

DISCUSSION

A recent meta-analysis of studies of febrile infants ≤60 days of age showed that infants meeting the Rochester criteria had a lower probability of having SBI than if other strategies were employed.[21] The present study prospectively evaluated a large number of febrile infants to further test the ability of the Rochester criteria to accurately identify infants unlikely to have SBI. The negative predictive value of the Rochester criteria was chosen as the most appropriate test to identify infants *unlikely* to have SBI. The 95% confidence interval for the negative predictive value of the Rochester criteria for SBI (97.2% to 99.6%) and for bacteremia (98.2% to 99.9%) confirm the ability of the Rochester criteria to identify febrile infants unlikely to have SBI.

Because the Rochester criteria were designed to identify infants unlikely to have SBI, only well appearing infants were included in the present study. By excluding ill appearing infants from the study population, the prevalence of SBI in our study is lower than that observed in previous studies (7% vs 9%).[9] While the negative predictive value of the Rochester criteria may be lower when the criteria are applied to a population including ill appearing infants (higher prevalence of SBI in this group), it is most appropriate to apply the Rochester criteria only to well appearing febrile infants. Although not stated as a criterion in early studies,[16,18] ill appearing infants have always been excluded when evaluating the low risk criteria. Most investigators agree that ill appearing infants have a higher likelihood of SBI than well appearing infants,[1,3,4,6,7] and there is little controversy regarding their management. The consensus is that such infants should be hospitalized and treated with antimicrobial therapy regardless of the remainder of their evaluation.

The present study shows that among well appearing infants the Rochester criteria work well. We believe the narrow confidence interval around the negative predictive value of the Rochester criteria supports the clinical use of these criteria.

Management of Infants Who Meet the Rochester Criteria

Our data strongly suggest that infants who meet the Rochester criteria can be carefully observed without parenteral antimicrobial agents. Over one-third of the low risk infants in the present study were not initially treated with antimicrobial therapy, and all did well. Four of five low risk infants with SBI did not receive antimicrobial therapy until cultures became positive. With careful observation and follow-up, appropriate therapy was initiated when SBI was diagnosed and no infant experienced untoward effects. One low risk infant with *N. meningitidis* bacteremia initially received antimicrobial therapy, and the outcome of this particular infant without antimicrobial therapy remains unknown. It has been shown, however, that in some cases bacteremia with this organism has resolved without antimicrobial therapy.[22] Other investigations support observation for low risk infants. In a study by Wasserman et al[15] five infants less than 3 months of age were hospitalized and observed without antimicrobial therapy until cultures of blood (1), urine (3), and stool (1) were reported positive for bacterial pathogens. Outcomes "did not appear to be altered by the delay in diagnosis and treatment".[15] A recent study by Baker et al[23] also demonstrated that selected febrile infants 29 to 56 days of age may be managed without antimicrobial therapy.

An alternative strategy for the management of the low risk febrile infant is to administer a single dose of intramuscular ceftriaxone following a complete laboratory evaluation for suspected sepsis (cultures of specimens of blood, CSF, and urine (obtained by bladder tap or catheterization)) and to provide as careful outpatient follow-up as possible. This approach was studied in infants ≤60 days of age by McCarthy et al[19] with no bad outcomes. Baskin et al[24] also managed selected febrile infants between 28 and 89 days of age as outpatients following a single dose of intramuscular ceftriaxone. All of the infants with SBI subsequently received appropriate antimicrobial therapy and except for a 7-day delay in the diagnosis of osteomyelitis in one patient, all were well at follow-up. Outpatient management of selected febrile infants with a single dose of intramuscular ceftriaxone was found to be cost effective as analyzed by Lieu et al.[25] This strategy mandates that a lumbar puncture be done and blood, CSF, and urine specimens be obtained for culture.

It is important to recognize that the administration of parenteral antimicrobial agents to a febrile infant is not a substitute for careful observation. The decision to observe a low risk febrile infant at home with or without administering a parenteral antimicrobial agent should be made only after careful assessment of the caregiver and guaranteeing the availability of a responsible physician. The caregiver must appreciate that the infant's condition may change and should be told what to watch for and when to call. Parents of infants managed as outpatients can be given written instructions to assess the infant at least every 4 hours and to call the physician for any concerns or for any changes, such as onset or change in skin rash, cyanosis or mottling, poor feeding or vomiting, difficulty consoling or arousing, jerking movements or eye rolling, or bulging fontanelle. Caregivers should have a telephone, have the telephone number of the responsible physician, and if the infant's condition changes, be able to meet the physician within 30 minutes. Obviously, such rigid standards cannot be met in many urban Emergency

Department settings, and hospitalization may be necessary.

Recommendation

Based on data from this study and other reports, we make the following recommendation:

Febrile infants ≤60 days of age who meet the Rochester criteria may be managed by observation without antimicrobial therapy or alternatively may receive intramuscular ceftriaxone as a single dose. Blood and urine specimens for bacterial culture should be obtained on all infants, and, if antimicrobial therapy is chosen, a lumbar puncture should be performed and cerebrospinal fluid cultured for bacterial pathogens prior to the administration of the antimicrobial agent. These management options may be exercised in either the inpatient or outpatient setting. Infants who are managed as outpatients require close observation by competent caregivers at home and availability of a responsible physician for follow-up. Infants who meet the Rochester criteria but who cannot be adequately observed at home should be hospitalized though not necessarily treated. In our study, low risk infants randomized to be observed in hospital without receiving antimicrobial agents were discharged from the hospital an average of one day earlier than low risk infants who were hospitalized and treated (Febrile Infant Collaborative Study Group).

Reappraisal of the Rochester Criteria

While the Rochester criteria identify febrile infants who are unlikely to have SBI, 88% of the infants studied who did not meet the low risk criteria also did not have SBI. Evaluation of the individual components of the low risk criteria suggest that the criteria could be modified to include additional infants in the low risk group without missing SBI. Three components of the criteria warrant further discussion and evaluation:

Medical History

Seven history items were used to define previously healthy infants (Table 1). In our study, no infant who had received perinatal antimicrobial therapy, had been hospitalized longer than the mother, or both, but was otherwise low risk had SBI. Neither of the two infants with chronic illness had SBI. Each of the other history items identified infants with SBI who would otherwise have been classified as low risk. Though the numbers are small in this study, the data suggest that perinatal antimicrobial therapy and hospitalization longer than mother could be omitted as medical history components of the low risk criteria.

Physical Examination

Skin, soft tissue, skeletal, and ear infections in young infants have been associated with SBI.[26–29] Dagan et al[16] reported that none of 13 infants excluded from the low risk group only because of otitis media had systemic infections. In a second study, Dagan and colleagues performed tympanocenteses on 40 febrile infants ≤60 days of age.[18] Ten of 11 infants with nonpurulent middle ear fluid met all low risk criteria and did well without antimicrobial therapy. In the present study no infant excluded from the low risk group only because of otitis media had a systemic infection. In a recent study, 60 of 827 well appearing febrile infants <2 months of age had no evidence of bacterial infection except otitis media and only 1 had SBI (UTI).[30] These results support the findings of the present study and suggest that infants who are excluded from the low risk group only because of otitis media are at low risk for systemic bacterial disease. Outpatient management with oral antimicrobial therapy for infants with otitis media who meet all other low risk criteria merits further study.

Skin, soft tissue, and skeletal infections were used to exclude infants from the low risk group, but, because of the potential for bacteremic disease, were also used in the definition of SBI. Infants with skin and soft tissue infections are similar to infants who appear ill, because antimicrobial therapy is clearly indicated. Such infants should be completely evaluated for possible sepsis, but it may be possible to manage selected infants as outpatients with appropriate systemic antimicrobial agents.

Urinalysis

Previous studies have suggested that as many as 50% of infants with UTI may have a normal urinalysis.[31] In our study, 35% of the infants with UTI had a normal urinalysis, and three of these infants met all low risk criteria for SBI. Although bacteriuria in the absence of inflammatory cells in the urine could represent asymptomatic bacteriuria,[32] these infants met the study definition for having a UTI. Since urinary tract infections comprised over half of the SBI in the present study, there is a clear need for improved methods to identify UTI before culture results are known. A recent study demonstrated that, when fresh urine (<10 minutes after collection) is evaluated for the presence of bacteria by Gram stain or phase microscopy in addition to testing for either nitrite and leukocyte esterase or WBC, most UTIs can be diagnosed.[33] Urinalysis should continue to be part of the evaluation of febrile infants. How the urine should be analyzed needs clearer definition.

Conclusion

The suggested modifications of the low risk criteria will need to be prospectively validated on a large cohort of febrile infants ≤60 days of age. Until UTI can be more accurately diagnosed by urinalysis all febrile infants should have a sterile (bladder catheterization or suprapubic tap) urine specimen cultured. Final management decisions for all febrile infants in this age group will depend upon the ability of caregivers to carefully observe their infants, the ease of access to medical care if the infants should clinically worsen, and the assurance of careful follow-up.

ACKNOWLEDGMENTS

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MOUNTING SENSE OF JOB MALAISE PROMPTS MORE HEALTH-CARE WORKERS TO JOIN UNIONS

In search of job security and a voice in health-care reform, a growing number of workers at hospitals, nursing homes, and rehabilitation facilities are joining labor unions.

Hospital workers filed 158 petitions for union elections in 1993, up from only 19 in 1989, according to a study by Management Science Associates, Inc, a labor consulting firm. And unions won 58% of health-care elections in 1993—the highest win rate in the industry since 1984, according to Modern Health Care, an industry journal.

Tomsho R. *The Wall Street Journal.* 1994.

Noted by J.F.L., MD

Febrile Infants at Low Risk for Serious Bacterial Infection––An Appraisal of the Rochester Criteria and Implications for Management

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Ambulatory care of febrile infants younger than 2 months of age classified as being at low risk for having serious bacterial infections

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We prospectively examined whether febrile infants younger than 2 months of age who were defined as being at low risk for having bacterial infection could be observed as outpatients without the usual complete evaluation for sepsis and without antibiotic treatment. A total of 237 previously healthy febrile infants were seen at the Pediatric Emergency Room over 17½ months. One hundred forty-eight infants (63%) fulfilled the criteria for being at low risk: no physical findings consisting of soft tissue or skeletal infections, no purulent otitis media, normal urinalysis, <25 white blood cells per high-power field on microsopic stool examination, peripheral leukocyte count 5000 to 15,000/mm³ with <1500 band cells/mm³. One infant appeared too ill to be included, and had sepsis and meningitis. None of the 148 infants at low risk had bacterial infections, versus 21 of 88 (24%) of those at high risk (P <0.0001); eight of 88 (9%) had bacteremia. Of the 148 infants classified as being at low risk for having bacterial infection, 62 (42%) were discharged to home, and 72 (49%) were initially observed for ≤24 hours and then discharged. Seventeen infants (11%) were hospitalized: in six, low risk became high risk; six had indications other than fever; and five because the study physicians could not be found. The 137 nontreated infants were closely observed as outpatients. The duration of fever was <48 hours in 42%, and less than 96 hours in 91%. All infants were observed for at least 10 days after the last examination. The fever resolved spontaneously in all infants but two, with otitis media, who were treated as outpatients. Our data suggest that management of fever in selected young infants as outpatients is feasible if meticulous follow-up is provided. (J Pediatr 1988;112:355-60)

Febrile infants younger than 2 months of age may have a serious illness such as meningitis or septicemia.[1-14] It is generally believed that outpatient evaluation does not always contribute to the diagnosis of such conditions and may even be misleading.[1-14] It is therefore the policy of many pediatric centers to hospitalize febrile infants younger than 2 months of age and to initiate treatment with parenteral antibiotics after studies for sepsis (blood, urine, and cerebrospinal fluid culture) have been done.[9, 11, 15-18] On the other hand, hospitalization can lead to iatrogenic complications and emotional and financial burdens for the family.[16, 19-24] Moreover, private physicians do not always hospitalize febrile young infants.[12, 15, 25, 26]

We have shown recently that simple and objective criteria could identify a substantial proportion of previously healthy infants younger than 3 months of age, who were

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hospitalized for suspected sepsis, as being at low risk for having serious bacterial infection.[27] The purpose of our prospective study was to determine whether febrile infants younger than 2 months of age who are considered as being at low risk for having serious bacterial infection can be managed as ambulatory patients, without a complete evaluation for sepsis and without administration of antibiotics.

METHODS

Soroka University Medical Center is the only medical center of the Negev area, Israel. It serves two main populations, who live within a radius of 60 miles: Bedouins, who are Arabs in transition from seminomadism to settlement (approximately 50,000 inhabitants), and Jews, who resemble Western populations, mostly of middle and lower socioeconomic status (approximately 250,000 inhabitants). Most of the Jews live in Beer-Sheva, the main city of the Negev, in which the Soroka University Medical Center is located; the others are scattered in small towns and rural settlements. The average yearly number of births is 7500 (about two thirds are Jews).

The Pediatric Emergency Room is visited by 20,000 to 30,000 infants and children yearly (surgical and trauma cases not included). The emergency room includes an adjacent six-bed unit that serves as an independent ambulatory pediatric unit during the daytime and an observation unit from 3:00 PM to 8:00 AM.

All previously healthy Jewish infants younger than 2 months of age brought to the emergency room between 8:00 AM and 8:00 PM from February 1, 1985, to July 15, 1986, were entered into the study. We chose to include the Jewish population only, because of their similarity to Western populations and because of the poor compliance of the Bedouins, which excludes them from being good candidates for ambulatory follow-up.

It was decided that if the infant appeared too ill to await evaluation, treatment would be started immediately after blood, CSF, and urine cultures.

"Previously healthy" included only infants who were born at term, had no perinatal complications, had no previous or underlying diseases, and had not received antibiotics before being evaluated. Fever was defined as rectal temperature $\geq 38°$ C, at home or in the emergency room.

The study was approved by the local committee for human investigations.

Within 2 hours after being seen in the emergency room, each infant was examined by one of the senior study physicians (R.D., S.S.). After oral consent was obtained, data regarding the nature and duration of the signs and symptoms were recorded. Laboratory tests included complete blood count with differential, and urinalysis for all infants; chest roentgenograms were obtained for most of the patients. Bacterial cultures included blood from all infants, urine and CSF from infants considered at high risk for serious bacterial infection, and soft tissue and middle ear aspirates when appropriate. Microscopic examination of stool for fecal white blood cells and stool culture were performed whenever a history of findings of loose, watery, mucous, or bloody stool was present.

Suprapubic aspiration was performed in all infants with abnormal urine findings. Urinary tract infection was defined as the presence of $>10^5$ colonies/mL of a single organism. Urine was considered abnormal if there were >10 leukocytes per high-power field in a centrifuged urine specimen. Normal white blood cell and differential counts were defined an WBC 5000 to 15,000/mm^3 and <1500 band cells or younger forms/mm^3, respectively. Tympanocentesis was performed in each infant with clinical findings of otitis media. Purulent otitis media was defined by the presence of pus in the middle ear aspirate, as noted by the otolaryngologist who performed the aspiration.

Bacterial infections considered serious included bacteremia, meningitis, cellulitis, osteomyelitis, septic arthritis, gastroenteritis, urinary tract infection, and culture-positive purulent otitis media. Pneumonia was diagnosed only when the chest roentgenogram yielded positive findings, but was not considered per se as a serious bacterial infection.

Infants were considered at low risk for serious bacterial infection if they had no findings consistent with a soft tissue or skeletal infection, no purulent otitis media, normal white blood cell and differential counts, normal urine, and <25 WBC/high-power field (×40) in microscopic stool examination (when diarrhea was present).

If evaluation results indicated high risk for the presence of serious bacterial infection, clinical care was given as prescribed by the emergency room physician, and the patient continued to be observed by the study physicians. If the infant fulfilled the criteria for low risk, one of three decisions was made: hospitalization if indications other than fever were present (e.g., respiratory distress, dehydration); observation for <24 hours in the observation unit; or discharge to home. Lumbar puncture and suprapubic aspiration were not a part of the evaluation for the group defined as being at low risk, nor were antibiotics administered to these infants. Daily follow-up was performed until the fever resolved. When the infant was discharged, the parents were instructed to contact the study physicians (by telephone or by visit to the emergency room every 12 to 24 hours. If they failed to contact the physicians, they were located by the study group to ascertain that no clinical deterioration had occurred.

Table I. Designation of risk groups for presence and frequency of serious bacterial infections

	No. of infants	Infants with serious bacterial infection (%)		Infants with bacteremia	
		n	%	n	%
Low risk	148	0		0	
High risk	88	21	24	8	9
Too ill to be included	1	1		1	
Total	237	22	9	9	4

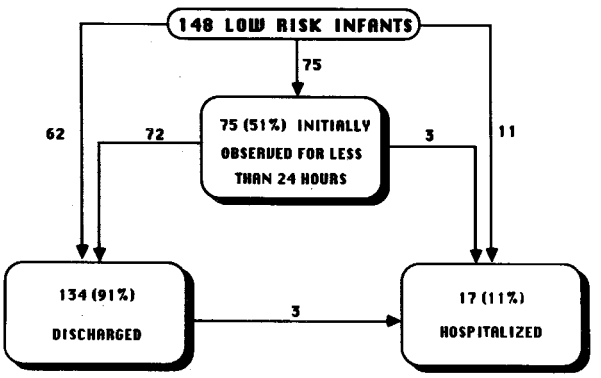

Figure. Management of 148 febrile infants defined as being at low risk for having serious bacterial infection.

If after 24 hours the infant still had fever (temperature ≥39° C) or was considered sicker by the physicians or the parents, urinalysis and complete blood cell count with differential were repeated, in addition to physical examination. If repeated tests indicated a high risk for serious bacterial infection, the infant was hospitalized, a complete sepsis evaluation was performed, and antibiotics were administered parenterally pending culture results.

All families were contacted by telephone or returned 10 to 14 days after the initial visit. Time to defervescence, and outcome were recorded.

Statistical analysis was performed by chi-square test (with Yates correction for small numbers) and Student t test. $P < 0.05$ was considered significant.

RESULTS

A total of 237 previously healthy febrile infants younger than 2 months were enrolled during the 17½-month study period. Thirty-two infants were enrolled on the basis of a history of fever at home, but of those, 28 had at least one febrile episode during follow-up. The male/female ratio was 1.3:1 ($P < 0.001$). Patients ranged in age from 3 to 60 days (median 34 days); 29 (12%) were younger than 15 days, 64 (27%) were 15 to 30 days of age, 86 (36%) were 31 to 45 days of age, and 59 (25%) were older than 45 days.

The maximal rectal temperature before or at the time of the emergency room visit was 38° to 38.5° C in 93 (39%) of the 237 infants, 38.6° to 39° C in 81 (34°%), 39.1° to 39.5° C in 38 (16%), and >39.6° C in 25 (11%).

The duration of fever at the time of the visit was <12 hours in 124 of the 237 infants (52%), 12 to 14 hours in 77 (32%), 24 to 48 hours in 25 (11%), and >48 hours in 11 infants (5%).

Designation of risk group and identification of infection. One hundred forty-eight (63%) of the 237 study patients met all criteria for inclusion in the group at low risk for serious bacterial infection; 88 (37%) did not meet one or more criteria and were therefore considered at high risk, and one appeared too ill to await evaluation (Table I). The majority of the infants at high risk (62 of 88, 70%) failed to meet only one inclusion criterion for low risk, 20 (23%) failed to meet two criteria, and six (7%) failed to meet three.

No differences regarding age and temperature were noted between the groups at low and higher risk. Forty infants were diagnosed as having otitis media, and underwent tympanocentesis. Purulent middle-ear fluid was found in 29 of the 40 (73%). Ten of the 11 infants with nonpurulent otitis media had all other criteria to be included in the low-risk group and therefore were not treated.

Twenty-two infants (9%) had serious bacterial infections; none of the 148 infants in the low-risk group had infections, compared with 21 of 88 (24%) in the high-risk group ($P < 0.0001$); the only infant who was initially too ill to be evaluated had *Haemophilus influenzae* type b sepsis with meningitis. Table II presents the organisms isolated from the 22 infants with serious bacterial infections and the site of isolation.

Management and outcome in infants at high and low risk. The emergency room physicians did not treat 15 of the 88 infants (15%) despite their being classified at high risk for having serious bacterial infections, because in their judgment the infants did not look ill. Of those, eight (11%) were not hospitalized. None of these infants had complications.

Of the 148 infants classified as being at low risk for having serious bacterial infections, 62 (42%) were discharged to home and 75 (51%) were initially observed for ≤24 hours (Figure). Of the 75 infants initially observed, three (4%) were redefined as being at high risk, because of

Table II. Organisms isolated from infants with serious bacterial infections, and type of infection

Infection	Organism	No. of infants
Bacteremia		
Without focus	*Streptococcus pneumoniae*	1
With focus		
Urinary tract infection	*Escherichia coli*	2
Otitis, meningitis	*Haemophilus influenzae* type b	1
Soft tissue infection	*Staphylococcus aureus*	3
	E. coli	1
	Group A β-hemolytic streptococcus	1
Urinary tract infection	*E. coli*	5
	Enterobacter cloacae	1
Otitis media*	*S. pneumoniae*	2
	Group A β-hemolytic streptococcus	2
	E. coli	1
	S. aureus	1
Gastroenteritis	*Salmonella typhimurium*	1
Total		22

*Middle ear aspirates not plated on chocolate agar.

Table III. Reasons for hospitalization and management of fever in infants at low risk for having serious bacterial infections

Reason for hospitalization	No. of infants	No. given antibiotic therapy
Study physician not located	5	5
Dehydration	3	0
Respiratory distress	1	0
No vacant bed in observation unit	1	0
Cyanosis during cry	1	0
Initially at low risk but fever persisted and repeat blood cell count indicated high risk	6	6
Total	17	11

results of the repeat blood cell counts, and were hospitalized and treated. Therefore, initially 134 (91%) were discharged. Of those, three (3%) were later hospitalized and treated because their fever did not subside and the repeat blood cell count indicated leukocytosis, leukopenia, or increased band cell count. Eleven other infants initially classified as being at low risk were hospitalized for various reasons (Table III).

Eleven (64%) of the hospitalized infants were treated, five because no study physicians could be located and six who were reclassified as being at high risk during follow-up. None of the six hospitalized low-risk infants who continued to be observed by the study physicians was given antibiotics.

Chest roentgenograms were obtained for 206 of 237 infants (87%). Eight of the 126 (6%) low-risk infants had evidence for pneumonia, versus 12 of 79 (15%) at high risk ($P < 0.05$). None of the eight infants at low risk who had pneumonia were given antibiotics.

At least one telephone or ambulatory unit follow-up visit was made to all infants. Forty-six of the 131 (35%) infants whose entire management was ambulatory had two follow-up visits, and seven (5%) had three visits.

The total duration of fever in the 148 infants at low risk was <24 hours in three (2%), 24 to 48 hours in 62 (42%), 49 to 72 hours in 34 (23%), 73 to 96 hours in 36 (24%), and >96 hours in 13 (9%) infants. All 137 untreated infants were contacted ≥10 days after the last examination. In two infants otitis without fever developed, and was treated successfully with amoxicillin. In the other 135 infants fever resolved spontaneously, with no relapse.

Twenty-two infants at low risk (15%) who did not receive antibiotics developed at least one symptom or laboratory finding, which usually could be attributed to antibiotic therapy. Eight of 53 (15%) infants in whom a second blood cell count was obtained developed neutropenia (<1000 polymorphonuclear cells/mm^3). Twelve percent of all infants at low risk developed generalized rash, and 4% developed mild diarrhea.

DISCUSSION

It is generally accepted that febrile infants younger than 2 or 3 months deserve special attention, but there is no

agreement on treatment.[14] Fever in neonates leads generally to a "sepsis workup" and treatment[28, 29], but the appropriate management of the febrile infant who is old enough to be discharged from the nursery but is still in the first weeks of life, remains controversial.[13, 15, 17]

Fever that appears following discharge from the nursery often represents community acquired viral illnesses; bacterial diseases originating from the birth canal gradually become less common.[15, 18, 30-33] Hospitalizing and treating all febrile young infants may result in numerous complications, as demonstrated by DeAngelis et al.[16] Furthermore, hospitalizing all febrile infants is expensive and may result in long-term sequelae such as behavior problems and poor reading.[16, 20, 21]

DeAngelis et al.[17] found that in a large university medical center, despite an unwritten policy of admitting all febrile infants younger than 2 months of age, 106 of 303 (35%) febrile infants seen in the outpatient department were discharged. None of these 106 infants suffered morbidity that could be directly related to their not having been hospitalized.

Green et al.[15] found that more than two thirds of chief residents indicated lumbar puncture to be a routine part of the evaluation of fever in infants, but only 16% of practitioners accepted this. More than half of the chief residents versus only 9% of the practitioners estimated that 90% to 100% of febrile infants were admitted.

Roberts[14] claims that we should recognize in ourselves a need to do something to relieve our own anxiety. We want to declare our concern and gain maximum benefit while still observing primum non nocere. He suggests that hospitalization must be weighed against care at home, and the decision to observe should be based on the characteristics of the illness, the infant, the care giver, and the physician.

Our data emphasize the short, self-limiting nature of fever in most infants younger than 2 months. In previous series, the natural course of febrile illness could not be assessed because most infants were hospitalized and given antibiotics for at least 48 to 72 hours, so improvement related to treatment could not be ruled out. Furthermore, side effects such as rash, diarrhea, and neutropenia could easily be attributed to drug reaction. In our series, during follow-up, 15% of the untreated patients had such findings.

We reviewed retrospectively 50 charts of febrile infants younger than 2 months who were hospitalized and received treatment in our institution before the initiation of the present study, and from whom no bacterial pathogens were isolated (unpublished data). The median time to defervescence was 36 hours, and median hospitalization 5 days. We can estimate, therefore, that a total of 655 hospitalization days were saved in this series. We also can assume that if all febrile infants had been given parenteral antibiotics pending culture results (generally 72 hours), 393 days of parenteral antibiotic therapy were saved.

Our criteria for identification of low risk for serious bacterial infections were based on a previous series of infants younger than 3 months hospitalized because of suspected sepsis in Rochester, New York. Two changes have been introduced to our previous criteria: (1) When diarrhea was present, identification of more than 25 fecal white blood cells per high-power field excluded infants from the low-risk group, because it was observed by us and by others that bacterial gastroenteritis, including bacteremia, can occur with a normal blood count.[24, 34] (2) The presence of otitis excluded infants from the low-risk group only if pus was present in the middle ear as documented by tympanocentesis, because in our previous study otitis media without abnormal blood count was not associated with bacteremia.[27]

The bacteriologic results in our series suggest that the main organism causing sepsis in early infancy described in the United States and Western Europe, group B streptococcus, may not be an equally important causative organism in other geographic areas. Group B streptococcus was not isolated from any of our patients. This observation may explain why only one of the nine infants with bacteremia had no apparent focus on physical examination: the main pathogen causing septicemia without apparent focus in early infancy is group B streptococcus. As suggested by Anbar et al.,[34] it may not be possible, therefore, to extrapolate our data to other areas.

In the present study no lumbar puncture was performed in infants at low risk. In our previous study we showed that CSF pleocytosis was present in 21% of the infants at low risk. The proportion of febrile infants with pleocytosis was even greater during the summer and fall seasons, and was associated mainly with enterovirus infection.[13, 28] All low-risk infants with pleocytosis had aseptic meningitis, which in the very young infant is often unsuspected clinically. We assume, therefore, that a substantial proportion of the low-risk infants in the present series had aseptic meningitis. However, its presence should not alter the management in the febrile infant because it is a self-limiting, short-term disease.

We conclude that managing fever in selected infants younger than 2 months as outpatients is feasible, although not simple. The clinician who takes the responsibility for ambulatory follow-up without antibiotic administration should be willing to reexamine the child daily, or more often if the condition worsens, as long as the fever persists,

and be ready to change course when new findings appear. If close outpatient follow-up is not possible, observation in hospital must be recommended.

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Costs and Infant Outcomes After Implementation of a Care Process Model for Febrile Infants

WHAT'S KNOWN ON THIS SUBJECT: Febrile infants in the first 90 days may have life-threatening serious bacterial infection. Well-appearing febrile infants with serious bacterial infections cannot be distinguished from those without by examination alone. Variation in care resulting in both undertreatment and overtreatment is common.

WHAT THIS STUDY ADDS: The systemwide implementation of an evidence-based care process model for the care of febrile infants in Intermountain Healthcare was associated with increased delivery of evidence-based care, improved infant outcomes, and lower costs. This model adopted nationally can improve value.

abstract

OBJECTIVE: Febrile infants in the first 90 days may have life-threatening serious bacterial infection (SBI). Well-appearing febrile infants with SBI cannot be distinguished from those without by examination alone. Variation in care resulting in both undertreatment and overtreatment is common.

METHODS: We developed and implemented an evidence-based care process model (EB-CPM) for the management of well-appearing febrile infants in the Intermountain Healthcare System. We report an observational study describing changes in (1) care delivery, (2) outcomes of febrile infants, and (3) costs before and after implementation of the EB-CPM in a children's hospital and in regional medical centers.

RESULTS: From 2004 through 2009, 8044 infants had 8431 febrile episodes, resulting in medical evaluation. After implementation of the EB-CPM in 2008, infants in all facilities were more likely to receive evidence-based care including appropriate diagnostic testing, determination of risk for SBI, antibiotic selection, decreased antibiotic duration, and shorter hospital stays ($P < .001$ for all). In addition, more infants had a definitive diagnosis of urinary tract infection or viral illness ($P < .001$ for both). Infant outcomes improved with more admitted infants positive for SBI ($P = .011$), and infants at low risk for SBI were more often managed without antibiotics ($P < .001$). Although hospital admissions were shortened by 27%, there were no cases of missed SBI. Health Care costs were also reduced, with the mean cost per admitted infant decreasing from $7178 in 2007 to $5979 in 2009 (−17%, $P < .001$).

CONCLUSIONS: The EB-CPM increased evidence-based care in all facilities. Infant outcomes improved and costs were reduced, substantially improving value. *Pediatrics* 2012;130:e16–e24

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KEY WORDS
fever, infant, outcomes, cost

ABBREVIATIONS
CBC—complete blood count
EB-CPM—evidence-based care process model
ED—emergency department
EDW—enterprise data warehouse
IPCP—Intermountain Pediatric Clinical Program
LOS—length of stay
PCMC—Primary Children's Medical Center
RMC—regional medical center
SBI—serious bacterial infection
UTI—urinary tract infection

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Evaluation of fever in infants aged 1 to 90 days is common, yet there are no national guidelines addressing management. Approximately 10% will have serious bacterial infection (SBI), which can be life threatening.[1,2] However, the majority of infants have viral infections, and infants with laboratory and clinically confirmed viral infections are less likely to have SBI.[1,3–5] Independent recommendations for care of the febrile infant published in 1993 and revised in 2000 did not address viral infections.[6,7] Compliance with these recommendations is limited, and variation in care is substantial.[8–11]

In the Intermountain Healthcare system, we noted variation in care delivered at regional medical centers (RMCs) compared with Primary Children's Medical Center (PCMC, Salt Lake City, UT), a tertiary children's hospital. For example, in 2004, the proportion of febrile infants who had urinalysis ranged from 19% in 1 RMC to 70% at PCMC, although urinary tract infection (UTI) is the most common SBI in febrile infants.

The Intermountain Pediatric Clinical Program (IPCP) undertook a quality improvement initiative to address care of febrile infants. The IPCP has administrative, laboratory, nursing, and physician representatives from all Intermountain Healthcare regions and includes pediatricians from the University of Utah. The IPCP used Six Sigma methodology (Table 1) to develop an evidence-based care process model (EB-CPM) for febrile infants.[12–14] CPMs are designed to decrease variation, improve quality, and support local preferences.[15]

The EB-CPM for febrile infants incorporated evidence derived from local institutions[1,4,5,16–23] and others.[2,7,8,24–42] We defined 6 quality measures by consensus of representatives serving on the IPCP and their constituents. Quality measures targeted laboratory testing, SBI risk determination, antibiotic selection, hospital admission, and discharge. After in-person and web-based training, education, and feedback with clinical personnel at PCMC and 3 RMCs during 2007, the EB-CPM was implemented at all Intermountain Healthcare facilities on January 1, 2008. Web-accessible tools including algorithms, orders, antibiotic recommendations, and references were available at the points of care in all facilities. All facilities received monthly performance feedback from the IPCP. The objectives of this article are to describe the changes in (1) care delivery, (2) outcomes of febrile infants, and (3) costs before and after the implementation of the EB-CPM.

TABLE 1 Modified Six Sigma Process Used to Develop and Implement the EB-CPM for Febrile Infants

Six Sigma Steps	Actions of the Pediatric Clinical Programs Guidance Council
Define	Identify febrile infants
	• Developed method for identification using electronic administrative data
	• Map the process flow to be improved
	• Created flow diagrams from patient, nursing, laboratory, and physician perspectives
Measure	Develop a data collection plan
	• Developed through iterative process
	Collect data from Intermountain Healthcare facilities
	• Baseline data for all quality measures generated
	• Reports generated for individual facilities and combined target facilities
Analyze	Analyze data collected to determine root causes for defects and sources of variation
	• Baseline data demonstrated poor compliance with laboratory testing with root causes including lack of equipment, laboratory schedules, and courier services
	• Identify and prioritize opportunities for improvement
	• Identify gap between current performance and goal
Improve	Design creative solutions using technology
	• Web-based tools including care algorithms, standard order sets, parent information
	• In-person and web-based training modules
	Develop and deploy implementation plan
	• All target hospitals participated in 2007
Control	Develop and document an ongoing monitoring plan
	• Monitor all quality and balance measures monthly
	• Monitor critical outcomes of febrile infants including deaths and missed SBI
	• Address equipment, laboratory, and courier schedules
	Institutionalize performance by modification of systems and structures
	• Care of febrile infant uses web-based tools available to all providers
	• All hospital representatives receive institutional feedback monthly
	• Hospital representatives inform providers of performance and outcome data
	• Individual provider data for those participating in maintenance of certification

METHODS

Protection of Human Subjects

The Institutional Review Boards of Intermountain Healthcare and the University of Utah approved this study. Informed consent was waived. Provider use of the EB-CPM was voluntary.

Setting

This observational study was performed at Intermountain Healthcare,

a not-for-profit, integrated health care system that provides care for ~85% of Utah children and a higher proportion of infants. The 21 Intermountain Healthcare hospitals include PCMC and 3 RMCs located in Ogden, Provo, and St George, Utah. The RMCs and PCMC provide care for most febrile infants and were designated target facilities. Midlevel providers and resident and attending physicians practicing family medicine, pediatrics, and adult and pediatric emergency medicine staff target facilities. All facilities had the same viral diagnostic technology and electronic record system throughout the study.

Identification of Febrile Infants

Febrile infants were identified from the Intermountain enterprise data warehouse (EDW). The EDW contains clinical, laboratory, and administrative data for all facilities. We developed a definition for febrile infants based on age, reason for visit, admitting diagnosis, *International Classification of Diseases, Ninth Revision*, and All Patient Refined DIagnosis Related Groups (APR-DRGs) coding and validated it against a prospectively collected sample.[1] The definition has a sensitivity and specificity of 93% and 90%, respectively.[43] SBI was identified through the EDW and was defined as culture-confirmed bacteremia, meningitis, or UTI. UTI was defined as ≥50 000 colony forming units/mL of a single pathogen.[44] An infant with missed SBI was defined as having SBI and treatment either only in the emergency department (ED) or hospital admission within 5 days of ED discharge.

EB-CPM Recommendations

The full EB-CPM for outpatients and inpatients is available in the Supplemental Information. The EB-CPM is for well-appearing febrile infants aged 1 to 90 days. Separate CPMs are available for early-onset neonatal sepsis in the nursery[45] and for infants and children with findings consistent with sepsis or septic shock.[46] Providers determine well appearance and whether use of a CPM is appropriate.

The febrile infant EB-CPM includes a history and physical examination and recommends obtaining a complete blood count (CBC) and urinalysis for all infants. Infants are classified as high-risk for SBI using a modification of the Rochester criteria.[31,47] A recent review demonstrated the Rochester criteria and Philadelphia criteria have similar diagnostic accuracy in predicting SBI, and the Rochester criteria were more accurate in neonates.[48] High-risk infants are those aged ≤28 days or with history of preterm birth (<37 weeks), chronic medical conditions, abnormal CBC (<5000 or >15 000 white blood cells per mm^3) or urinalysis results (>10 white blood cells/high power field).[47] The electronic record and orders capture risk designation.

Management without antibiotics is recommended for infants not identified as high risk and thus considered low risk for SBI. The EB-CPM, consistent with other expert guidance,[6,7] recommends admission and antibiotic treatment of high-risk infants. Viral diagnostic testing is recommended for all admitted infants, including testing for enteroviruses by polymerase chain reaction between June and November or if cerebral spinal fluid pleocytosis[18] is present and testing for respiratory viruses by direct fluorescent assay or polymerase chain reaction year-round. Antibiotic recommendations reflect the epidemiology and resistance of SBI pathogens at Intermountain Healthcare.

For admitted infants, duration of antibiotic therapy and length of stay (LOS) are based on results of bacterial and viral diagnostic testing at 24 hours. Admitted culture-negative infants at high risk for SBI and who test positive for a viral pathogen or who are at low-risk for SBI are eligible for discontinuation of antibiotics and discharge at 24 hours. All other culture-negative infants are eligible for the same at 36 hours. Given the distance between RMCs and the central laboratory (Salt Lake City, UT), we allowed 6 hours for specimen transport and measured the proportion of infants discharged within 42 hours of specimen collection.

Statistical Analysis

We identified 6 quality measures and 4 balancing measures to assess unintended consequences of EB-CPM implementation. We compared performance on these measures at the target facilities during baseline (July 1, 2004–December 31, 2007) and implementation (January 1, 2008–December 31, 2009) by using general linear models for continuous measures (with log transformations when the data had a skewed distribution) and logistic regression models for binary outcomes. A temporal analysis for performance changes during the baseline period was performed and did not yield significant year-to-year differences in individual facilities or the system.

Cost data were derived from the Intermountain Healthcare cost-accounting program, an activity-based microcosting system that identifies and aggregates the variable and fixed-cost components of hospital services and products according to the date of service.[15] Because of the nonnormality of cost data, we used the Wilcoxon-Mann-Whitney test to compare the mean cost per infant during the 2 periods. Costs were adjusted for inflation to 2009 dollars.

RESULTS

Participants

There were 8044 infants with 8431 febrile episodes resulting in evaluation at Intermountain Healthcare facilities (Table 2); 6991 (83%) occurred in target facilities. Infants at evaluation had a mean age of 45 days; 54% were boys, and 62% were white, 26% Latino, 2% African American, 2% Pacific Islander, 1%

TABLE 2 Characteristics of Febrile Infant Episodes Across All Intermountain Healthcare Facilities

Variable	Base and Training, $n = 5444$[a] (%)	Implementation, $n = 2987$[a] (%)	*P* Value
Episode at Target Facility	4524 (83)	2467 (83)	.600
Age			.001
≤28 d	1617 (30)	787 (26)	
29–90 d	3827 (70)	2200 (74)	
Inpatient admission	2516 (46)	1424 (48)	.200
Observation unit admission	372 (7)	284 (10)	<.001
Any admission	2888 (53)	1708 (57)	<.001
Infants with any SBI[b]	440 (8)	295 (10)	.006
UTI	360 (7)	257 (9)	<.001
Bacteremia	112 (2)	60 (2)	.328
Meningitis	16 (0.3)	7 (0.2)	.670
Infants with SBI admitted at first encounter	378/440 (86)	267/295 (91)	.070
Infants with bacteremia or meningitis admitted at first encounter	117/128 (91)	66/67 (99)	.060
Death	2 (0.04)	1 (0.03)	1.000

[a] Unless otherwise indicated.

[b] Infants may have ≥1 type of SBI.

Asian, 1% Native American, and 6% unknown. In 3781 (45%) episodes, infants were classified as high risk for SBI.

Of all febrile episodes, 735 of 8431 (9%) had culture-confirmed SBI. Among infants with bacterial cultures of blood, urine, or cerebrospinal fluid ($n = 6363$), 735 (12%) had SBI. Infants were more likely to be diagnosed with SBI during the implementation period because of an increase in the diagnosis of UTI (+29%, $P < .001$; Table 2). The proportion of admitted infants with SBI increased from 13% to 16% after implementation (+23%, $P = .011$).

Performance of Quality Measures in Target Facilities

Laboratory Testing

The proportion of infants with recommended laboratory testing increased in all target facilities during the implementation period (Table 3). By 2009, almost all admitted infants had CBC (93%) and urinalysis (99%), and there was little variation between facilities. Infants were more likely to have blood (73% vs 79%) and urine cultures (74% vs 79%) after implementation ($P < .001$ for both). Infants were also more likely to have viral testing during the implementation and the proportion of admitted infants diagnosed with an enterovirus or respiratory virus increased from 25% to 36% (+40%, $P < .001$).

Admission of Infants With SBI at Initial Evaluation

Admission of infants subsequently proven to have SBI was associated with increased laboratory evaluation during the implementation period. The proportion of infants with SBI who were admitted at the initial evaluation increased from 86% to 91% and those with bacteremia or meningitis increased from 91% to 99%. Of the 28 infants with SBI discharged from the ED during the implementation period, 27 had UTI and received antibiotic treatment as outpatients. There were no missed cases of meningitis during the implementation period. This compares with the preimplementation period when there were 68 infants subsequently identified with SBI discharged from the ED including 8 with bacteremia and 3 with meningitis.

Antibiotic Selection and Treatment

Febrile infants in target facilities received antibiotic therapy in 4229 of 6991 (61%) of episodes. Infants classified as high risk for SBI were more likely to receive antibiotics than those classified

TABLE 3 Comparison of Key Quality and Balancing Measures for the EB-CPM in Target Facilities

	Target Facilities Base and Training Periods, $N = 4524$,[a] *n* (%)	Target Facilities Implementation Period, $N = 2467$,[a] *n*(%)	Absolute Difference in Propositions (95% CI, *P* value)
Quality measure			
Obtain both CBC and urinalysis	3040 (67)	1975 (80)	13% (11% to 15%, <.001)
Determine risk status for SBI	3057 (68)	1836 (74)	7% (5% to 9%, <.001)
Perform viral testing for admitted Infants	1992/2620 (76)	1296/1540 (84)	8% (6% to 11%, <.001)
Administer only formulary antibiotic therapy for admitted infants receiving antibiotics	1167/1511 (77)	826/901 (92)	15% (12% to 17%, <.001)
Discontinue antibiotics within 36 h for infants with negative bacterial cultures	547/1172 (47)	415/658 (63)	16% (12% to 21%, <.001)
Discharge eligible infants by 42 h	682/1418 (48)	586/777 (75)	27% (23% to 31%, <.001)
Balancing measure			
Lumbar Puncture	2261 (50)	1281 (52)	2% (−0.5% to 4.4%, .120)
Infants admitted within 72 h post ED discharge	92/1904 (5)	45/927 (5)	0.02% (−1.7% to 1.7%, 1.000)
Readmission within 72 h after discharge inpatient or observation unit	21/2620 (0.8)	10/1540 (0.6)	−0.2% (−0.7% to 0.4%, .710)
Missed SBI after admission	0	0	NA

CI, confidence interval; NA, not applicable.

[a] Unless otherwise denoted.

as low risk (85% vs 63% $P < .001$). Infants classified as low risk were less likely to receive antibiotics in the inpatient (91% vs 85%, −7%, $P = .005$) or outpatient setting 43% vs 34%, −26%, $P = .002$) after implementation.

The recommended antibiotics are ampicillin, gentamicin, cefotaxime, and ceftriaxone. Infants admitted after the introduction of the EB-CPM were more likely to receive only recommended antibiotics (77% vs 92%, +15%) and to have antibiotics discontinued by 36 hours (47% vs 63%, +16%, $P < .001$ for both). In 94% of all episodes of SBI and 99% of meningitis episodes, the recommended antibiotics were active against the recovered pathogens.

Hospital Length of Stay

The mean hospital LOS for infants without SBI decreased from 60 to 44 hours after implementation (−27%, $P < .001$), resulting in 1644 fewer hospital days. The LOS at PCMC was increasing 2.4% annually in 2004–2008 (Fig 1). After implementation, there was a 12.0% decrease in LOS in 2009 compared with 2008 ($P = .001$). The LOS in all RMCs decreased significantly, and all target facilities achieved a common baseline for LOS by 2009 (Fig 1).

Balancing Measures and Cost

The performance of lumbar puncture remained stable, and there were no cases of missed meningitis after implementation. Although LOS was significantly decreased, there was no increase in readmissions and no readmissions with SBI after hospital discharge.

In our cohort, 91% of the costs for febrile infants occurred in the inpatient setting. Thus, although mean laboratory costs in the ED increased at PCMC ($153 vs $184, $P < .001$) and in the RMCs ($44 vs $69, $P < .001$), these costs were more than offset by the decreased costs for admitted infants. After implementation, the mean cost per admitted infant fell from $7178 in 2007 to $5979 in 2009 (−17%, $P < .001$).

Implementation was associated with reduced inpatient costs in all RMCs ($8037 vs $6206, −23%, $P < .001$). At PCMC, baseline inpatient costs were lower than at the RMCs (−$1914 in 2007) but were increasing at a faster annual rate ($233 vs −$366). After implementation of the EB-CPM, the mean inpatient cost per infant at PCMC declined 11.6% ($P < .001$). Variation in the LOS and costs between the RMCs and PCMC were virtually eliminated by 2009.

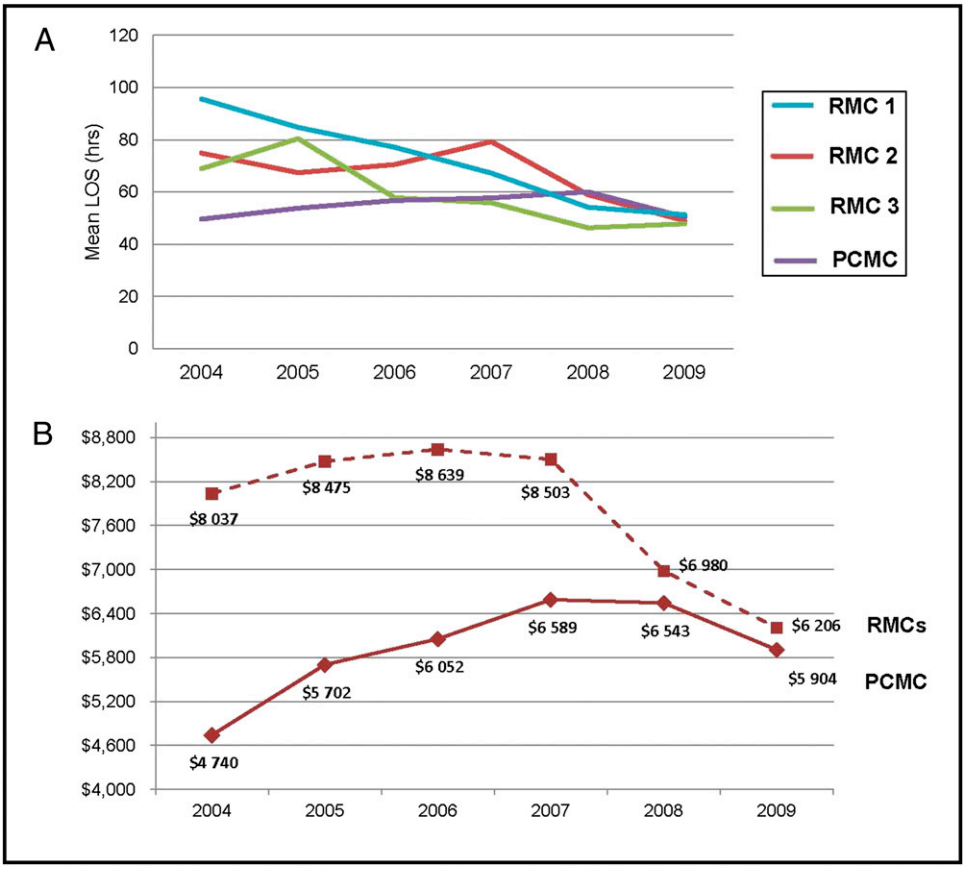

FIGURE 1
A, LOS for inpatient or observation unit episodes at target facilities. B, Cost for RMCs and Primary Children's Medical Center.

The mean cost per admitted infant was lower in 2009 than in 2004 (Fig 2). Savings were realized through decreased LOS and reductions in antibiotic prescribing and ancillary testing not recommended by the EB-CPM. Using a model based on a rate of inflation equal to the CPI, costs in 2009 were predicted to be 18% greater than in 2004. In contrast, our data demonstrated that costs in 2009 were 3% lower than in 2004 (Fig 2). In 2009, the cost per admitted infant was $1270 less than predicted resulting in an estimated savings of ~$1.9 million.

DISCUSSION

We report the successful implementation of an EB-CPM for the care of febrile infants. Implementation was associated with an increase in evidence-based care delivered by a diverse group of providers at a children's hospital and in community RMCs. Following implementation, there was a slight increase in the admission rate of febrile infants, an increased documentation of UTIs and viral infections, a higher percentage of patients with SBI who were admitted after UTI detection, a decreased length of stay, a more appropriate use of recommended antibiotics, and a similar rate (with trends toward improvement) in admission of patients with meningitis and bacteremia compared with the preimplementation period. Implementation was also associated with a considerable reduction in costs. Although the infrastructure and resources devoted to quality improvement in Intermountain Healthcare may not be available in all settings, the creation of facility specific care process models with internal process control and performance evaluation is a flexible tool that can be adapted by other health care systems to improve care and outcomes while reducing costs.[49]

The care of the febrile infant is controversial, and there are variations in care associated with site of care and type of provider.[8–11,50–54] Strategies for classification of infants at risk for SBI, admission of high-risk infants, and treatment of low-risk infants as outpatients have been extensively evaluated and discussed.[7,24,26,36,37,55] Variation in practice continues, perhaps because of the lack of an accepted guideline and the absence of research comparing different care processes to determine if any are associated with better outcomes or lower costs.

The EB-CPM was created to define best practices for Intermountain Healthcare and to create a common process for delivering quality care across many hospitals. Intermountain hospitals, although widely separated geographically and using different provider staffing models, are all committed to quality improvement, have representation through the IPCP, and share common laboratory and electronic medical record resources.[15] These elements were vital to the development and dissemination of the EB-CPM.

Implementation of the EB-CPM resulted in increased evidence-based care delivery as measured by 6 indicators. The investigators worked with target facilities to ensure that the indicators were relevant to the medical providers and that processes were in place to support delivering recommended care without interrupting workflow. The increase in delivery of evidence-based care demonstrates the value of providing decision support at the point-of-care to guide clinicians. Parents of febrile infants anywhere in Utah can now be assured that their infant will receive high-quality care anywhere in the Intermountain Healthcare system, whether evaluated in RMCs by nonpediatric providers or at PCMC by pediatricians and pediatric subspecialists.

Increased evidence-based care was associated with improved infant outcomes. On the basis of studies demonstrating the low rate of SBI among infants with viral infection[1,3–5,41] and data demonstrating that the majority (~85%) of all positive blood cultures in this population are detected within 24 hours,[33,38] the EB-CPM recommends discharge for admitted infants with positive viral testing and negative bacterial cultures at 24 hours. Diagnoses of viral illnesses increased by 40% after implementation resulting in opportunities for earlier discharge and discontinuation of antibiotics for many infants.

Implementation of the EB-CPM improved recognition and treatment of SBI. The increasing proportion of admitted febrile infants with SBI in the postimplementation period supports the use of screening criteria to identify well-appearing infants

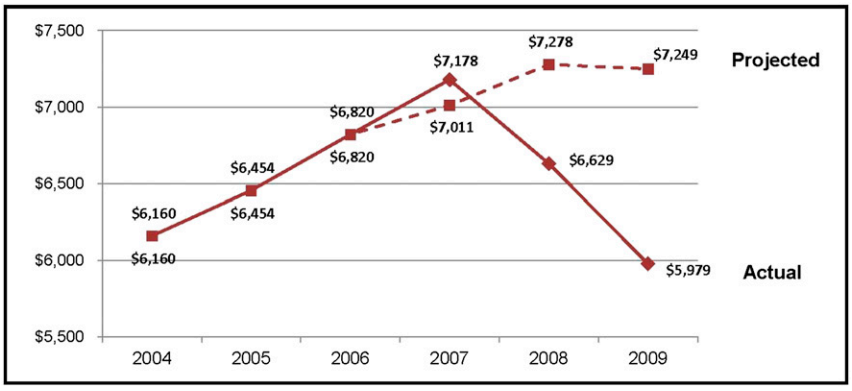

FIGURE 2
Average total cost per admitted infant at target facilities.

at high-risk for SBI. The increase in urinalysis testing identified infants with UTI who may have been missed before implementation. Bacteremia and meningitis are rare but potentially life-threatening occurrences. After implementation, 99% of infants with bacteremia or meningitis were admitted at the initial evaluation compared with 91% before implementation. Although this difference did not reach statistical significance, the value of early recognition and treatment of bacteremia and meningitis in nearly all infected infants cannot be discounted. Finally, the EB-CPM improved antibiotic treatment decisions with infants benefitting from the selection of antibiotics appropriate for SBI pathogens and reductions in antibiotic use in low-risk and culture-negative infants.

We detected no adverse consequences after implementation of the EB-CPM. The performance of lumbar puncture, considered invasive by many parents and clinicians, did not increase, and yet there were no cases of missed meningitis. There was a modest increase in the proportion of infants admitted because of an increase in admissions of <24 hours in observation units, and 75% of all admitted infants were discharged from the hospital by 42 hours. Although the mean hospital LOS was 16 hours shorter than before implementation, the readmission rate was stable at <0.5%, and there were no cases of missed SBI after hospital discharge.

The implementation of the EB-CPM reduced costs and increased the value of the health care delivered. Variations in care can unnecessarily increase cost through overtreatment, including excess testing, inappropriate antibiotic use, or prolonged LOS, and through undertreatment, resulting in delayed recognition and treatment of SBI. By 2009, the target facilities all had similar LOS and costs, indicating adoption of similar process for the evaluation and management of febrile infants. Infants and families benefitted from improved health outcomes, shorter hospital stays, and lower cost. Savings for the hospital system were realized through lower direct care costs, improvements in care that may reduce medical liability, and reduction in hospital days, which can delay the need for new bed construction and reduce long-term capital outlay.

This study has several strengths and limitations. Strengths include the size of the febrile infant cohort, the largest ever reported. The results are also strengthened by the quality of the shared EDW, which allowed us to evaluate outcomes across the system including readmissions and missed SBI. The study is limited to a single health care system; however, we examined multiple hospital facilities with different characteristics, suggesting that an EB-CPM could be successfully implemented in other settings. Documentation of training was not required for providers. Since 2009, pediatricians have been able to use the EB-CPM for maintenance of certification (MOC). Evaluation of performance of trained providers using the EB-CPM for maintenance of certification compared with all providers is ongoing. The observation period after implementation was only 2 years; however, we continue to monitor the quality measures monthly through the IPCP and have seen either maintenance or additional improvement in all measures through 2011. For example, in 2011, 90% of admitted infants with negative bacterial cultures were discharged by 42 hours compared with 75% in 2008–2009. The changes observed may have been due to factors other than the introduction of the EB-CPM. However, there were no significant changes in the environment such as availability of diagnostic testing or new external guidelines over the entire study period. Furthermore, the fact that there were no significant changes observed during the 4-year baseline period and the sustained monthly improvements in the 6 quality measures that occurred in all facilities after the implementation of the EB-CPM makes this unlikely. Finally, there were likely unmeasured sources of variation that may have resulted in failure to achieve universal compliance with the EB-CPM. We seek to identify and address these factors through our monthly IPCP meetings and update the EB-CPM and available support as new data become available.

CONCLUSIONS

The introduction of an EB-CPM changed the culture of caring for febrile infants across a large health care system. Variation in care was substantially reduced. Infant outcomes were exceptional, and significant savings were realized. The EB-CPM for febrile infants is an example of value-driven health care that addresses a common problem and can be used to inform guidelines disseminated nationally.

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Costs and Infant Outcomes After Implementation of a Care Process Model for Febrile Infants

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Original Investigation

Blood Culture Time to Positivity in Febrile Infants With Bacteremia

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IMPORTANCE Blood cultures are often obtained as part of the evaluation of infants with fever and these infants are typically observed until their cultures are determined to have no growth. However, the time to positivity of blood culture results in this population is not known.

OBJECTIVE To determine the time to positivity of blood culture results in febrile infants admitted to a general inpatient unit.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, retrospective, cross-sectional evaluation of blood culture time to positivity. Data were collected by community and academic hospital systems associated with the Pediatric Research in Inpatient Settings Network. The study included febrile infants 90 days of age or younger with bacteremia and without surgical histories outside of an intensive care unit.

EXPOSURES Blood culture growing pathogenic bacteria.

MAIN OUTCOMES AND MEASURES Time to positivity and proportion of positive blood culture results that become positive more than 24 hours after placement in the analyzer.

RESULTS A total of 392 pathogenic blood cultures were included from 17 hospital systems across the United States. The mean (SD) time to positivity was 15.41 (8.30) hours. By 24 hours, 91% (95% CI, 88-93) had turned positive. By 36 and 48 hours, 96% (95% CI, 95-98) and 99% (95% CI, 97-100) had become positive, respectively.

CONCLUSIONS AND RELEVANCE Most pathogens in febrile, bacteremic infants 90 days of age or younger hospitalized on a general inpatient unit will be identified within 24 hours of collection. These data suggest that inpatient observation of febrile infants for more than 24 hours may be unnecessary in most infants.

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Blood cultures are routinely performed in the evaluation of infants with fever. These infants are typically hospitalized for 36 to 48 hours or longer to receive antibiotics while physicians await blood culture results.[1,2]

Few data support a standard observational period for infants. Several prior studies have demonstrated that a substantial proportion of positive blood culture results may become positive after 24 or 36 hours,[3-5] with some suggesting inpatient observation periods as long as 96 hours.[6,7] However, these studies included infants admitted to intensive care units (ICUs) who are at higher risk for serious bacterial infection than the typical febrile infant and for pathogens that may have longer incubation times (eg, *Candida* species [spp]).[3] Two studies argued for a shorter period of observation; however, neither targeted the febrile infant 90 days old or younger.[8,9] One large hospital system implemented discharge criteria of 24 to 36 hours without adverse consequences.[10] Commonly used care guidelines[11] and textbooks[2,12] disagree on the necessary period of observation and none are firm in their conclusions, reflecting the wide variation in practice in the management of infants with fever.

While there are several published guidelines for the treatment of febrile infants up to 90 days of age,[13,14] we believe that the inconclusive nature of the current literature regarding the management of the febrile, but otherwise healthy, infant admitted to the general inpatient unit has hindered a standardized approach to the length of inpatient observation. Further-

more, the rarity of bacteremia in this population, estimated at 0.9% to 2%,[10,15] and the geographical limitations of single-region microbiologic data[16] necessitate a national approach. We present a large, geographically diverse examination of the time to positivity (TTP) of blood culture results in febrile, but otherwise healthy, infants 90 days of age or younger. Specifically, our primary aim was to determine the proportion of positive blood culture results that become positive more than 24 hours of incubation. As a secondary aim, we attempted to provide information regarding the epidemiology of bacteremia in this population and predictors of TTP in the most common bacterial species.

Methods

This multicenter, retrospective, cross-sectional evaluation of TTP of blood culture results included febrile infants 90 days of age and younger with bacteremia outside of the ICU. In total, 17 hospital systems affiliated with the Pediatric Research in Inpatient Settings Network across all major regions of the United States participated: Children's Hospitals and Clinics of Minnesota, Minneapolis; Children's Medical Center Dallas, Dallas, Texas; Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Children's Hospital Colorado, Aurora; The Children's Hospital of The King's Daughters, Norfolk, Virginia; Children's Hospital Los Angeles, Los Angeles, California; Children's Hospital of Illinois, Peoria; Nemours/A.I. DuPont Hospital for Children, Wilmington, Delaware; Children's National Medical Center, Washington, DC; Albany Medical Center, Albany, New York; Tufts University School of Medicine, Boston, Massachusetts; University of Rochester Medical Center, Rochester, New York; Packard Children's Hospital at Stanford, Palo Alto, California; St Joseph's Mercy Hospital, Ann Arbor, Michigan; State University of New York Upstate, Syracuse; University of Iowa Children's Hospital, Iowa City; and Virginia Commonwealth University School of Medicine, Richmond.

Study dates varied by site secondary to the availability of data and feasibility of collection. However, every site collected at least 2 consecutive years of data ending January 1, 2013; the median duration of data collection was 4 years (range, 2-6 years). All sites used a BACTEC automated blood culture detection system throughout the collection period. Institutional review board approval with waiver of informed consent was obtained at each participating site.

Study Design

Each site obtained a data set from their microbiology laboratory of all positive blood culture results from infants 90 days of age and younger drawn in a non-ICU setting. A preliminary review of each record was performed by individual site investigators to determine eligibility. Cultures were included if the results were positive for bacteria, obtained from an infant 90 days old or younger with a temperature of 38.0°C or greater recorded on presentation or reported by caregiver, analyzed using a fully automated detection system, and treated as a pathogen by the medical team (this did not include empirical therapy and was specifically defined as prescribing a full course of antibiotics intended to treat the bacteria identified by blood culture). Cultures drawn in any manner other than peripheral venipuncture in an ICU from patients admitted to the ICU within 5 hours after culture; from patients with central catheters or histories of intraabdominal, intracranial, or intrathoracic surgical procedures; or drawn from a hospital or clinic outside the system of any participating site were excluded.

For cultures meeting study criteria, site investigators collected patient age, sex, the location of the patient where the culture was drawn, antibiotics that were received within 24 hours preceding the culture, highest recorded temperature within 1 hour before or after obtaining the blood culture, blood culture TTP in minutes (calculated as the time at which the culture was placed in the detection system subtracted from the time the machine alarmed as positive), and the bacterial species identified. Each infant was stratified as low risk or nonlow risk based on a modification of the Rochester criteria used previously.[10,14] As has been done previously, culture results from infants not meeting all of the low-risk criteria, even if all classifying data were unavailable, were placed in the nonlow-risk group.[14]

Data Analysis

Data on bacterial species were previously reported for 6 of the 17 participating sites; data on TTP were not previously reported for any site.[16] Time to positivity was compared between groups using the Wilcoxon rank sum test. Because our study criteria allowed the inclusion of common contaminants if the physician team prescribed a full treatment course of antibiotics for the specific bacterium, we performed a comparison of TTP between all included cultures and all cultures after the removal of common contaminants (viridans group streptococci, coagulase-negative *Staphylococcus*, *Micrococcus* spp, *Corynebacterium* spp, and *Bacillus* spp).[17] A multivariate analysis using a generalized linear model was performed to assess the impact of age, sex, prior antibiotics, and fever on TTP of the most common pathogenic bacterial species. Owing to the potential of type I error, the significance level, adjusted using Bonferroni correction, was set at .017 for this multivariate analysis.

To assess variability between sites, χ^2 analysis was used to compare the prevalence of 3 categories of bacteria: *Escherichia coli*, group B *Streptococcus* (GBS), and all other bacterial species. Bacterial prevalence was compared between the 8 highest-enrolling sites, with the remaining sites pooled into 1 group for comparison. A univariate analysis accompanied by a generalized linear model was performed to assess the variability in TTP between species and between study sites.

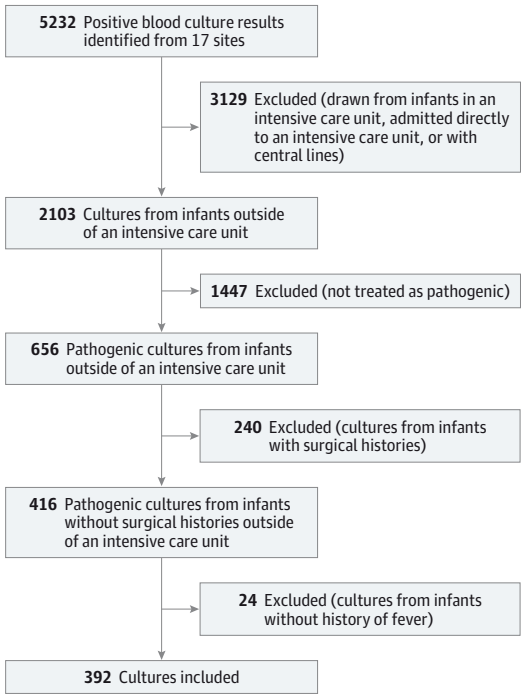
Data analysis was performed by 2 statisticians and the lead author (J.R., C.A., and E.A.B.). Statistical significance was set at a $P < .05$, unless otherwise noted, and all confidence intervals are reported at 95%. The statistical program used was SPSS version 21.

Results

Time to Positivity

A total of 5232 positive blood culture results were identified via initial search from the 17 systems. After exclusion criteria

Figure 1. Flow Diagram of Included and Excluded Infants and Blood Cultures



were applied, 392 pathogenic cultures remained for analysis (**Figure 1**). The mean (SD) TTP was 15.41 (8.30) hours and the median TTP was 13.00 hours (range, 5.22-68.30 hours). When compared with infants aged 61 to 90 days, there was a significantly shorter TTP in cultures drawn from infants 30 days and younger and 31 to 60 days old (**Table 1**). Cultures from infants with a temperature 38.0°C or greater within an hour of culture had a shorter TTP than those who did not (Table 1). Time to positivity was not significantly different in infants of different sexes or Rochester criteria risk stratification. When the 39 common contaminants (32 viridans group streptococci, 5 coagulase-negative *Staphylococcus*, 1 *Micrococcus* spp, and 1 *Bacillus* spp) were excluded, the TTP of the remaining cultures (mean [SD], 14.74 [7.18] hours) was not significantly different from the overall TTP (P = .18). Only 6 infants (2%) received antibiotics prior to obtaining the blood culture; therefore, this variable was not assessed in our model.

By 24 hours, 355 of the 392 blood culture results (91%; 95% CI, 88-93) were positive. By 36 and 48 hours, 378 (96%; 95% CI, 95-98) and 386 (99%; 95% CI, 97-100) had become positive, respectively (**Figure 2**). Of the bacteria growing after 24 hours, 30% (11 of 37) were *Escherichia coli* and 24% (9 of 37) were common contaminants (5 viridans group streptococci, 3 coagulase-negative *Staphylococcus*, and 1 *Micrococcus* spp). The median TTP was not statistically different in bacteria growing after 24 hours when common contaminants were included and removed (median, 31.9 vs 31.9 hours; P = .89).

A multivariate analysis was performed on the 4 most prevalent species known to be definite pathogens in culture (**Table 2**). For infants with *E coli* bacteremia, cultures drawn from those in the 0- to 30-day age range were more likely to have shorter TTP than those in the 61- to 90-day age range (mean, 13.3 vs 16.1 hours; P = .009). Cultures from infants with *Staphylococcus aureus* bacteremia in the 31- to 60-day age range took longer to grow than cultures from infants in the 61- to 90-day age

Table 1. Clinical Characteristics and Time to Positivity

Description	No. (%)	Time to Positivity, Mean (SD), h	*P* Value
Total No.	392 (100)	15.4 (8.3)	
Sex			
Male	201 (51)	15.4 (7.7)	.90
Female	191 (49)	15.5 (8.8)	
Age at blood drawn, d			
0-30	155 (40)	13.9 (4.9)	<.001
31-60	154 (39)	15.6 (9.0)	.01
61-90	83 (21)	17.9 (10.8)	1 [Reference]
Highest temperature recorded within 1 h, C°[a]			
<38.0	107 (27)	17.0 (9.9)	.006
≥38.0	210 (54)	14.9 (7.8)	
Infant risk stratification			
Low	99 (25)	15.7 (9.1)	.56
Nonlow	293 (75)	15.3 (8.0)	
Site			
1	87 (22)	14.9 (5.4)	1 [Reference]
2	53 (14)	17.0 (8.6)	.06
3	44 (11)	19.3 (13.5)	<.001
4	36 (9)	13.7 (4.3)	.24
5	31 (8)	14.1 (8.9)	.45
6	27 (7)	14.5 (6.8)	.74
7	23 (6)	12.9 (6.4)	.13
8	17 (4)	16.6 (11.8)	.30
9	14 (4)	14.3 (3.2)	.69
10-17	60 (15)	14.9 (7.9)	NA

Abbreviation: NA, not applicable.

[a] Seventy-five (19%) had no temperature recorded within 1 hour of the blood culture.

Figure 2. Kaplan-Meier Curve Representing the Time to Positivity of Blood Culture Results

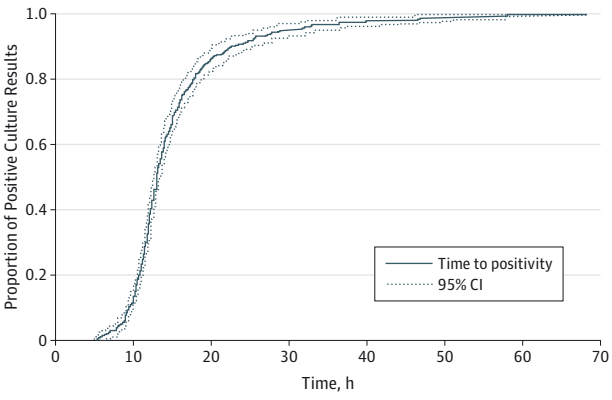


Table 2. Multivariate Analysis of Demographics and Mean Time to Positivity Within Common Species[a]

Demographic	*E coli*			GBS			*S aureus*			*S pneumoniae*		
	No.	Mean (SD)	*P* Value	No.	Mean (SD)	*P* Value	No.	Mean (SD)	*P* Value	No.	Mean (SD)	*P* Value
Sex												
Female	78	15.3 (7.0)	.27	47	11.1 (3.7)	.31	11	17.8 (5.8)	.55	10	16.4 (7.1)	.30
Male	81	13.9 (3.9)		40	11.2 (5.6)		12	20.7 (6.5)		8	15.8 (5.8)	
Age, d												
0-30	68	13.3 (3.3)	.009	34	11.2 (5.6)	.98	8	17.2 (3.2)	.72	2	14.4 (3.0)	.44
31-60	58	15.2 (6.9)	.65	41	11.2 (5.6)	.54	11	21.1 (8.2)	.01	5	18.7 (10.0)	.11
61-90	33	16.1 (6.7)	1 [Reference]	12	10.6 (2.7)	1 [Reference]	4	18.7 (2.9)	1 [Reference]	11	15.2 (4.8)	1 [Reference]
Risk												
Low	19	13.4 (4.3)	.25	34	10.5 (3.2)	.01	7	19.0 (2.2)	.23	3	22.6 (11.7)	.04
Nonlow	140	14.7 (5.9)		53	11.5 (5.4)		16	19.5 (7.4)		15	14.8 (4.3)	
Fever, °C												
<38.0	36	14.8 (4.6)	.68	21	10.5 (2.9)	.08	8	21.1 (8.1)	.08	3	20.0 (7.6)	.06
≥38.0	93	15.0 (6.6)		54	10.9 (4.0)		13	18.8 (5.2)		11	15.5 (7.0)	

Abbreviation: GBS, group B *Streptococcus*.

[a] Bonferroni correction significance set at 0.017.

Table 3. Epidemiology of Bacteremia and Generalized Linear Model Comparing Median Time to Positivity Between Species

Organism	No. (%)	Time to Positivity, Median (Range), h	*P* Value
E coli	159 (41)	13.0 (7.8-53.3)	1 [Reference]
GBS	87 (22)	10.5 (5.2-39.5)	<.001
Viridans group streptococci[a]	32 (8)	17.2 (10.3-57.2)	<.001
S aureus	23 (6)	18.5 (12.4-40.1)	<.001
S pneumoniae	18 (5)	14.3 (11.2-36.1)	.19
Enterococcus spp	14 (4)	15.3 (9.8-25.7)	.46
Klebsiella spp	10 (3)	12.0 (8.9-15.0)	.10
Enterobacter spp	8 (2)	13.0 (9.2-19.0)	.38
Salmonella spp	6 (2)	15.1 (12.3-22.0)	.44
S pyogenes	5 (1)	13.6 (9.1-37.3)	.10
Other γ-hemolytic *Streptococcus*	5 (1)	14.1 (5.6-14.8)	.20
CoNS[a]	5 (1)	27.2 (15.0-68.3)	<.001
Moraxella spp	4 (1)	39.8 (22.7-56.0)	<.001
Neisseria spp	3 (1)	23.5 (17.6-27.2)	.003
Serratia spp	2 (0)	17.0 (16.2-17.8)	.46
Pseudomonas spp	2 (0)	29.0 (11.9-46.0)	<.001
Micrococcus spp[a]	1 (0)	58.8 (58.8-58.8)	<.001
Other	8 (2)	19.9 (9.4-58.2)	<.001

Abbreviations: GBS, group B *Streptococcus*; CoNS, coagulase-negative *Staphylococcus*; spp, species.

[a] Considered common contaminants.

range (mean, 21.1 vs 18.7 hours, respectively; $P = .01$). Time to positivity did not differ significantly in infants with temperatures 38.0°C or greater within 1 hour of obtaining the culture and those with temperatures of less than 38.0°C.

Epidemiology and Variability

E coli was the most prevalent species (159 of 392, 41%), followed by GBS (87 of 392, 22%), viridans group streptococci (32 of 392, 8%), *S aureus* (23 of 392, 6%), and *Streptococcus pneumoniae* (18 of 392, 5%). *E coli* was also the most common species identified in infants 30 days or younger (68 of 155, 44%), followed by GBS (34 of 155, 22%). Group B *Streptococcus* had the shortest median TTP among all species identified (10.5 hours; range, 5.2-39.6 hours). Our linear model suggested significant variability in TTP between bacterial species, as the TTP of the reference bacteria (*E coli*) was significantly different from several other species including GBS, *S aureus*, and viridans group streptococci (**Table 3**).

A generalized linear model was used to compare bacterial species between sites for variation in TTP. Data from the largest site were used as a reference. There was statistically significant TTP variation of *E coli* in 5 of the 17 sites, of GBS in 2 sites, and of *S aureus* in 1 site. *S pneumoniae* showed no variation in TTP between sites (Table 1).

Discussion

While inpatient evaluation of an otherwise healthy, febrile infant is a common clinical scenario encountered by physicians and discharge is often based on negative culture results, there is a lack of consensus on the time of inpatient observation while awaiting culture results. Furthermore, the rarity of bacteremia in this population[10] and the variability of bacterial epidemiology between geographic regions in the United States[16] warrants a national approach to this question.

In our large geographically diverse investigation, we estimated that 91%, 96%, and 99% of blood cultures from this population will turn positive by 24, 36, and 48 hours, respectively. Assuming an incidence of 0.9% to 2% for bacteremia in this population,[10,15] our data suggest an observation period beyond 24 hours would capture 1 additional bacteremic infant for every 556 to 1235 febrile infants evaluated. Similarly, observation for more than 36 hours and more than 48 hours would identify 1 bacteremic infant for every 1250 to 2778 and 5000 to 11111 infants, respectively.

A standard inpatient observation time of 48 to 72 hours for blood cultures in infants with fever was initially established when cultures were manually observed for bacterial growth at infrequent intervals.[18,19] Automated, continuous-monitoring blood culture systems have since been instituted in most laboratories and are able to detect bacterial growth significantly sooner than manual methods.[20,21] In addition to advances in blood culture monitoring, the changing epidemiology of pathogens causing bacteremia has resulted in evolving approaches to the evaluation and management of febrile infants.[10,16,22] There has also been a decrease in the reported rates of occult bacteremia since vaccinations for *Haemophilus influenzae* type B and *S pneumoniae* became universally available in the United States, as well as a decrease in early-onset sepsis caused by GBS since the implementation of widespread intrapartum antibiotic prophylaxis.[23-25]

Recent studies have reported a decrease in the TTP for blood culture results in pediatric patients; however, these studies were small single-center examinations or focused on populations very different from the classic febrile infant admitted to a general inpatient unit for observation.[3,8,9,23,26-28]

Our data suggest that 24 hours (as opposed to the generally accepted 48-hour inpatient observation period) is adequate to detect most clinically significant bacteremia and by using this cutoff, we can minimize the number of nights spent in the hospital for these infants and caregivers. We were unable to examine the TTP of urine and cerebrospinal fluid cultures, typically followed as part of the febrile infant evaluation; however, analyses of urine and cerebrospinal fluid samples (eg, white blood cell count and Gram stain) can be performed within hours of presentation and have high sensitivity for urinary tract infection and meningitis, respectively.[15,29,30]

While there remains an established risk for serious bacterial infection in young infants with fever, the expanding body of research leads the practitioner to continually weigh the benefits of treatment and the risks posed by health care interventions. Hospitalized patients are at risk for iatrogenic complications such as intravenous infiltration, hospital-acquired infections, and adverse medication effects.[31,32] Parents also experience significant stress when a child is hospitalized in terms of both concern for the child's health and time spent away from other daily responsibilities.[33] Additionally, hospital charges for the evaluation of low-risk febrile infants are estimated at $6613 per infant (adjusted to 2013 dollars).[31,32] Finally, recent data suggest the incidence of hospital-acquired infection on a general pediatric unit is 1 per 1000 patient-days[34]; therefore, it can be estimated that for every case of bacteremia identified at more than 24 hours in infants who remain hospitalized, 1 nosocomial infection will also occur.

As has been done previously,[16] we defined pathogenic bacteria as those that were treated with a full course of antibiotics rather than simply excluding bacteria commonly considered to be contaminants. While this method did result in the inclusion of several cultures that are often considered contaminants, it did not significantly alter the overall TTP and allowed us to exclude many cases in which contamination may have otherwise been equivocal (eg, *Acinetobacter* spp).

Our study had several limitations. First, we were unable to account for the time between collection of the blood culture and placement in the machine. Blood is typically drawn directly into culture media; therefore, our data may underestimate the total time needed for bacteria to grow. While the hospitals in our study have different blood draw protocols, it is generally assumed that cultures take less than 30 minutes from collection to placement in the automated detection system. Second, criteria for ICU admission vary by institution and this may have introduced some unidentified heterogeneity in our population. Third, there was some variability in TTP of a few specific bacterial species at a minority of sites. While it is possible that there are specific bacterial attributes that differ geographically or that the differing inclusion dates between some sites introduced variation in TTP, another plausible explanation is that we were unable to control for the amount of blood inoculated, which does impact TTP.[35] Fourth, we were unable to identify clinical predictors for a culture result taking more than 24 hours to become positive and therefore cannot suggest likely outcomes for these infants should they be discharged prior to the culture result becoming positive. Furthermore, because we did not collect data regarding negative culture results, we cannot provide information regarding overall risk for serious bacterial infection to our population or by subgroup. Finally, our subgroup analyses included testing for multiple variables and while we did use Bonferroni correction for multiple testing, there was the possibility of type I error in those analyses.

Conclusions

Our study found that most pathogens in febrile bacteremic infants 90 days of age and younger will be identified within 24 hours of collection. These data could support a national standardized approach to the duration of inpatient observation of the febrile infant.

ARTICLE INFORMATION

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Study concept and design: Biondi, Mischler.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Biondi, Mischler, Jerardi, French, Evans, Lee, Chen.
Critical revision of the manuscript for important intellectual content: Biondi, Mischler, Jerardi, Statile, Evans, Asche, Ren, Shah.
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Enhanced Urinalysis Improves Identification of Febrile Infants Ages 60 Days and Younger at Low Risk for Serious Bacterial Illness

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ABSTRACT. *Objective.* **Investigators have sought to establish "low-risk" criteria to identify febrile young infants who can be observed safely without antibiotics. Previous studies have used criteria for standard urinalysis to identify suspected urinary tract infection; however, cases of urinary tract infection have been missed. Enhanced urinalysis, using hemocytometer cell count and Gram stain performed on uncentrifuged urine, has been shown to have greater sensitivity and negative predictive value than standard urinalysis. The objective of this study was to evaluate the ability of criteria that incorporate enhanced urinalysis to identify febrile young infants who are at low risk for serious bacterial illness (SBI).**

Methods. **Institutional guidelines were established in 1999 to evaluate in a retrospective cohort study infants who were ≤60 days of age with temperature ≥38.0°C. "Low-risk" criteria included 1) well appearance without focal infection (excluding otitis media); 2) no history of prematurity, illness, or previous antibiotics; 3) peripheral white blood cell count (WBC) between 5 and 15 000/mm³; 4) absolute band count ≤1500/mm³; 5) cerebrospinal fluid WBC ≤5/mm³ with a negative Gram stain; 6) enhanced urinalysis with WBC ≤9/mm³ with a negative Gram stain; 7) stool WBC <5/high power field in infants with diarrhea; and 8) chest radiograph without lobar infiltrate(s) in infants with respiratory signs or symptoms. SBI was defined as a lobar infiltrate on chest radiograph or presence of a bacterial pathogen in blood, urine, cerebrospinal fluid, stool, or culture obtained from the soft tissue. The hospital records of all infants who presented to the emergency department for evaluation of fever after January 1999, including those who did not meet low-risk criteria, were reviewed; data were collected regarding history, physical examination, laboratory test results, treatment, and clinical course.**

Results. **During the study period, 434 infants presented to the emergency department for evaluation of fever. Thirty patients were excluded from additional analysis because of incomplete data; 60 patients were identified immediately as "not low risk" on the basis of history or physical examination. Of the 344 remaining infants, 127 were identified as "low risk" on the basis of laboratory criteria; 83 (65.4%) were observed without antibiotics. None of the "low-risk" infants had an SBI. A total of 217 well-appearing infants were classified as "not low risk" on the basis of laboratory criteria; 28 (12.9%) had an SBI. The overall incidence of SBI in infants with complete data was 10.1%, whereas the incidence of SBI in all "not low-risk" infants was 14.8%. The negative predictive value for the "Pittsburgh" criteria was 100% (95% confidence interval: 96.7%–100%); the sensitivity was 100% (95% confidence interval: 89.7%–100%).**

Conclusions. **The application of low-risk criteria using enhanced urinalysis improves identification of infants who are at low risk for SBI.** *Pediatrics* **2001;108:866–871;** ***bacteremia, low risk criteria, enhanced urinalysis, serious bacterial illness.***

ABBREVIATIONS. ED, emergency department; SBI, serious bacterial illness; CSF, cerebrospinal fluid; IV, intravenous; WBC, white blood cell count; CXR, chest radiograph; UTI, urinary tract infection; cfu, colony forming units; CI, confidence interval.

Fever is an extremely common symptom among infants and young children who present for evaluation at an emergency department (ED). The incidence of serious bacterial illness (SBI) in those infants in the first 2 months of life has been reported to be as high as 15%.[1–8] Traditionally, a conservative approach has been recommended for febrile infants <2 months of age, in whom the signs and symptoms of infection can be nonspecific. This conservative approach includes obtaining specimens of blood, urine, and cerebrospinal fluid (CSF) for laboratory analysis and culture on all children who subsequently are admitted to the hospital and given intravenous (IV) antibiotics for 48 to 72 hours. Despite these recommendations, there is considerable variability in the extent of evaluation and approach to treatment among general pediatricians, family practitioners, and ED physicians.[9,10]

As an alternative to the conservative approach, several studies have shown that a combination of historical, physical examination, and laboratory criteria can be used to identify a subset of febrile infants who are at low risk for SBI.[1–5,11] Investigators have concluded that these infants can be observed without antibiotic therapy. The previously established criteria include standards for normal white blood cell counts (WBC) in the blood and CSF, negative CSF Gram stain, urinalysis showing <10 WBC/high-power field with a negative Gram stain, and normal chest radiograph (CXR) and stool WBC examinations on selected infants; the negative predictive value of these criteria for SBI has ranged from 95% to 100%. Although many physicians have adopted a less conservative approach to fever in infants as a result of these investigations, concerns remain about the potential for missing cases of SBI.[6]

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Urinary tract infection (UTI) is the most common SBI among febrile young infants, as well as the most commonly missed SBI in studies that evaluate low-risk criteria.[1–3,12] In the study of low-risk criteria by Jaskiewicz et al,[2] 35% of patients with UTI had normal standard urinalyses and 3 patients with UTI met all low-risk criteria; other studies that evaluated low-risk criteria failed to specify what proportion of patients with UTI were identified by standard urinalysis.[2–7] Standard urinalysis and Gram stain have been shown to have a relatively poor sensitivity, ranging from 48% to 65%.[13–15] Enhanced urinalysis, using hemocytometer cell count and Gram stain on uncentrifuged urine specimens, has been shown in several prospective studies to have superior negative predictive value and sensitivity when compared with standard urinalysis and Gram stain.[14,16,17] This modification of the traditional urinalysis results in an improved ability to detect UTI and therefore may reduce the risk of failure to identify cases of SBI in febrile infants.

We sought to evaluate the ability of low-risk criteria that incorporate enhanced urinalysis to identify febrile young infants who are at low risk for SBI. In addition, we hoped to foster a more standardized approach to the evaluation and treatment of febrile young infants at our institution.

METHODS

In January 1999, guidelines were established at Children's Hospital of Pittsburgh, a large, urban, academic children's hospital, for the evaluation and treatment of infants who were ≤60 days of age and had a documented temperature of ≥38.0°C. These guidelines included elements of history, physical examination, and laboratory findings to identify "low risk" infants. These criteria are shown in Table 1.

The guidelines recommended that any infant who did not meet low-risk criteria be admitted to the hospital and given IV antibiotics until all culture results were known. The recommendation for infants who met low-risk criteria was to admit the infant to the hospital for observation without antibiotics or with oral antibiotic therapy for infants with otitis media, for 24 hours. If the infant remained well-appearing, cultures remained negative, and close follow-up with a primary care provider could be ensured, then the infant could be discharged to home. Any low-risk infant whose clinical status deteriorated or whose cultures became positive was to be given IV antibiotics until culture results were known. The evaluation, treatment, and disposition of all febrile infants remained at the discretion of the ED physician, in consultation with the family and the primary care provider.

TABLE 1. Guidelines for Classification of Febrile Infants as "Low Risk"

Historical items
Full term (>35 6/7 weeks' gestation)
No chronic/underlying illnesses
No previous hospitalizations
No perinatal antibiotics (if <14 days old)
No antibiotics within the past 7 days
No siblings with group B streptococcal disease
Examination
Well appearing to an experienced physician
No focal infection (excluding otitis media)
Laboratory
Peripheral WBC 5000 to 15 000/mm³
Peripheral absolute band count ≤1500/mm³
Enhanced urinalysis WBC ≤9/mm³ and negative Gram stain
CSF WBC ≤5/mm³ and negative Gram stain
If bloody, WBC:RBC ≤1:500
Stool WBC <5 per high-power fields in infants with diarrhea
CXR normal in infants with respiratory findings

The hospital records of all febrile infants who had been evaluated for fever between January 1, 1999, and August 31, 2000, were reviewed. Demographic and clinical data collected for each patient included age, sex, birth history (gestational age, complications, maternal group B streptococcal colonization status, type of delivery, need for resuscitation or neonatal intensive care unit stay), maximum recorded temperature, pertinent medical history, and documented appearance and examination by the supervising ED physician (fellow or attending). Laboratory data collected included peripheral WBC and absolute band count, CSF cell count, differential and Gram stain, enhanced urinalysis (uncentrifuged urine used for hemocytometer cell count and Gram stain), any radiograph results, stool WBC results on infants with diarrhea, and all culture results. Other information recorded included treatment with antibiotics, disposition, and clinical course. For children who were treated with IV antibiotics despite meeting low-risk criteria, the reason for treatment was documented whenever possible.

Our guidelines, as shown in Table 1, included examination and culture of the CSF. At our institution, the CSF evaluation occasionally is omitted in infants who are older than 6 weeks of age and are to be observed without antibiotics; we included infants in our analysis when the examination of the CSF was omitted intentionally and the infant was observed without antibiotic therapy. Children were excluded from analysis if they received antibiotics and did not have a sample of CSF for cell count, Gram stain, and culture or did not have an enhanced urinalysis, peripheral CBC, or cultures of blood and urine performed.

SBI was defined as a lobar infiltrate on CXR (reviewed by an attending radiologist); growth of a bacterial pathogen from the CSF, blood, stool, or soft tissue; or growth of ≥50 000 colony forming units (cfu)/mL of a single pathogenic organism from a urine specimen obtained by catheter. Demographic and clinical data are reported as means or proportions. The sensitivity, specificity, and positive and negative predictive values of the low-risk criteria were computed using Yates-corrected χ^2. This study was approved by the Human Rights Committee at the Children's Hospital of Pittsburgh.

RESULTS

Between January 1999 and August 2000, 434 febrile infants <2 months of age presented to the ED for evaluation (Fig 1). Thirty infants, who did not have a complete laboratory database as outlined above, were excluded from additional analysis. Of the remaining 404 infants, 60 were identified as "not low risk" on the basis of history and/or physical examination. Of the 344 previously healthy, well-appearing infants with complete data, 127 were classified as "low risk" according to our established guidelines and 217 were classified as "not low risk." There were a total of 41 cases of SBI (10.1%): 25 infants with UTI; 8 with pneumonia; 3 with bacteremia; 2 with meningitis; and 1 each with bacterial gastroenteritis, pertussis, and chlamydia. The diagnoses and causative agents for infants with SBI are shown in Table 2.

Patient Demographics

A total of 222 boys and 212 girls presented to the ED with fever during the study period; data were incomplete for 16 boys and 14 girls. The patients ranged in age from 2 to 60 days, with a mean age of 34 days. The overall age distribution, including breakdown by risk group and proportion with an SBI, is included in Table 3. Among male patients, 139 (67.4%) with complete data were classified as "not low risk," whereas 67 (32.6%) were classified as "low risk"; 15 (7.3%) had an SBI. Among female patients, 138 (69.7%) with complete data were classified as

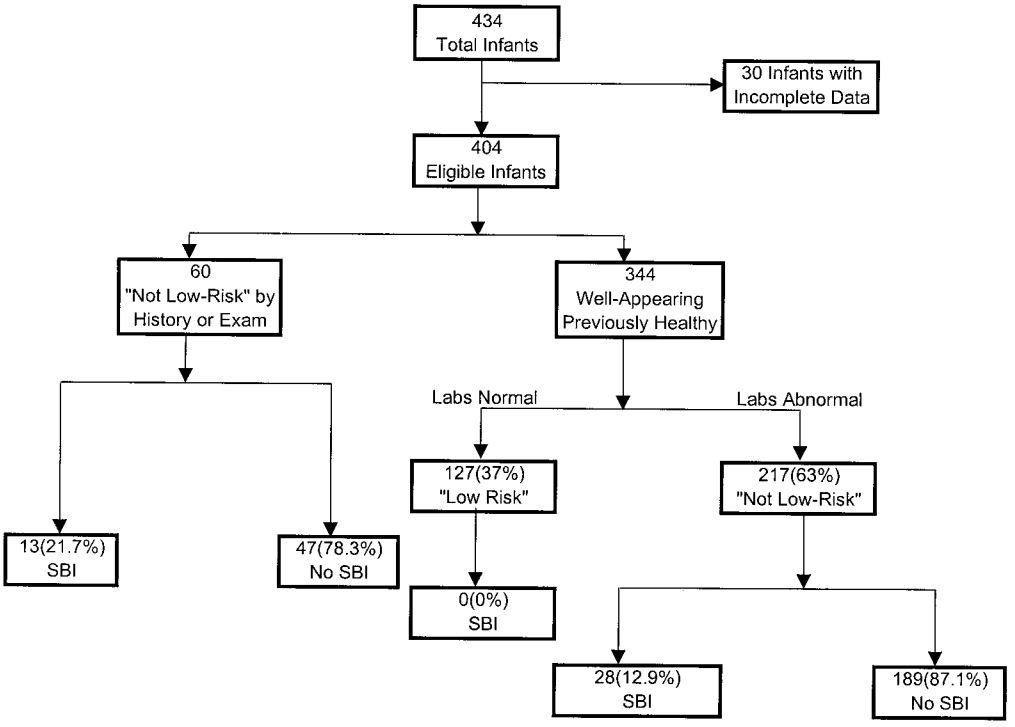

Fig 1. Flow diagram of febrile infants.

"not low risk," whereas 60 (30.3%) were classified as "low risk"; 27 (13.6%) had an SBI. The overall risk of SBI was not significantly different between boys and girls ($P = .05$).

Patients With Incomplete Data

Two infants with SBI in the group of 30 infants had incomplete data. One patient was a 45-day-old infant who had a history of short gut and a central IV catheter and was treated with IV antibiotics for presumed line sepsis without examination of the CSF; *Enterococcus faecalis* was recovered from the blood culture. The second patient was a 25-day-old infant who had clinical findings of omphalitis and did not have a sample of CSF obtained; *Escherichia coli* grew from the culture of the wound. Both of these patients would have been classified as "not low risk" by historical or examination criteria, respectively; in fact, 17 of 30 of the patients with incomplete data met historical, examination, and/or laboratory criteria for classification as "not low risk."

TABLE 2. Bacterial Illnesses Among Eligible Infants

Site of Infection	No. (%)
UTI	25 (6.3%)
Escherichia coli	23
With bacteremia	4
Klebsiella pneumoniae	1
With bacteremia	0
Pseudomonas aeruginosa	1
With bacteremia	0
Respiratory	10 (2.5%)
Bacterial pneumonia	8
Chlamydia trachomatis	1
Bordetella pertussis	1
Bacteremia*	3 (0.7%)
Streptococcus pneumoniae	1
Streptococcus agalactiae	1
Staphylococcus aureus	1
Meningitis	2 (0.5%)
Streptococcus pneumoniae	1
Enterobacter cloacae	1
Gastroenteritis	1 (0.2%)
Campylobacter jejuni	1

* Bacteremia with no other identified SBI.

Infants Classified as "Not Low Risk" on the Basis of History or Examination

Of the 60 infants who were classified as "not low risk" on the sole basis of history and/or physical examination, 13 (21.7%) had and SBI. The reasons for classification as "not low risk," as well as the proportion with SBI, are listed in Table 4. Nine of the 13 infants (69.2%) with SBI also would have been classified as "not low risk" on the basis of laboratory criteria. The 4 infants who had an SBI and met "low-risk" laboratory criteria but were identified as "not low risk" by history or examination included 1) a 38-day-old infant who had respiratory distress and lethargy and received a diagnosis of chlamydial pneumonitis; 2) a 52-day-old infant who had focal findings on examination of the lungs and received a diagnosis of lobar pneumonia by CXR; 3) a 12-day-old infant who had respiratory distress and received a diagnosis of lobar pneumonia by CXR; and 4) a 30-day-old infant who had a history of lethargy and poor feeding and was febrile, mottled, and lethargic on examination and grew *Streptococcus agalactiae* from a blood culture.

Infants Classified as "Not Low Risk" on the Basis of Laboratory Results

Of the 217 well-appearing, previously healthy infants who were classified as "not low-risk" according

TABLE 3. Age Distribution and Occurrence of SBI by Risk Group

Age (Days)	Evaluated (n = 404)	Low Risk (%)	SBI (%)	Not Low Risk (%)	SBI (%)
0–14	49 (12.1%)	18 (36.7%)	0 (0%)	31 (63.3%)	3 (9.7%)
15–28	104 (25.7%)	25 (24%)	0 (0%)	79 (76%)	9 (11.4%)
29–45	138 (34.2%)	47 (34%)	0 (0%)	91 (66%)	19 (20.9%)
46–60	113 (28%)	37 (32.7%)	0 (0%)	76 (67.3%)	10 (13.2%)

to laboratory criteria, 28 (12.9%) had SBI. The laboratory abnormalities, excluding infants from the low-risk group and the proportion with an SBI, are shown in Table 5. All "not low-risk" infants with SBI received IV antibiotics after their initial evaluation, and all did well. Twenty-two infants who were classified as "not low risk" by laboratory examination were observed without antibiotic therapy; none had an SBI, and all did well. Fifty-six patients in our study were classified as "not low risk" on the sole basis of the CSF findings; the WBC in the CSF ranged from 6 to 673/mm^3, and 1 patient had a positive CSF culture. Six of the 8 patients with lobar infiltrates on CXR also had abnormal WBCs and/or absolute band counts; 2 of these patients required admission to the intensive care unit for severe respiratory distress. Five infants who were classified as "not low risk" by laboratory examination had otitis media documented on examination; all received IV antibiotics for at least 48 hours, and none had an SBI.

Low-Risk Infants

None of the 127 infants who were classified as "low-risk" by our criteria had SBI. Eighty-three (65.3%) were observed without IV antibiotic therapy, whereas 44 (34.7%) were treated with IV antibiotics despite meeting low-risk criteria. The reason for treatment was not documented in the majority of cases, although concurrent jaundice, high percentage of bands (although absolute band count was within acceptable range), and primary care physician's request were cited in several cases. Twenty-one infants who were observed without antibiotic therapy did not have a lumbar puncture performed; none of these patients had an SBI, and all did well. Four infants who were not treated initially with antibiotics were started on antibiotics within 48 hours. Two patients developed increased work of breathing and were found later to have respiratory syncytial virus infection. One patient had increased work of breathing with a normal CXR and was treated for 24 hours until culture results were known to be negative. One patient had persistent fever and was treated for 48 hours, at which time all cultures were negative.

TABLE 4. Nonlaboratory Reasons for Exclusion From the Low-Risk Group and Proportion With SBI

Reason for Classification as "Not Low Risk"	Total (%)	Number With SBI (%)
Previous hospitalization	7 (11.7%)	0 (0%)
Medical history	9 (15%)	5 (55.6%)
Previous antibiotics	3 (5%)	0 (0%)
Prematurity	12 (20%)	0 (0%)
Ill appearance	25 (41.7%)	7 (28%)
Focal examination	4 (6.6%)	1 (25%)

There were 14 "low-risk" infants who were diagnosed with otitis media; 5 were treated with oral antibiotics, whereas 9 were given IV antibiotics for 48 hours. None of the infants with otitis media had bacteremia or other SBI. The negative predictive value for our low-risk criteria was 100% (95% confidence interval [CI]: 96.7%–100%).

Infants Who Were ≤28 Days

A total of 166 infants (38.2%) who were ≤28 days of age were evaluated for fever during our study period. Of these, 153 had complete data for evaluation. Among eligible infants, 17 (11.1%) were classified as "not low risk" by history or examination, 93 (60.8%) were classified as "not low risk" by laboratory criteria, and 43 (28.1%) were classified as "low risk." There were 12 patients (7.8%) with SBI in this age group, all of whom were classified as "not low risk": UTI (6), meningitis (2), pneumonia (2), pertussis (1), and bacteremia in a central line (1). Among the 12 infants who were ≤28 days with an SBI, 11 were identified as "not low risk" by laboratory criteria; 2 of these infants also were deemed ill-appearing on physical examination, and 1 had a history of surgery and hospitalization. Only 1 of the 12 infants had low-risk laboratory values: a 12-day-old infant with a lobar infiltrate on CXR and respiratory distress that required admission to the intensive care unit. Eighteen (41.9%) of the 43 low-risk infants who were ≤28 days of age were observed without antibiotics, and 25 (58.1%) were treated; all infants did well. There was a statistically significant difference in the percentage of "low-risk" patients observed without antibiotics between the group of patients who were >28 days and those who were ≤28 days ($P <$ .005).

Infants With Positive Urine Cultures

Twenty-five infants (6.2% of eligible infants) had growth of >50 000 cfu/mL of a single organism from a urine culture. This group included 19 girls (76%) and 6 boys (24%), with an age range from 13 to 58 days and a mean age of 38 days. The difference in proportion with UTI between male and female patients was statistically significant ($P <$ .01). Twenty-one (84%) infants had growth of >100 000 cfu/mL, whereas 4 (16%) had growth of >50 000 cfu/mL. All of the patients with positive urine cultures were identified as "not low risk" by our criteria. Although our criteria for abnormal enhanced urinalysis included either a positive Gram stain or ≥10 WBC/mm^3, the majority of patients (21 [84%] of 25) with UTI had bacteriuria and pyuria; 17 (68%) of 25 also had abnormal peripheral WBC and/or absolute band counts. Only 1 patient with growth of >50 000 cfu/mL had a normal enhanced urinalysis; this pa-

TABLE 5. Laboratory Finding(s) Excluding Infants From the Low-Risk Group and Proportion With SBI

Abnormal Laboratory Finding	Number (%)	Number With SBI (%)
WBC only	39 (17.8%)	0 (0%)
Absolute band count only	19 (8.7%)	2 (10.5%)
CSF only	56 (25.6%)	1 (1.8%)
Enhanced urinalysis only	22 (10%)	6 (27%)
CXR only	2 (0.9%)	2 (100%)
Combination	81 (37%)	19 (23%)

tient was described as ill-appearing and had abnormal WBC and absolute band counts. The sensitivity and negative predictive value of the enhanced urinalysis in our study were 96% (95% CI: 78.9%–99.8%) and 99.7% (95% CI: 98.5%–100%), respectively. Four of the infants who received a diagnosis of UTI also had bacteremia; the same organism was isolated from blood and urine cultures (16%). All of the patients with bacteremia had growth of >100 000 cfu/mL from the urine culture. Only 3 infants in our study group had growth of between 10 000 and 50 000 cfu/mL of a single organism from a urine culture. All of these infants were identified as high risk on the basis of the results of the enhanced urinalysis but were not considered to have a positive culture by our criterion.

DISCUSSION

The evaluation and treatment of infants who are <2 months of age and present to the ED with fever remains controversial. Concerns about health care costs, emerging antibiotic resistance, and potential complications from routine hospitalization and antibiotic therapy have prompted many clinicians to question the traditional conservative approach to the treatment of febrile young infants.[1–5,11,18–20] The establishment of treatment guidelines at our institution was an attempt to identify systematically infants who are at low risk of SBI and who could be observed without antibiotic therapy.

Our guidelines differ from previously published criteria in several important ways: 1) we incorporated an enhanced urinalysis and Gram stain in an attempt to improve the sensitivity and negative predictive value of the criteria, 2) we did not consider acute otitis media to be an SBI and allowed infants with otitis media to be classified as "low risk" when they met the remaining criteria, and 3) we included infants who were ≤28 days of age.

In many of the previous studies, pneumonia was considered an SBI only when there was confirmation of bacterial infection by positive blood culture, tracheal aspirate culture, or bacterial antigen testing. We chose to include infants with lobar infiltrates on CXR in the SBI group for several important reasons. First, it is widely known that microbiologic confirmation of bacterial pneumonia is extremely difficult and not frequently achieved in childhood pneumonia; bacteremia occurs in between 1% and 8% of cases, bacterial antigen tests are not readily available, and tracheal aspirate or lung biopsy is not practical for the vast majority of patients.[21,22] Second, all of the patients who received a diagnosis of pneumonia in our study had respiratory signs and symptoms, fever, and lobar infiltrates on CXR; in addition, 6 of 8 had abnormal WBC or absolute band counts, and 3 of 8 had severe respiratory distress that required admission to the intensive care unit.

Some previous studies did not include CSF findings in their low-risk criteria, although they included meningitis among the SBIs identified in their study patients.[1,2,4] Although infants and children with meningitis may be ill-appearing or have laboratory abnormalities other than CSF pleocytosis, it is possible for a patient with bacterial meningitis, especially a young infant, to have only CSF findings to suggest the diagnosis. In fact, our patient who received a diagnosis of *Enterobacter cloacae* meningitis was identified as "not low risk" on the sole basis of CSF pleocytosis. We believe that it is important to include CSF examination in any low-risk criteria for febrile young infants, and we recommend lumbar puncture for all of these patients. Although we did classify as "low risk" a small percentage of well-appearing patients who did not have a CSF examination performed, these patients were observed carefully without antibiotic therapy, which would allow for detection of any deterioration in clinical status that might suggest bacterial meningitis or other SBI.

In our study population, our guidelines allowed for the identification and safe observation of infants who were at low risk for SBI without antibiotic therapy. In agreement with previous studies, otitis media among the febrile young infants in our cohort was not associated with a significant risk of SBI.[1,2] Although the number of patients with otitis media in this study was small, it seems that these infants can be treated safely with oral antibiotics and close observation when the remainder of the evaluation is unremarkable. All components of the evaluation, including a thorough history, complete examination, and full laboratory testing, are necessary for classifying an infant as low risk for SBI.

There are several limitations to this study. Not all infants who were identified as "low risk" for having SBI according to these guidelines were observed without antibiotics. Although no cases of SBI were diagnosed, we cannot know with certainty that the outcome for these infants was not affected by the antibiotic therapy. The assessment of the infants and the ultimate treatment decisions were made by numerous physicians with variable approaches to the febrile infant. It is impossible to determine whether infants who were deemed "ill-appearing" by one physician would have been classified as "well-appearing" and low risk by another; infants who had an SBI and were treated solely on the basis of ill appearance may have been observed without administration of antibiotics by a different physician. Finally, important historical information, such as siblings with group B streptococcal disease, gestational age, previous antibiotics, and previous hospitalizations, was not always recorded systematically.

As observed in previous studies, UTI was the most commonly diagnosed SBI in our group of febrile infants. UTI occurs in 5% or more of such patients, and a substantial proportion of these infants have

concomitant bacteremia.[15,23] Our criterion for significant bacteriuria (≥50 000 cfu/mL) was based on studies by Hoberman et al,[14,16,17] who found that the majority of patients with UTI have growth of >50 000 cfu/mL. They also showed that the likelihood of contamination and asymptomatic bacteriuria is much higher in those with growth of <50 000 cfu/mL. Other investigators have found that UTI is the SBI most likely to be missed with the application of low-risk criteria, because of the relatively poor sensitivity of standard urinalysis. The use of hemocytometer cell counts on uncentrifuged specimens eliminates the variability of cell counts associated with centrifugation time and volume of resuspension commonly encountered with standard urinalysis. Enhanced urinalysis uses the same technique as cell counts on other body fluids, such as blood and CSF; the training, cost, and time required to perform the test do not differ substantially from standard urinalysis. The enhanced urinalysis has been proved to be superior to standard urinalysis, and its use results in improved identification of UTI in febrile infants and children. The incorporation of the enhanced urinalysis in our evaluation of febrile infants led to the identification of 100% of patients with positive urine cultures and aided in the identification of 100% of patients with SBI.

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CONTENT VERSUS PROCESS

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Enhanced Urinalysis Improves Identification of Febrile Infants Ages 60 Days and Younger at Low Risk for Serious Bacterial Illness

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Epidemiology of Bacteremia in Febrile Infants in the United States

WHAT'S KNOWN ON THIS SUBJECT: Bacteremia occurs in 2.2% of febrile infants who have a blood culture drawn. Regional data suggest that *Escherichia coli*, group B *Streptococcus*, and *Staphylococcus aureus* are leading causes; however, the geographic boundaries of these data limit universal applicability.

WHAT THIS STUDY ADDS: This is the first national study examining epidemiology of bacteremia in febrile infants admitted to a general inpatient unit. The most common pathogens were *Escherichia coli* (42%), group B *Streptococcus* (23%), and *Streptococcus pneumoniae* (6%). No *Listeria monocytogenes* was identified.

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KEY WORDS

febrile infant, bacteremia, *Escherichia coli*, epidemiology, antibiotic use

ABBREVIATIONS

AMC—Albany Medical Center
CHCM—Children's Hospitals and Clinics of Minnesota
CHKD—The Children's Hospital of The King's Daughters
CHLA—Children's Hospital Los Angeles
CHOI—Children's Hospital of Illinois
CoNS—coagulase-negative *staphylococcus*
CSF—cerebrospinal fluid
GBS—group B *Streptococcus*
GCHS—Golisano Children's Hospital at Strong
SBI—serious bacterial infection
SSTI—skin or soft-tissue infection
UTI—urinary tract infection

Dr Biondi conceptualized and designed the study, collected data, served as the central site principal investigator, coordinated data collection at all 6 study sites, drafted much of the initial manuscript, and participated in statistical analysis; Dr Evans aided in study conceptualization and design, collected data at her institution, served as participating site principal investigator, and drafted parts of the initial manuscript; Dr Mischler aided in study conceptualization and design, collected data at his institution, served as participating site principal investigator, drafted parts of the initial manuscript, and aided in statistical analysis; Dr Bendel-Stenzel aided in data collection, served as principal investigator at his institution, and reviewed drafts of this manuscript; Dr Horstmann aided in data collection, served as principal investigator at her institution, drafted parts of the initial manuscript, and reviewed drafts of the manuscript; Dr Lee aided in data collection, served as principal investigator at her institution, and reviewed drafts of the manuscript; Dr Aldag provided statistical analysis of the compiled data and critically reviewed and drafted aspects of the methodology and results sections; Dr Gigliotti aided in conceptualization and study design, provided supervision and mentorship at the central site, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

(Continued on last page)

abstract

BACKGROUND: Fever in infants is a common clinical dilemma. The objective of this study was to present data from hospital systems across the northeast, southeast, mid-west, and western United States to identify the pathogens causing bacteremia in febrile infants admitted to general care units.

METHODS: This was a retrospective review of positive blood culture results in febrile infants aged ≤90 days admitted to a general care unit across 6 hospital systems. Data were collected from January 1, 2006 through December 31, 2012 from emergency departments and general inpatient units. Cultures from ICUs, central lines, or infants who had complex comorbidities were excluded, as were repeat cultures positive for the same bacteria. Common contaminants were considered pathogens if they were treated as such.

RESULTS: We identified 181 cases of bacteremia in 177 infants. The most common pathogen was *Escherichia coli* (42%), followed by group B *Streptococcus* (23%). *Streptococcus pneumoniae* was more likely in older infants ($P = .01$). Non-low-risk bacteremic infants were more likely to have *E coli* or group B *Streptococcus* than low-risk bacteremic infants. We identified no cases of *Listeria monocytogenes*. Variation between sites was minimal.

CONCLUSIONS: This is the largest and most geographically diverse study to date examining the epidemiology of bacteremia in infants. We suggest *E coli* is the most common cause of bacteremia in previously healthy febrile infants admitted to a general inpatient unit. We identified no cases of *L monocytogenes* and question whether empirical therapy remains necessary for this pathogen. *Pediatrics* 2013;132:990–996

Fever in infants is a common problem faced by pediatricians and is often the only sign of serious bacterial infection (SBI) in this age group.[1] It is estimated that 2% of infants presenting with fever without a source will have bacteremia, but it is often difficult to clinically predict which infants have bacteremia before obtaining blood culture results.[2–6] For this reason, empirical broad spectrum antibiotic coverage is classically recommended until specific pathogens can be isolated or excluded; however, the recommended antibiotics have changed very little in the last few decades.[7,8]

Recent regional data suggest that the epidemiology of bacteremia in term infants is shifting, and that *Escherichia coli* is now the most common cause of bacteremia in febrile infants ≤90 days old.[2] Once considered the most common cause of bacteremia in infants, estimates suggest that group B *Streptococcus* (GBS) may now account for as few as 16% of cases and was only the third most common cause of bacteremia in 1 study.[6,9] Early-onset GBS has declined dramatically since the early 1990s from 1.7 cases per 1000 live births to 0.34 to 0.37 in recent years.[10] Additionally, although evidence-based guidelines regarding empirical antibiotics continue to include coverage for *Listeria monocytogenes*,[8] there is evidence that the incidence of listeriosis has been decreasing.[11]

The subpopulation of febrile infants who are well-appearing enough to be admitted to a general inpatient unit is important. These infants are exposed to empirical antibiotic coverage pending culture results, colloquially termed the "rule out sepsis" evaluation, but rarely demonstrate true bacteremia. A review of the literature identified no multicenter studies examining this issue, and regional studies were limited to <100 cases of bacteremia.[5,6,10] The low prevalence of bacteremia in this group, and potential geographic variability, make it difficult for regional or single-site studies to provide generalizable epidemiological data, and thus warrant a national examination. Furthermore, although patients stratified as low or non-low risk by the Rochester criteria[12] can differ in risk for SBI by greater than eightfold,[5] a literature review did not identify a study examining bacterial epidemiology by risk.

The purpose of this study was to provide geographically diverse data on the epidemiology of bacteremia in previously healthy, febrile infants admitted to a general inpatient unit; to determine the incidence of *L monocytogenes* in this population; and to determine whether age or infant risk can predict the epidemiology of bacteremia.

METHODS

This was a multicenter, retrospective review of positive, pathogenic blood cultures in previously healthy, febrile infants aged ≤90 days admitted to a general inpatient unit between January 1, 2006 and December 31, 2012. This study was independently approved by the Institutional Review Boards at all 6 participating institutions. Informed consent was waived.

Study Design

The central site for this study was Golisano Children's Hospital at Strong (GCHS) at the University of Rochester Medical Center, a tertiary care children's hospital located in Rochester, New York. Participating sites included The Children's Hospital of Illinois (CHOI), The Children's Hospital of The King's Daughters (CHKD), Children's Hospitals and Clinics of Minnesota (CHCM), The Children's Hospital at Albany Medical Center (AMC), and Children's Hospital Los Angeles (CHLA). Table 1 describes the demographic attributes of the participating sites. All sites use a BACTEC automated blood culture detection system.

Each participating site obtained from their microbiology laboratory an initial database of all positive blood cultures drawn from infants ≤90 days old within their hospital system. Inter-site study dates varied secondary to availability of data and feasibility of collection.

A preliminary review of culture data allowed exclusion of cultures drawn in an ICU and a full chart review was then performed on the remaining cultures to determine whether study criteria were met. To qualify for inclusion, cultures must have been positive for bacteria, drawn from an infant ≤90 days of age, treated as a pathogen, and drawn from a patient who had either a fever per history or a recorded temperature of ≥38.0° C. Cultures drawn in any manner other than peripheral venipuncture, from children requiring an ICU level of care (defined as drawn in an ICU or from a patient admitted directly to an ICU), from patients with central lines, intra-abdominal, intracranial, or intra-thoracic surgical histories, or repeat cultures growing the same bacteria from the same infant were excluded. Cultures that grew common contaminants such as diphtheroids, *Propionibacterium* sp., or coagulase-negative *Staphylococcus* (CoNS) were generally excluded unless the culture was treated by the attending physician as a pathogen (eg, a full course of antibiotic therapy).

For cultures meeting study criteria, clinical and demographic information was collected using a standardized extraction tool. Abstracted information included age at the time of culture, gender of the infant, bacterial species isolated from the blood, and infant risk based on modified Rochester Criteria similar to that used by others.[12,13] Each infant was stratified as either low risk or non-low risk. Low risk infants were defined as those without evidence of focal infection, previous antibiotic administration, treatment of hyperbilirubinemia, previous hospitalization, history

of preterm birth (<37 weeks), chronic medical conditions, abnormal white cell count (<5000 or >15 000 white blood cells per mm^3), absolute band cell count of >1500 per mm^3, or urinalysis results (>10 white blood cells/high power field).[7,8] As in previous studies, patients who did not meet all of the low risk criteria, or who had classifying data that were unavailable, were placed in the non-low risk group.[12–14] When available, cerebrospinal fluid (CSF) and urine culture results were recorded if drawn within 24 hours of the positive blood culture to assess for concurrent urinary tract infection (UTI) and/or meningitis. In cases of *Staphylococcus aureus* bacteremia, a further chart review was done to determine whether there was concern for skin or soft-tissue infection (SSTI) at the time of blood culture. The principal investigator at each site was responsible for ensuring that cultures from their site met study criteria and data were reported to GCHS for analysis.

Data Analysis

Prevalence of bacterial species among infants was calculated and reported along with a basic statistical summary. χ^2 was used to determine variance in bacterial prevalence among the 6 sites (the 2 smallest sites were combined) for prevalence of *E coli* compared with all other bacterial species and GBS compared with all other bacterial species. The 95% confidence interval for *L monocytogenes* was determined by using a method proposed for numerators of zero.[15,16] χ^2 or Fisher's exact tests were used to test dichotomous variables, with statistical significance set at $P < .05$. The statistical program used was SPSS version 21 (IBM SPSS Statistics, IBM Corporation).

RESULTS

We identified 2901 positive blood cultures from infants ≤90 days of age within the study period (Fig 1). Eighteen hundred were excluded because they were drawn from patients who were in a neonatal or pediatric ICU, admitted directly to the ICU, or who had central lines. Of the remaining cultures, 811 were either identified as a contaminant or not treated as a pathogen and therefore did not meet inclusion criteria, the majority of which were CoNS (59%). Because of complex comorbidities, an additional 96 cultures were excluded. Of the remaining 194 cultures, 9 were not obtained from an infant who had a fever history and 4 were duplicate cultures growing the same bacteria from the same patient, leaving 181 cultures for analysis obtained from 177 infants. Table 2 displays demographic information for cultures by site and in total. *E coli* was the most prevalent pathogen in all but 1 hospital system. There was no statistically significant difference in the prevalence of *E coli*, GBS, or all other bacteria species between sites ($\chi^2 = 9.9$, $P = .28$).

Nineteen different bacterial species were identified (Table 3). The most common pathogen recovered from all blood cultures was *E coli* (76/181, 42%), followed by GBS (41/181, 23%), *Streptococcus pneumoniae* (10/181, 6%), and *S aureus* (9/181, 5%). Of the infants we identified with *S aureus* bacteremia, 56% (5/9) had evidence of SSTI on presentation. There were no cases of *L monocytogenes* (95% confidence interval, 0%–2% of total cases).

Urine cultures were obtained in 172 (95%) cases and 85 (49%) of these were

TABLE 1 Characteristics of Participating Pediatric Hospital Systems

Site	Location	Annual Pediatric Admissions	Annual Pediatric ED Visits	Study Dates
CHCM	St Paul and Minneapolis, MN	12 000	90 000	1/2008 to 8/2012
CHLA	Los Angeles, CA	11 000	62 000	1/2009 to 12/2012
GCHS	Rochester, NY	6000	27 000	1/2009 to 2/2012
CHKD	Norfolk, VA	5500	47 000	10/2007 to 9/2012
AMC	Albany, NY	3500	13 000	1/2009 to 9/2012
CHOI	Peoria, IL	1800	15 000	1/2006 to 10/2012

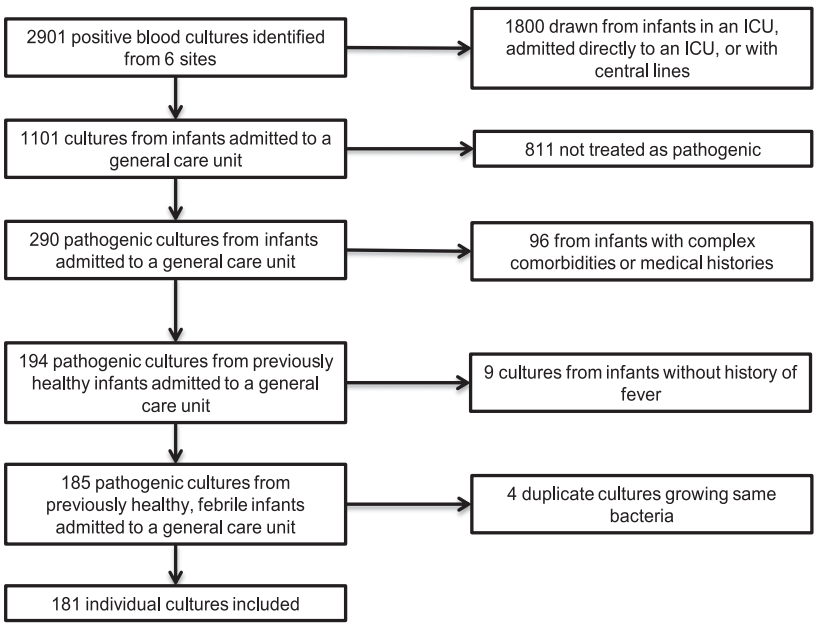

FIGURE 1
Flow diagram of included infants and blood cultures.

TABLE 2 Inter-Site Characteristics of Positive Cultures Drawn From Infants

Site	*n*	Male (%)	Median Age in Days (Range)	Non-Low Risk (%)	Most Common Organisms (%)[a]
CHCM	86	44 (51)	38 (7–88)	69 (80)	*E coli* (50) GBS (17)
CHKD	29	13 (45)	36 (10–81)	26 (90)	*E coli* (41) GBS (21)
CHLA	25	16 (64)	39 (6–90)	21 (84)	*E coli* (44) GBS (24)
CHOI	23	12 (52)	42 (3–81)	15 (65)	GBS (39) *E coli* (17)
GCHS	10	3 (30)	23 (15–66)	6 (60)	GBS (40) γ strep (20)
AMC	8	3 (38)	33 (9–73)	7 (88)	*E coli* (63) GBS (13)
Total	181	91 (50)	34 (3–90)	144 (80)	*E coli* (42) GBS (23)

Percentages may not add to 100 owing to rounding.
[a] AMC also had *Neisseria* sp. (13) and *S aureus* (13).

positive for bacteria. Of the 76 blood cultures that grew *E coli*, 75 (99%) had an associated urine culture collected and 68 (91%) of these were found to have concurrent *E coli* UTI. Of the 105 blood cultures positive for other bacterial species, 97 (92%) had associated urine cultures and 16 (15%) had concurrent UTI.

CSF cultures were obtained in 151 (83%) cases, 20 (13%) of which were positive for bacteria. GBS was the bacterial species most likely to cause concurrent meningitis (10/37, 27%). There was also 1 case of *Pantoea sp.* bacteremia with concurrent GBS meningitis. Of the 76 cases of *E coli* bacteremia, 63 had CSF cultures obtained and 5 (7%) had concurrent meningitis. Two infants who had *E coli* bacteremia and *E coli* UTI also had concurrent *E coli* meningitis (2/68, 3%). Of the 10 cases of *S pneumoniae* bacteremia, 4 had CSF cultures obtained and 1 of these had concurrent meningitis.

TABLE 3 Bacterial Pathogens Identified From Infants With Bacteremia

Pathogen	*n* (%)	Male (%)	Median Age in Days (Range)	Concurrent UTI (%)	Concurrent Meningitis (%)
All Species	181 (100)	91 (50)	34 (3–90)	86/174 (49)	20/152 (13)
E coli	76 (42)	44 (58)	31 (5–87)	69/75 (92)[a]	5/63 (8)
GBS	41 (23)	18 (44)	36 (11–88)	4/39 (10)	10/37 (27)
S pneumoniae	10 (6)	3 (30)	65 (10–81)	0/9 (0)	1/4 (25)
S aureus	9 (5)	3 (33)	35 (20–58)	1/8 (13)[b]	0/8 (0)
Klebsiella sp.	8 (4)	5 (63)	30 (11–90)	6/8 (75)	0/7 (0)
Viridans *streptococci*	8 (4)	5 (63)	34 (7–78)	1/8 (13)	0/7 (0)
Enterococcus sp.	7 (4)	2 (29)	33 (6–71)	1/7 (14)	1/6 (17)
γ-heme Strep.	4 (2)	1 (25)	32 (23–85)	0/3 (0)	0/3 (0)
Salmonella sp.	3 (2)	1 (33)	31 (25–40)	1/3 (33)[c]	0/3 (0)
S pyogenes	3 (2)	2 (67)	42 (11–74)	0/3 (0)	0/3 (0)
Pseudomonas sp.	2 (1)	1 (50)	25 (11–39)	1/1 (100)	0/1 (0)
Moraxella sp.	2 (1)	2 (100)	86 (84–88)	0/1 (0)	0/2 (0)
Neisseria sp.	2 (1)	0 (0)	54 (33–74)	0/2 (0)	1/1 (100)
CoNS	1 (1)	1 (100)	24 (24)	0/1 (0)	1/1 (100)
Citrobacter sp	1 (1)	1 (100)	21 (21)	1/1 (100)	0/1 (100)
B cereus	1 (1)	1 (100)	28 (28)	0/1 (0)	0/1 (0)
Pantoea sp.	1 (1)	0 (100)	15 (15)	0/1 (0)	1/1 (100)[a]
H influenzae	1 (1)	1 (100)	3 (3)	0/0	0/1 (0)
Enterobacter sp.	1 (1)	1 (100)	24 (24)	0/1 (0)	0/1 (0)

[a] One culture grew GBS.
[b] Culture grew *E coli*.
[c] Culture grew *Klebsiella* sp.

In the majority of cases, infants were non-low risk (144/181, 80%). Four (3%) of these were placed into this category owing to missing data. There was no difference in gender ($P = .88$) or age ($P = .97$) between risk groups. Table 4 highlights the characteristics of infants who had bacteremia from the 5 most common pathogens. Non-low risk bacteremic infants were significantly more likely than low risk bacteremic infants to have *E coli* ($P = .001$) or GBS ($P = .01$). In the non-low risk cohort, 4% (8/181) of cultures grew *Klebsiella* sp. as compared with none (0/37) in the low risk infant cohort. Infants who had *S pneumoniae* bacteremia were significantly more likely to be older than infants who had other causes of bacteremia ($P = .01$).

DISCUSSION

This multiregional study examined the epidemiology of bacteremia in previously healthy febrile infants outside of the ICU. A national approach is particularly salient to the question of bacterial epidemiology in our patient population for 2 reasons. First, bacteremia in this group is a rare event and combining data from 6 centers allows us a more rigorous examination than would otherwise be possible. Second, patterns of bacterial prevalence may vary geographically, potentially limiting generalizability of regional data.

Our study demonstrates an increasingly prominent role for *E coli* as a cause of bacteremia in febrile infants in the United States. These results are largely consistent with single-region observations, although we do demonstrate a slightly lower percentage of bacteremia caused by Gram-negative organisms (53%) than previous studies (63%–80%).[2,10,17]

The majority of infants who had *E coli* bacteremia had concurrent UTI. It has been suggested that infants who have *E coli* UTI may not require a lumbar

TABLE 4 Characteristics of Infants by the Most Common Pathogenic Blood Culture Species

Variable	Male (*P*)	Non-Low Risk (*P*)	0–30 d	31–60 d	61–90 d	*P*
E coli	44 (.08)	69 (.001)	37	22	17	.48
GBS	18 (.35)	27 (.01)	18	15	8	.86
S pneumoniae	3 (.16)	8 (.99)	2	2	6	.01
S aureus	3 (.24)	6 (.33)	3	6	0	.07
Klebsiella sp.	5 (.72)	8 (.36)	4	2	2	.87
All other	18 (.82)	26 (.12)	16	14	7	.80

puncture.[18] However, in infants who had *E coli* UTI and bacteremia, we identified 2 cases (3%) of concurrent meningitis. GBS remains a common cause of bacteremia and was the most common bacteria to cause concurrent meningitis (27%).

Consistent with previous regional data, we found no cases of *L monocytogenes* bacteremia.[2,10,17] There has been an overall decrease in laboratory-confirmed listeriosis in recent decades, likely owing to prohibitions regarding the sale of potentially contaminated food and public education campaigns targeted at high-risk populations, including pregnant women.[19] Although *L monocytogenes* is generally considered a cyclical pathogen, making it possible that our data were gathered during a "lull" in incidence, we collected geographically diverse data over several years during which time there were several nationally reported outbreaks of listeriosis.[20] Historically, physicians have been taught that bacteremia in young infants is caused by GBS, *E coli*, and *L monocytogenes*.[21,22] This classic teaching stems from studies performed decades ago when *L monocytogenes* was a more common cause of food-borne infection.[23,24] Based on our data and regional studies performed previously, we suggest that the etiologies of SBI taught to physicians in training and documented in written text should be revised to reflect current epidemiology.[9,18]

Classifying each culture as coming from either a low or non-low risk infant was done in an attempt to determine whether children who had certain bacteria were more likely to be "sicker." As would be expected, most infants who had bacteremia were classified as non-low risk by the Rochester criteria. The finding of bacteremia in low risk infants is not a critique of the performance of published guidelines for the management of low risk febrile infants,[12] as we examined only children who had bacteremia. Therefore, we are not attempting to provide data regarding risk for bacteremia in either risk cohort. What our data suggest is that, in infants who have bacteremia, those classified as non-low risk are more likely to have bacteremia attributable to *E coli* or GBS than low risk infants. It is notable that, although sample size limits statistical significance, we did not find a single case of *Klebsiella* sp. in our low risk infant population.

Current recommendations for empirical antibiotic coverage for febrile infants typically include the combination of either ampicillin and gentamicin or ampicillin and a third-generation cephalosporin.[21,22] The importance of ampicillin in the empirical antibiotic regimen for febrile infants has been maintained for coverage of both *L monocytogenes* and *Enterococcus* sp.[25] Although a large prospective examination is necessary before firm recommendations regarding a change in empirical therapies can be made, we identified no cases of *L monocytogenes* bacteremia and only 4% of infants had bacteremia caused by *Enterococcus* sp. Given that the overall risk for bacteremia in our population is estimated at 2%,[2,5] we suggest that incidence of *Enterococcus* bacteremia may be $<0.1\%$. Future prospective studies examining resistance patterns and incidence may confirm that empirical monotherapy with a third-generation cephalosporin, such as cefotaxime, may be adequate. Cefotaxime is well tolerated in young infants and should provide coverage for the vast majority of pathogens we identified.[26,27] This study also highlights the emergence of *S aureus* as a leading pathogen in bacteremia in young infants, similar to that seen previously,[2,10] and it should be considered particularly for febrile infants in whom SSTI is suspected.

Our decision to use treatment with a full course of antibiotics as an aspect of our study criteria warrants some explanation, although this is not the first time that treatment has been used in some way to determine contamination.[2] Although there are bacteria that should always represent a true infection,[28] and some that almost always represent contamination in an otherwise healthy child,[28,29] using bacterial species alone to determine contamination is unlikely to be sufficient, because many common contaminants can also represent true bacteremia.[28–30] For this reason we feel that, although we did potentially exclude up to 3 cases of true bacteremia (1 culture grew several species including *S aureus*, and 2 others grew *E coli*; per chart review, none were treated and all did well), our method of determining contaminants allowed us to avoid including many cases that likely did not represent true bacteremia. One example was a febrile infant sent home from the emergency department without antibiotics after having blood cultures drawn that eventually grew *Enterococcus* sp. Further review revealed that the repeat cultures from the outpatient office showed no growth, and that the child was afebrile and doing well at 1 week follow-up. Our study criteria allowed us to exclude this patient, who would otherwise have been mistakenly included.

Our study had several limitations. First, the retrospective nature of the review

inhibited our ability to identify negative blood cultures, so we are unable to provide information regarding the overall risk for bacteremia. This limits our ability to provide firm recommendations regarding empirical antibiotic therapy and a prospective, national study is necessary. Second, criteria for ICU admission vary from institution to institution and this may have introduced some unidentified heterogeneity in our patient population. Third, when analyzing the difference in bacterial species between risk cohorts, statistical significance of some individual species was limited by small sample sizes (eg, *Klebsiella* sp.). Additionally, we assigned risk retrospectively after the infant was known to have bacteremia; risk classification is typically employed as a way to predict which infants will have an SBI before 1 being identified. Finally, the start date of data collection varied between sites by up to 14 months owing to limitations in the availability of data within each institution's microbiology database. However, our analysis found no statistically significant variability in the prevalence of *E coli*, GBS, or all other species (P = .28), which suggests uniformity across the dates of study.

CONCLUSIONS

We present the largest study to date examining the question of bacterial epidemiology in infants admitted to the general care unit with bacteremia. These data support the trend seen in previous regional publications that *E coli* has become the most common cause of bacteremia in febrile infants admitted to the general care unit, with GBS and *S pneumoniae* the second and third most common causes, respectively. Together, these 3 species account for 71% of positive blood cultures in our patient population. Not a single case of *L monocytogenes* was identified. In infants who have bacteremia, *E coli* and GBS are more likely to be identified as the cause in non-low risk than in low risk infants and *S pneumoniae* is more likely to be found in older infants. We suggest a prospective evaluation to determine whether a change in typical empirical antibiotic regimens is necessary.

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Biondi et al. Epidemiology of Bacteremia in Febrile Infants in the United States. *Pediatrics.* 2013;132(6):990–996

An error occurred in the article by Eric Biondi et al, titled "Epidemiology of Bacteremia in Febrile Infants in the United States" published in the December 2013 issue of *Pediatrics* (2013;132[6]:990–996; originally published online November 11, 2013; doi:10.1542/peds.2013-1759). On page 990, in Authors, this reads: "Vivan Lee; Children's Hospital of Los Angeles." This should have read: "Vivian Lee; Children's Hospital Los Angeles."

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Pickering et al. The Red Book Through the Ages. *Pediatrics.* 2013;132(5): 898–906

An error occurred in this article by Pickering et al, titled "The Red Book Through the Ages" published in the November 2013 issue of *Pediatrics* (2013;132[5]:898–906; originally published online October 14, 2013; doi:10.1542/peds.2013-2538). On page 899, under Early History of the COID, the first line reads: "After the establishment of the AAP in 1930 in the library of Harber Hospital…." This should have read: "After the establishment of the AAP in 1930 in the library of Harper Hospital…."

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Krakowski et al. Residual Scarring From Hidradenitis Suppurativa: Fractionated CO_2 Laser as a Novel and Noninvasive Approach. *Pediatrics.* 2014;133(1):e248–e251

A production error occurred regarding the article by Andrew C. Krakowski et al, titled "Residual Scarring From Hidradenitis Suppurativa: Fractionated CO_2 Laser as a Novel and Noninvasive Approach," published in the January 2014 issue of *Pediatrics* (2014;133[1]:e248–e251; doi:10.1542/peds.2012-3356). On the cover of the print edition, the title reads, "Meaningful Use of Adolescent Electronic Medical Records." This should have read, "Residual Scarring From Hidradenitis Suppurativa: Fractionated CO_2 Laser as a Novel and Noninvasive Approach."

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Simpson et al. A New Leukocyte Hyperadhesion Syndrome of Delayed Cord Separation, Skin Infection, and Nephrosis. *Pediatrics.* 2014;133(1):e257–e262

Two errors occurred in the article by Simpson et al, titled "A New Leukocyte Hyperadhesion Syndrome of Delayed Cord Separation, Skin Infection, and Nephrosis" published in the January 2014 issue of *Pediatrics* (2014;133[1]:e257–e262; doi:10.1542/2013-0884). On page e261, under Treatment With Glucocorticoids on line 31, this reads: "Whereas the exact mechanism causing the hyperadhesiveness of the integrins is not known, the symptoms bear resemblance to mice expressing constitutively active LFA-1 in which excessive adhesion prevents leukocytes from entering injured tissues and, when tested in vitro, causes increased adhesion and stalled migration.[15,16]" This should have not been inserted. Additionally, on the same page (e261) in the next section, Leukocyte Hyperadhesiveness, on line 12, this reads: "Whereas the exact mechanism causing the hyperadhesiveness of the integrins is not known, the symptoms bear resemblance to mice expressing constitutively active LFA-1 in which excessive adhesion prevents leukocytes from entering injured tissues and, when tested in vitro, causes increased adhesion and

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The Changing Epidemiology of Serious Bacterial Infections in Young Infants

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Background: Management of febrile young infants suspected of having serious bacterial infections has been a challenge for decades. The impact of changes in prenatal screening for Group B *Streptococcus* and of infant immunizations has received little attention in population-based studies.

Methods: This study analyzed all cultures of blood, urine and cerebrospinal fluid obtained from full-term infants 1 week to 3 months of age, who presented for care at Kaiser Permanente Northern California during a 7-year period utilizing electronic medical records.

Results: A total of 224,553 full-term infants were born during the study period. Of 5396 blood cultures, 129 bacteremic infants were identified (2%). Of 4599 urine cultures, 823 episodes of urinary tract infection (UTI) were documented in 778 infants (17%). Of 1796 CSF cultures, 16 infants had bacterial meningitis (0.9%). The incidence rate of serious bacterial infections (bacteremia, UTI and meningitis) and febrile serious bacterial infections was 3.75 and 3.1/1000 full-term births, respectively. *Escherichia coli* was the leading cause of bacteremia (78), UTI (719) and bacterial meningitis (7). There were 23 infants with Group B *Streptococcus* bacteremia including 6 cases of meningitis and no cases of *Listeria* infection. Nine percentage of infants had multiple sites of infection; 10% of UTIs were associated with bacteremia and 52% of bacteremia was associated with UTI.

Conclusions: Compared with earlier studies, UTIs now are found significantly more often than bacteremia and meningitis with 92% of occult infections associated with UTIs. These data emphasize the importance of an urinalysis in febrile infants.

Key Words: serious bacterial infections, infant, Group B *Streptococcus*, *Escherichia coli*, urinary tract infection

(*Pediatr Infect Dis J* 2014;33:595–599)

In an effort to develop a rational approach to the management of febrile infants, numerous studies have used serious bacterial infection (SBI) as an outcome measure.[1–16] It is estimated that 7–12.8%[1–16] of febrile infants <3 months of age will have a SBI, but the true incidence rate of SBIs in this age group is unknown. Accurately assessing the incidence of SBIs has been difficult for several reasons. First, most studies include bacterial meningitis, bacteremia and urinary tract infections (UTIs) in the definition of SBI, but some have also included bone and joint infections, skin and soft tissue infections, pneumonia and bacterial gastroenteritis.[14,17,18] Additionally, many studies describing the epidemiology of SBIs were conducted before routine immunization against *Haemophilus influenza* type b (Hib) and *Streptococcus pneumoniae* or were completed before implementation of changes in prenatal screening for Group B *Streptococcus* (GBS).[2,7,9–11,13,14] Finally, most studies describing the epidemiology of SBIs were not population based and have focused solely on febrile infants, although infants with SBI can present without fever.

Changes in healthcare practices over the last decade that may alter the incidence of infections in young infants include a decline in circumcision rates[19] and increasing use of intrapartum antibiotics (IPAs) that may increase the risk for late onset SBIs and ampicillin-resistant pathogens.[4,20,21]

Using a population-based approach in a large healthcare organization in Northern California, we aim to (1) describe the incidence rate of bacteremia, UTI and meningitis (SBIs), (2) determine the current epidemiology of SBIs and (3) better elucidate current clinical practice regarding acquisition of cultures.

MATERIALS AND METHODS

Approval to conduct this study was granted by the Institutional Review Board of Kaiser Permanente Northern California (KPNC). Informed consent was waived.

Study Design

This study retrospectively analyzed KPNC's electronic medical record system to identify all blood, urine and cerebrospinal fluid (CSF) cultures obtained in full-term infants born between January 1, 2005, and December 31, 2011, presenting for care to KPNC at 7–90 days of age.

Kaiser Permanente is the largest Health Maintenance Organization in the United States, with over 3.3 million members in Northern California with over 40 pediatric clinics, 19 emergency departments and 10 pediatric hospital wards. In 2008, 53% of enrolled women of child bearing age were Caucasian, 6% were African American, 23% were Asian and 14% were "Other". Eighteen percentage identified their ethnicity as Latino. The household income was $50–100,000 and >$100,000 in 48% and 28% of women, respectively. Six percentage were insured thru Medi-Cal (California's Medicaid program), a public health insurance program for low-income individuals.[22]

Subjects were previously healthy, full-term infants (≥37 weeks at birth), 1 week to 3 months of age. Infants with underlying medical conditions (neuromuscular, cardiovascular, respiratory, gastrointestinal, metabolic, hematologic, immunologic, other congenital or genetic, malignant or renal abnormalities) were excluded as determined by ICD-9 codes.[23,24] Potential cases were defined as infants with positive cultures collected in the outpatient setting, emergency department or first 24 hours of hospitalization. Additional cultures obtained within 3 days of a positive or negative culture were not considered a unique episode and were not included in the analysis unless they identified a new pathogen. Culture data

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obtained on infants with a prior SBI were collected but not included in all analyses.

SBI

An infant with bacteremia, UTI and/or bacterial meningitis was classified as having a SBI.

Bacteremia

All organisms identified in blood cultures were classified as contaminants or pathogens based on chart review (T.L.G.). Commensal organisms typically found on the skin (eg, coagulase-negative staphylococci, viridans group streptococci, *Micrococcus* species and diphtheroids) were considered contaminants unless obtained from 2 or more cultures and treated by a clinician as a pathogen.[25] Contaminants were included in the analysis as negative cultures.

UTI

Urinalysis results were considered positive if the specimen contained leukocyte esterase and/or nitrites. Urine microscopy was positive if the specimen had ≥10 white blood cells per high powered field. In infants 7–60 days, UTI was defined as a catheterized urine culture with ≥10,000 colony-forming units of a single organism per milliliter. In infants 61–90 days, diagnosis of UTI was defined as a catheterized urine culture with both pyuria and ≥50,000 colonies per milliliter of a single uropathogenic organism.[26] If the urine specimen was obtained from a perineal bag and ≥100,000 colony-forming units of a single uropathogenic organism per milliliter grew, chart review (T.L.G or E.L.) was conducted to determine whether the infant was treated for a UTI.

Meningitis

Bacterial meningitis was defined as a positive CSF culture for a known pathogen.

Clinical Characteristics

Fever was defined as a recorded temperature ≥100.4° Fahrenheit (F; 38.0°C) rectally. Documentation of a rectal or axillary temperature ≥100.4°F before arrival to medical care qualified as a fever. To be included in the "ill" category, 1 of the following terms had to be documented in the medical record: "toxic," "lethargic," "ill appearing," "nonresponsive" or "inconsolable".

Chest Radiographs

Chest radiographs were defined as abnormal if radiographic reading "pneumonia" or "suspicious for pneumonia".

Viral Testing

Nasopharyngeal specimens performed at clinician's discretion for viral culture and/or respiratory syncytial virus or influenza polymerase chain reaction.

Statistical Analysis

We conducted the Cochran-Armitage test for trend to examine the incidence rate by year. Fisher's test was used to compare categorical variables and determine *P* values. All statistical tests were 2-side and $P < 0.05$ was considered statistically significant. The statistical program used was SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

During this 7-year study, 224,553 full-term infants were born at KPNC. Of those infants, 92.4% remained in care for >90 days. Data on infants born outside KPNC, but enrolled before 90 days of age was not available. For purposes of analysis, 224,553 will be the denominator with confidence intervals (CIs) under the assumption that for every disenrolled patient, 0.5 or 1.5 infants born elsewhere enrolled by 90 days. Of 6780 infants with at least 1 blood, urine or CSF culture, 1640 cultures from 548 infants were excluded due to underlying medical conditions. Excluding duplicate cultures from the same source (eg blood, urine or CSF) obtained within 3 days of the initial culture, resulted in 5636 blood, 4599 urine and 1796 CSF cultures collected from 6232 infants.

SBIs occurred in 13.5% (842/6232) of infants. The 842 infants had 968 SBIs including 129 bacteremia, 823 UTIs and 16 bacterial meningitis. Forty-five UTIs occurred after a previously identified SBI, with 44 occurring after preceding UTI. Among infants 7–90 days with a first time SBI, 92% (778/842) had a UTI (Table 1). The incidence rate of first time SBI and febrile SBI was 3.75 (95% CI: 3.6–3.9) and 3.1 (95% CI: 3.0–3.26)/1000 full-term births, respectively. The incidence rate of bacteremia, UTI and meningitis was 0.57 (95% CI: 0.55–0.59), 3.46 (95% CI: 3.34–3.60) and 0.07 (95% CI: 0.069–0.074)/1000 full-term births, respectively. The sum of the incidence rate of individual SBIs is greater than the overall incident rate, because some infants had multiple sources of infection. Using the Cochran-Armitage test for linear trend, the incidence of SBIs over the 7 years of our study was not statistically significant ($P = 0.29$).

Infants 7–28 days were more likely to get a complete evaluation for SBI including blood, urine and CSF cultures (Table 2). The average number of cultures from separate sources obtained in infants during 7–28, 29–60 and 61–90 days was 2.6, 2.3 and 1.8, respectively ($P < 0.0001$). Sixty-two percentage of infants 7–28 days had a full evaluation compared with 40% of infants 29–60 days. Of infants 61–90 days, 13% had a complete evaluation, 59% had both urine and blood culture and 27% had only a urine culture.

Table 3 lists the pathogens causing bacteremia, UTI and meningitis. *Escherichia coli* was the leading cause of bacteremia (78), UTI (719) and bacterial meningitis (7). There were 23 infants with GBS bacteremia including 6 cases of meningitis. There were no cases of *Listeria* or meningococcal infection. Including only febrile infants did not appreciably change the distribution of

TABLE 1. Characteristics of Infants With First Episode of SBI

	Bacteremia	UTI	Meningitis
Variable	N = 129 (%)	N = 778 (%)	N=16 (%)
Male	74/129 (57)	462/778 (59)	7/16 (44)
Febrile	115/122 (94)	575/676 (85)	14/15 (93)
Ill-appearing	21/123 (17)	46/670 (7)	10/16 (63)
White blood cell count ≥15,000 × 10^9/L	57 /129 (44)	300/672 (45)	5/16 (31)
Viral co-infection	2 /34 (6)	11/119 (9)	0/6 (0)
Abnormal urinalysis	66/114 (58)	615/671 (92)	6/15 (40)
Abnormal chest radiograph	14/82 (17)	39/349 (11)	2 /13 (15)

TABLE 2. Culture Acquisition by Age in Infants With SBI

	Age (Days)			
Cultures Obtained	7–28	29–60	61–90	Total
Complete evaluation (blood, urine and CSF cultures)	147	137	33	317
Blood and urine cultures only	84	173	153	410
Blood and CSF only	1	1	0	2
Urine and CSF only	1	1	1	3
Blood culture only	1	2	3	6
Urine culture only	5	30	69	104
Total	239	344	259	842

TABLE 3. Most Common Bacterial Pathogens Detected in 129 Blood, 823 Urine and 16 CSF Cultures

Organism	Blood N (%)	Urine N (%)	CSF N (%)
Gram Negative			
E. coli	78 (60)	719 (87)	7 (34)
Klebsiella sp.	3 (2)	34 (4)	1 (6)
Salmonella sp.	3 (2)	0 (0)	0 (0)
Enterobacter sp.	0 (0)	17 (2)	0 (0)
Gram Positive			
GBS	23 (18)	4 (0.5)	6 (27.5)
S. aureus	8 (6)	0 (0)	0 (0)
Enterococcus sp.	3 (2)	17 (2)	0 (0)
S. pneumoniae	3 (2)	0 (0)	2 (12.5)

infections; however, all infants with multiple sources of infection were febrile.

Blood culture results from the 2005–2009 dataset were previously published.[25] Including the period 2010–2011 did not significantly change these results. Of 5636 blood cultures, 437 (8%) were positive, but only 129 (2%) were positive with a pathogen. Ninety-four percentage of infants were febrile, but only 17% were described as ill appearing (Table 1). Gram-negative organisms accounted for the majority (88/129, 68%) of bacterial pathogens and *E. coli* (78/129, 60%) was the most common overall (Table 3). *E. coli* and *Staphylococcus aureus* were evenly distributed through ages 7–90 days. Only 1 case of GBS occurred from 61 to 90 days. There were no cases of methicillin-resistant *S. aureus* or neonatal *S. pneumoniae*.

Of 4599 urine cultures obtained, 1085 urine cultures grew a potential pathogen. Excluding infants not treated for a UTI and those not meeting criteria for UTI resulted in 823 UTIs in 778 infants. A second UTI occurred in 5.7% (44/778) of which 6.8% (3/44) had a third UTI. Data on the 778 infants with first episode UTI are presented in Table 1. Males accounted for 59% and the vast majority (437/462, 95%) were uncircumcised. The most common urinary pathogens were *E. coli*, *Klebsiella* sp., *Enterobacter* sp. and *Enterococcus* sp (Table 3). Three of the *E. coli* isolates produced an extended spectrum beta lactamase.

Of 1796 CSF cultures, 73 (4%) were positive, but only 16 (0.9%) were positive with a pathogen. Ninety-three percentage (14/15) of infants were febrile and 63% ill appearing (Table 1). Seven cases of meningitis occurred during 7–28 days, 6 during 29–60 days and 3 additional from 61 to 90 days. There were no cases of neonatal *S. pneumoniae* meningitis and only 1 case of GBS meningitis from 29 to 90 days (Table 3).

Of 842 infants, 78 had multiple sources of infection (Fig. 1 and Table 4) These occurred more frequently in infants 7–28 days.

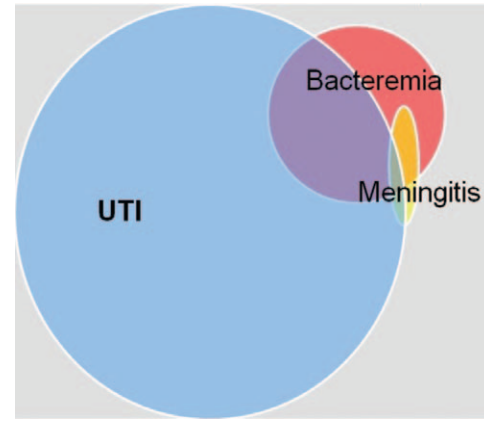

FIGURE 1. Venn diagram illustrating the distribution of infections with 1 source and >1 source.

TABLE 4. Pathogen Source: First Episode of SBI

	Age (Days)			
Source of Pathogen	7–28	29–60	61–90	Total
Blood only	22	22	9	53
Urine only	184	294	231	709
CSF only	0	1	1	2
Blood/urine	27	21	16	64
Blood/CSF	5	2	2	9
CSF/urine	1	1	0	2
Blood/urine/CSF	0	3	0	3
Total (>1 source)	239 (33)	344 (27)	259 (18)	842 (78)

Forty-three percentage occurred from 7 to 28 days compared with 35% and 23% occurring from 29 to 60 and 61 to 90 days, respectively (P = 0.008, 7–28 vs. 29–90 days). Of the 129 total cases of bacteremia, 76 (59%) occurred with another positive culture. In all but 1 case, the organisms were identical. Not all infants with UTIs had a complete evaluation. This difference was related to age. From 7 to 28, 29 to 60 and 61 to 90 days, 97%, 89% and 71% of infants with a UTI had a blood culture, respectively. In infants with UTIs with blood cultures obtained, UTI was associated with bacteremia in 13%, 8.5% and 8.9% of infants 7–28, 29–60 and 61–90 days, respectively (P = 0.0055, 7–28 vs. 29–90 days). Only 30% (232/778) of infants with a UTI had a CSF culture. Two cases of *E. coli* meningitis occurred with negative blood cultures, but positive urine cultures.

DISCUSSION

This study is the first to capture a large enrolled population of infants from the outpatient setting, emergency department and first 24 hours of hospitalization with positive cultures. The incidence rate of all SBIs was 3.75 (95% CI: 3.6–3.9)/1000 full-term infants. SBIs occurred infrequently in the general population, but frequently (13.5%) in those febrile or sick enough to have a culture obtained. Ninety-two percentage of the SBIs were UTIs. Excluding infants with temperature data missing and those who were afebrile did not appreciably change the distribution of infections. As in our previous study and other recent studies, *E. coli* remained the leading cause of bacteremia.[25,27] This pathogen was also the most common cause of UTI and bacterial meningitis. Similar to other recent publications, there were no cases of *Listeria* or meningococcal infection.[3,4,21] Blood and CSF culture contamination rates

were high. Seventy percentage of positive blood cultures and 78% of positive CSF cultures were contaminants.

The epidemiology of SBIs has changed over the last 3 decades.[3,4,6,15] Publications from the 1980s to 1990s report the composition of SBIs as: 20–30% bacteremia, 30–55% UTI and 0–14% meningitis.[9,11,14,28] This study demonstrates a shift in the distribution of SBIs, with a marked increase in the percentage of infants with UTI alone (84%) or in combination with other infections (8.2%). There was a corresponding decrease in the proportion of SBIs due to isolated bacteremia (6.3%) or isolated bacterial meningitis (0.2%).

The cause for this shift is multifactorial. A small proportion of the decline in bacteremia and meningitis can be attributed to the decline in Hib and *S. pneumoniae* infections due to herd immunity. The complete absence of *Listeria* infections in this large Northern California cohort is noteworthy. It may be a regional variation or due to improved food safety standards. In Northern California, we would not recommend adding ampicillin to an antibiotic regimen solely for *Listeria* coverage.

UTI was the most common SBI in our study. The percentage of positive urine cultures (17.9%) was higher than previously reported, which may be due to several factors.[1,3,4,6,15] Although we included both perineal bag and catheter specimens, infection rates are similar between bag and catheter specimens.[29,30] Excluding all bag specimens would reduce the percentage of positive cultures, but would likely underestimate the true UTI rates. The most likely contributing factors increasing the percentage positive were due to the selective testing by practitioners (eg testing infants with higher risk of UTI) and incomplete evaluations. Increasing the denominator from 4599 (infants with urine cultures) to 6232 (infants with blood, urine or CSF cultures) lowered the percentage positive to 13%, which correlates well with preceding studies.[1,3,4,6,15]

We identified a high proportion of patients with UTI and bacteremia. Data published in the 1990s describing the epidemiology of SBI among infants reported that 0–4% of bacteremia episodes occurred with UTI.[9–11,21,31] Fifty-two percentage of bacteremia episodes occurred with UTI. Of infants with UTIs and blood cultures obtained, 10% were bacteremic. Our population-based data are similar to data published over the last decade, reporting 4–11% of UTIs with bacteremia.[1,3,4,6,15,29,30] However, we report the highest rate of bacteremia occurring with UTI (52%) as previous studies varied from 17 to 45%.[1,3,4,6,15,29,30] The cause of this increase in bacteremia with UTI remains unclear. Removing infants without a complete evaluation, younger infants (7–28 days) continued to have a higher percentage of infections with more than 1 source. Additional research is needed to determine whether the presence of a UTI with bacteremia should be managed differently than a UTI alone.

Our study had some limitations. As already discussed, the precise denominator is unclear, but we have accounted for this in our analyses. Although KPNC is an established Health Maintenance Organization with the vast majority of enrolled patients receiving all their care from a KPNC facility, infants may have been seen elsewhere. If an infant was ill, the infant would likely return to a KPNC facility for follow up. It is possible that some infants received antibiotics before having cultures obtained and a small number of SBIs may have been missed. The demographics of KPNC patients are not representative of Northern California or the United States. With 76% of our population reporting a median income of > $50,000[21] at a time when United States median income was approximately $52,000, it is possible that rates in lower socioeconomic status groups will differ. Acquisition of a bacterial culture was at the clinician's discretion so it is likely our rates are higher than in studies where all febrile infants had complete sepsis workups. Some infants may have been afebrile at the time cultures were obtained. Fevers at home not recorded in the medical record would change the incidence of SBI in febrile infants, but not the overall incidence rate. Despite these limitations, given the rare occurrence of SBIs in this age group and the large population base, it is likely that our study accurately reports incident rates for bacteremia, UTIs and bacterial meningitis.

Finally, it is noteworthy that this population based study reflects the behavior of clinicians. The selective testing of infants (eg only 13% of infants 61–90 days with a SBI had blood, urine and CSF cultures obtained) may explain the decreased detection of infections with >1 source in the third month of life. The 2011 American Academy of Pediatrics Guideline on the management of UTIs[26] did not publish a recommendation for performing blood cultures in the third month of life; however, 70% of infants with a UTI had a blood culture performed. With an increasing number of UTIs with or without bacteremia, the antimicrobial regimen directed towards treating these infections becomes an increasingly important question with clinical implications.

The evidence presented in this cohort analysis suggests increased scrutiny for UTIs, emphasizes the importance of an urinalysis in febrile infants and potentially a selective approach in infants with UTI from 61–90 days. Given the extremely low risk of *Listeria*, providing additional antibiotic coverage for this organism seems unwarranted.

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