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Contemporary Approaches to the Febrile Infant

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Objectives

- Modern epidemiology of fever etiology in infants
- Evidence-based risk stratification
- Implementation of contemporary care
- Opportunities for quality improvement

Febrile Infants - Objectives

- *Why do we do what we do?*
  - How did we get here?
  - Where are we going?
- *What should **you** do?*
  - Be consumers of evidence-based literature
  - Know you are doing best for your patients

Benjamin

12 days old

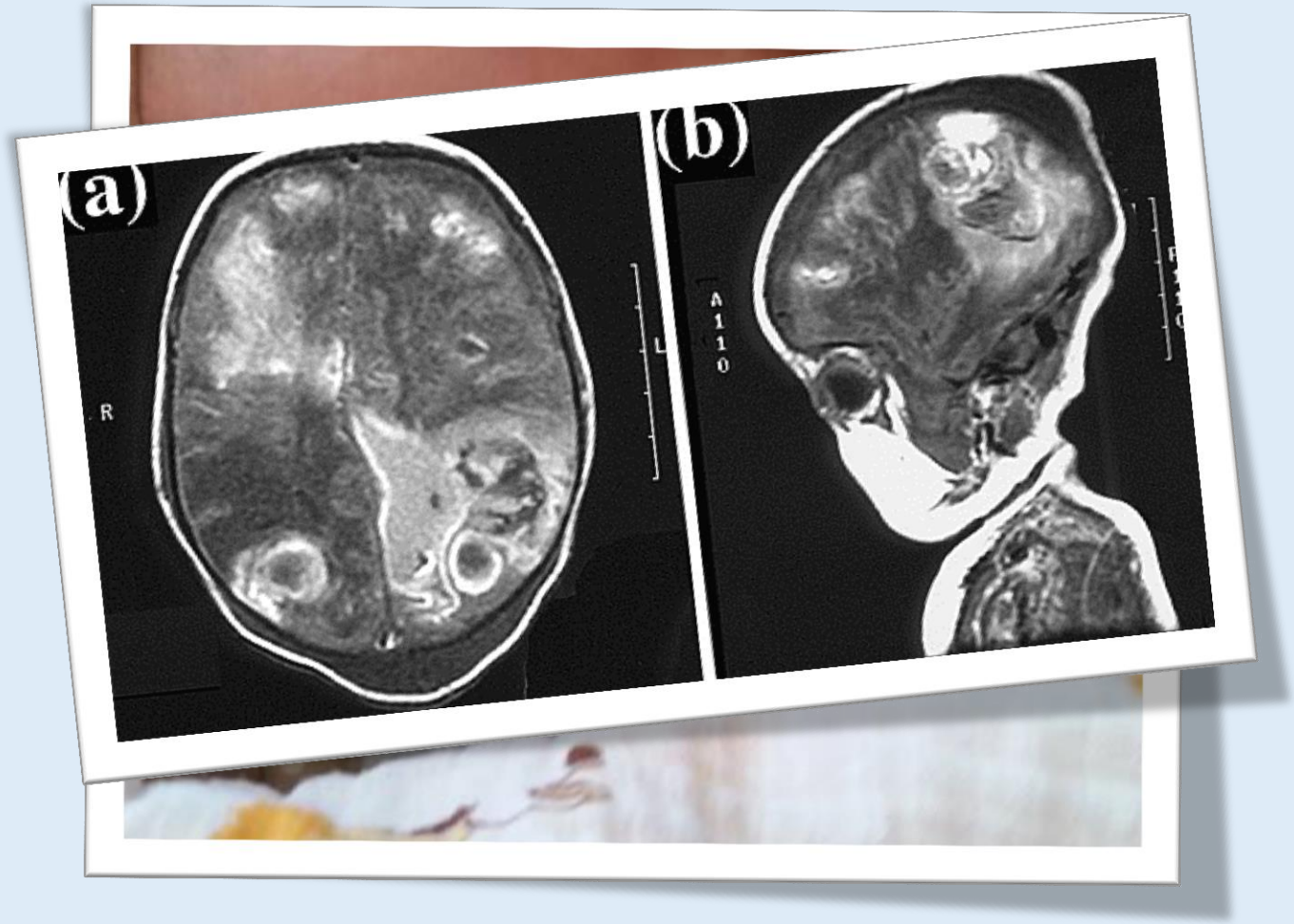
CC: fever and difficult to wake up

PMH: 38 wk gestation, born at home with midwife, saw pediatrician first 1 week ago – well at that visit

PE: T=101 HR=202 RR=55 O2=94%

Ill-appearing, sleepy, responds with a shrill cry to any stimulation, doesn't open his eyes, tachypneic with clear lung sounds, tachycardic, extremities cool and pale, full fontanelle

What's wrong with baby Benjamin?



What organism

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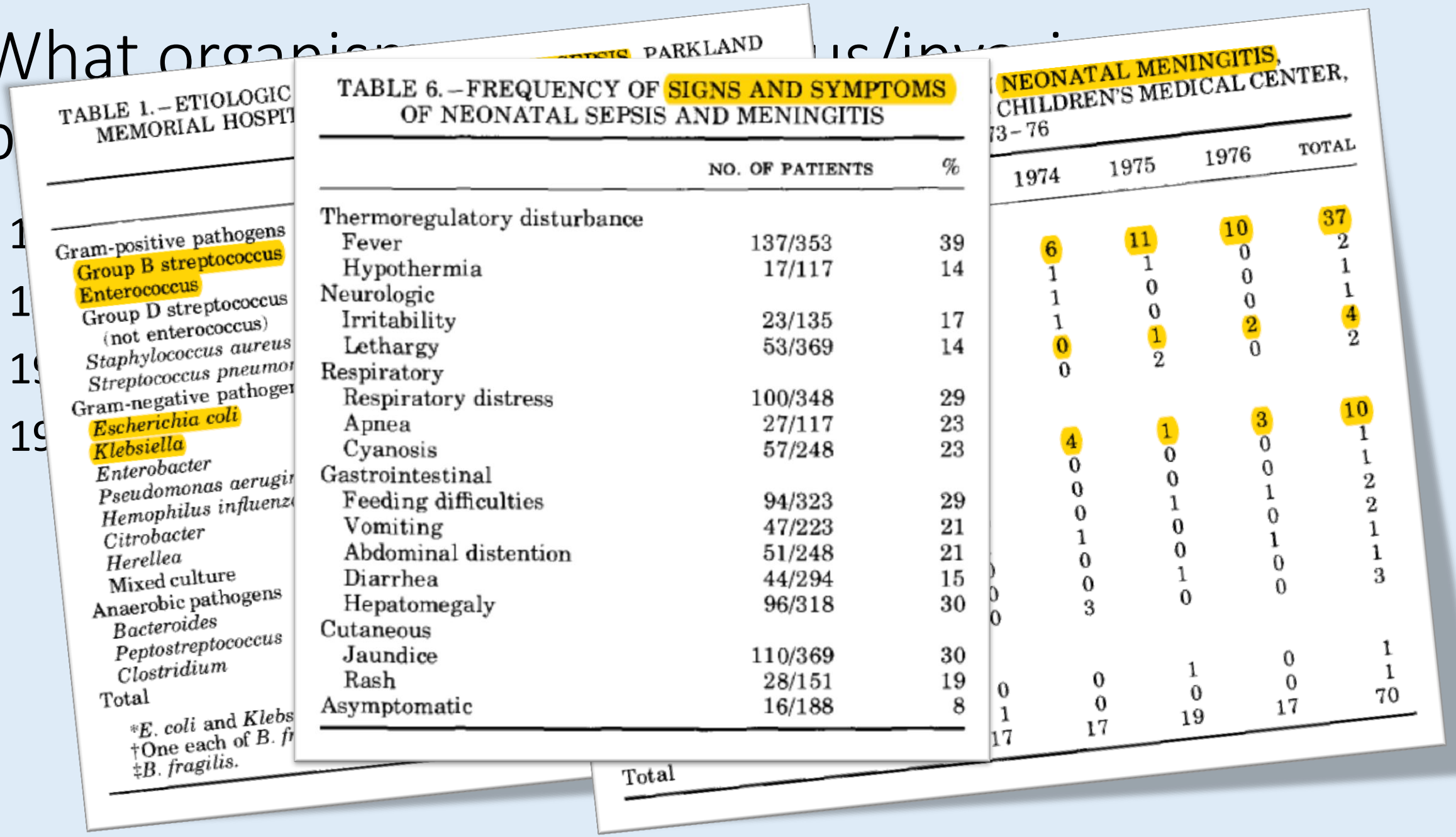


TABLE 1.—ETIOLOGIC
MEMORIAL HOSPIT

Gram-positive pathogens	
Group B streptococcus	
Enterococcus	
Group D streptococcus (not enterococcus)	
Staphylococcus aureus	
Streptococcus pneumo	
Gram-negative pathoge	
Escherichia coli	
Klebsiella	
Enterobacter	
Pseudomonas aerugi	
Hemophilus influenz	
Citrobacter	
Herellea	
Mixed culture	
Anaerobic pathogens	
Bacteroides	
Peptostreptococcus	
Clostridium	
Total	

*E. coli and Klebs
†One each of B. fr
‡B. fragilis.

PARKLAND

TABLE 6.—FREQUENCY OF SIGNS AND SYMPTOMS OF NEONATAL SEPSIS AND MENINGITIS

	NO. OF PATIENTS	%
Thermoregulatory disturbance		
Fever	137/353	39
Hypothermia	17/117	14
Neurologic		
Irritability	23/135	17
Lethargy	53/369	14
Respiratory		
Respiratory distress	100/348	29
Apnea	27/117	23
Cyanosis	57/248	23
Gastrointestinal		
Feeding difficulties	94/323	29
Vomiting	47/223	21
Abdominal distention	51/248	21
Diarrhea	44/294	15
Hepatomegaly	96/318	30
Cutaneous		
Jaundice	110/369	30
Rash	28/151	19
Asymptomatic	16/188	8

NEONATAL MENINGITIS,
CHILDREN'S MEDICAL CENTER,
73–76

1974	1975	1976	TOTAL
6	11	10	37
1	1	0	2
1	0	0	1
1	0	0	1
0	1	2	4
0	2	0	2
4	1	3	10
0	0	0	1
0	0	0	1
0	1	1	2
1	0	0	2
0	0	1	1
0	1	0	1
3	0	0	3
0	1	0	1
0	0	0	1
1	0	17	70
17	19		

Total

Wientzen, R. L., Jr. and G. H. McCracken, Jr. (1977). "Pathogenesis and management of neonatal sepsis and meningitis." Curr Probl Pediatr **8**(2): 1-61.

80s-90s

TABLE 3. The Three Most Common Strategies for Managing Febrile Infants

	Philadelphia Criteria[7]	Rochester Criteria[9]	Boston Criteria[8]
Age	29–60 d	≤60 d	28–89 d
Temperature	≥38.2°C	≥38.0°C	≥38.0°C
History	Not specified	• Term infant • No perinatal antibotics • No underlying disease • Not hospitalized longer than the mother	• No immunizations within preceding 48 h • No antimicrobial within 48 h • Not dehydrated
Physical examination	• Well-appearing • Unremarkable examination	• Well-appearing • No ear, soft tissue, or bone infection	• Well-appearing • No ear, soft tissue, or bone infection
Laboratory parameters (defines lower risk patients)	• WBC <15 000/mm³ • Band-neutrophil ratio <0.2 • UA <10 WBC/hpf • Urine Gram stain negative • CSF <8 WBC/mm³ • CSF Gram stain negative • Chest radiograph: no infiltrate[a] • Stool: no blood, few or no WBCs on smear[b]	• WBC >5000 and <15 000/mm³ • Absolute band count <1500/mm³ • UA ≤10 WBC/hpf • ≤5 WBC/hpf stool smear[b]	• CSF <10/mm³ • UA <10 WBC/hpf • Chest radiograph: no infiltrate[a] • WBC <20 000/mm³
Higher risk patients	Hospitalize + empiric antibiotics	Hospitalize + empiric antibiotics	Hospitalize + empiric antibiotics
Lower risk patients	• Home • No antibiotics • Follow-up required	• Home • No antibiotics • Follow-up required	• Home • Empiric antibiotics • Follow-up required
Reported statistics	Sensitivity 98% (92 100) Specificity 42% (38–46%) Positive predictive value 14% (11–17%) NPV 99.7% (98–100%)	Sensitivity 92% (83–97%) Specificity 50% (47–53%) Positive predictive value 12.3% (10–16%) NPV 98.9% (97–100%)	Sensitivity—not available Specificity 94.6% Positive predictive value—not available NPV—not available

[a] If obtained.
[b] If indicated.

Bachur et al. Predictive Model for Serious Bacterial Infections Among Infants Younger Than 3 Months of Age. *Pediatrics* 2001;108:311–316

What's changed since the 80s?

- Hib
- Prevnar
- Intrapartum penicillin
- FDA screen for Listeria

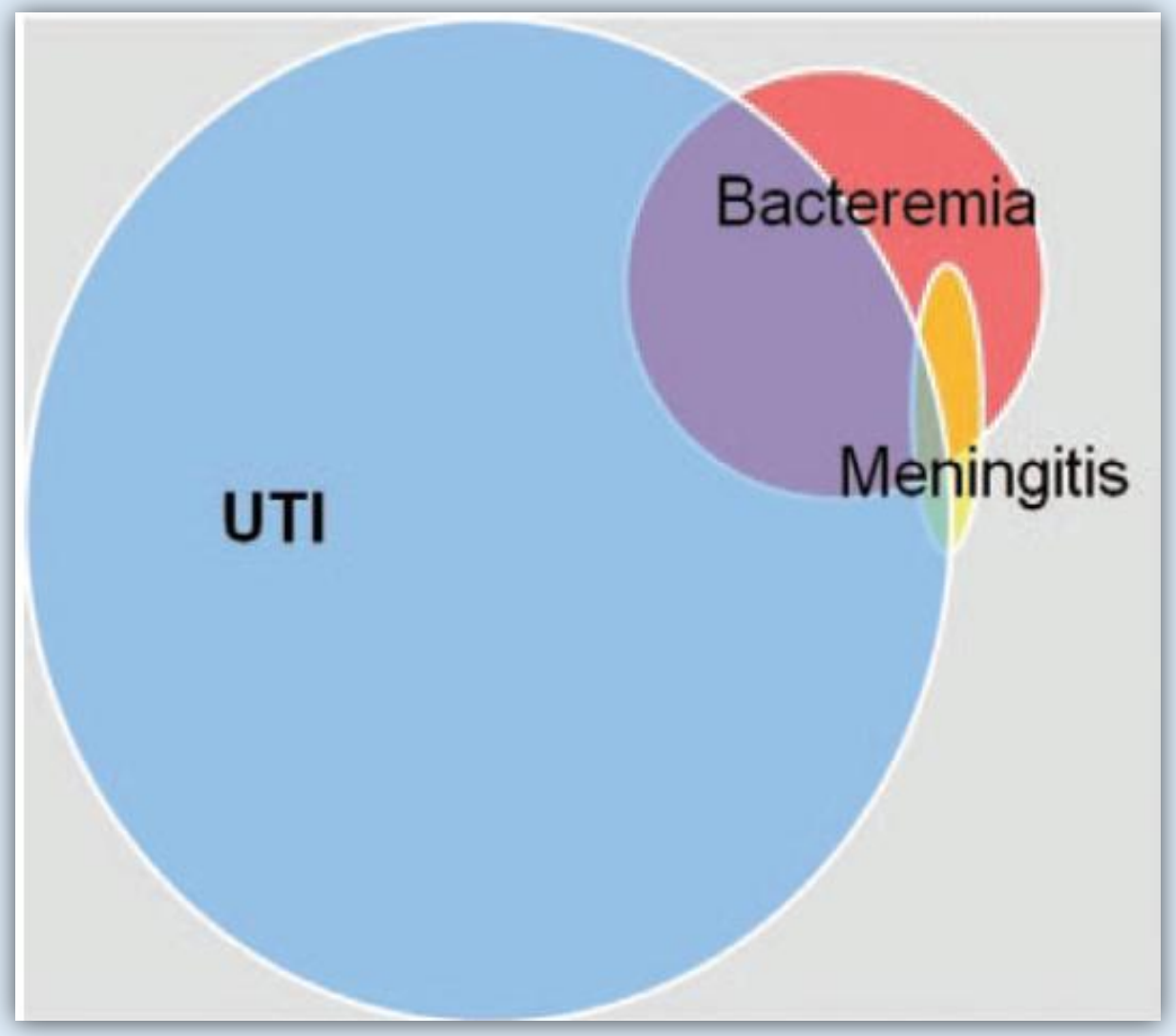


TABLE 3 Bacterial Pathogens Identified From Infants With Bacteremia

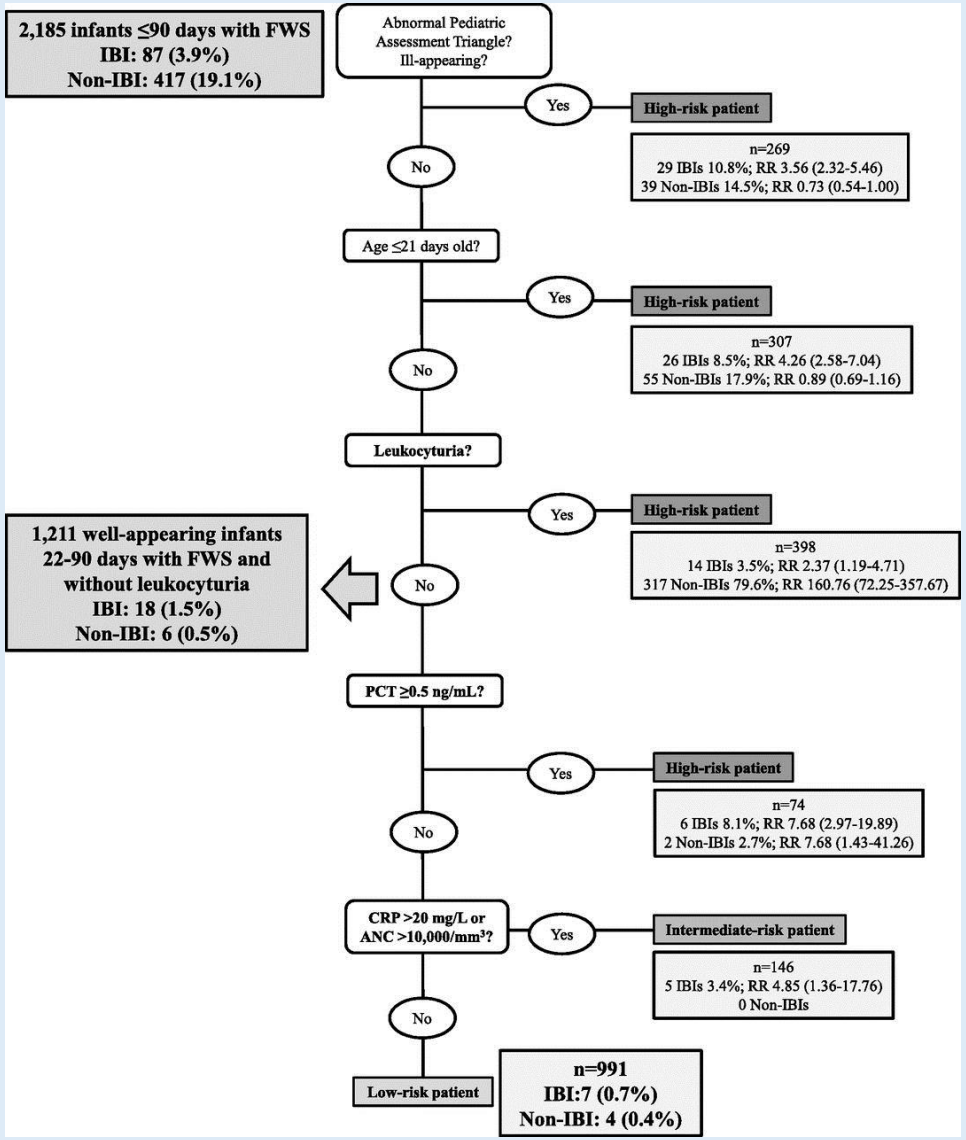
Pathogen	*n* (%)	Male (%)	Median Age in Days (Range)	Concurrent UTI (%)	Concurrent Meningitis (%)
All Species	181 (100)	91 (50)	34 (3–90)	86/174 (49)	20/152 (13)
E coli	76 (42)	44 (58)	31 (5–87)	69/75 (92)[a]	5/63 (8)
GBS	41 (23)	18 (44)	36 (11–88)	4/39 (10)	10/37 (27)
S pneumoniae	10 (6)	3 (30)	65 (10–81)	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.

Biondi, E., et al. (2013). "Epidemiology of bacteremia in febrile infants in the United States." Pediatrics **132**(6): 990-996.
Greenhow, T. L., et al. (2014). "The changing epidemiology of serious bacterial infections in young infants." Pediatr Infect Dis J **33**(6): 595-599.

Step -by- Step

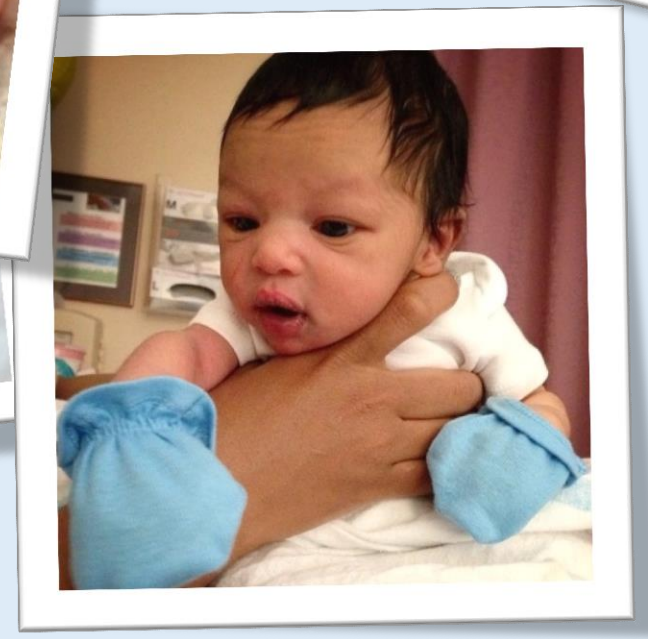
2016



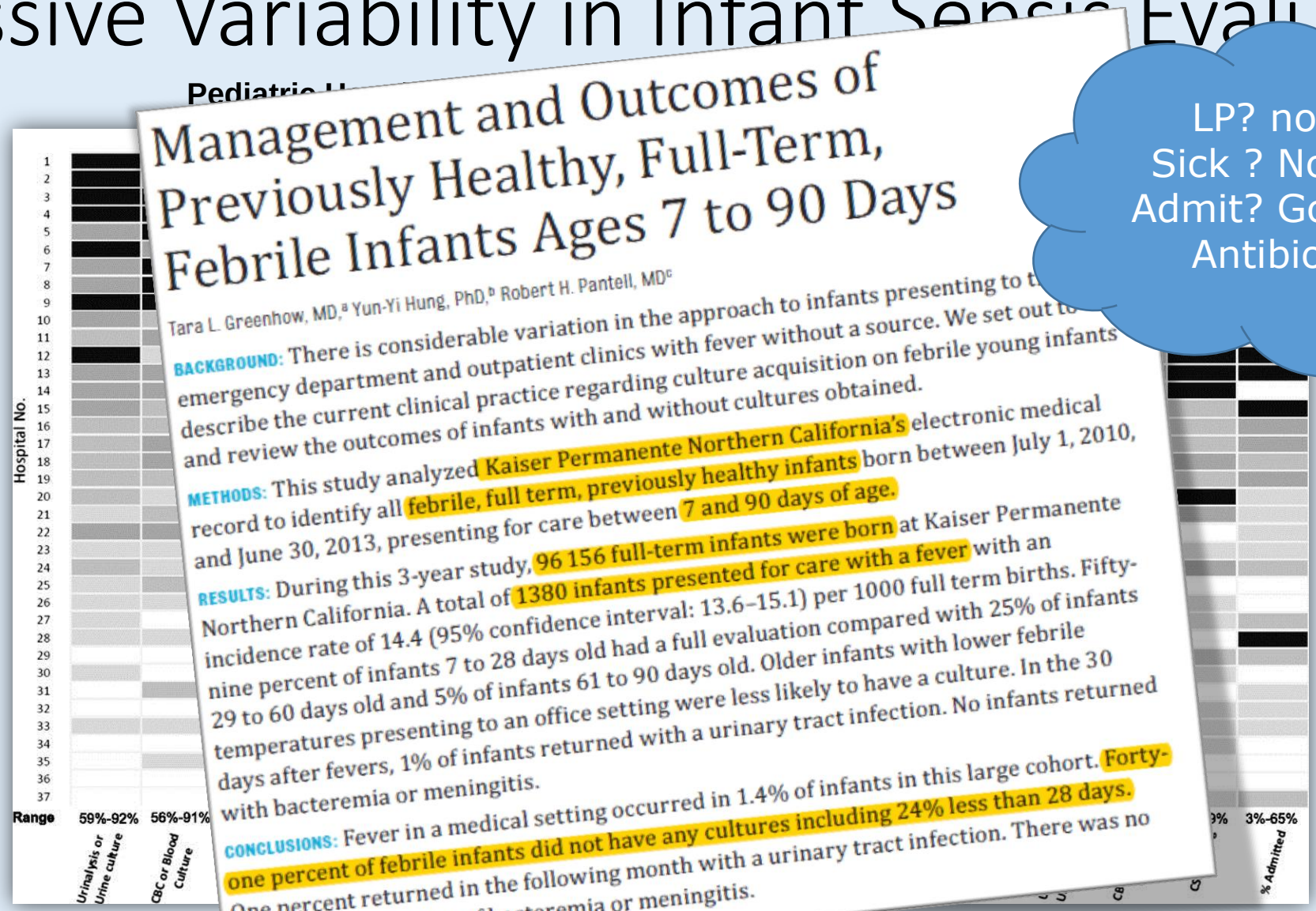
Rochester
Missed 16

Gomez B, Mintegi S, Bressan S, et al. Validation of the “Step-by-Step” Approach in the Management of Young Febrile Infants. *Pediatrics.* 2016;138(2):e20154381





Excessive Variability in Infant Sepsis Evaluation



Management and Outcomes of Previously Healthy, Full-Term, Febrile Infants Ages 7 to 90 Days

Tara L. Greenhow, MD,[a] Yun-Yi Hung, PhD,[b] Robert H. Pantell, MD[c]

BACKGROUND: There is considerable variation in the approach to infants presenting to the emergency department and outpatient clinics with fever without a source. We set out to describe the current clinical practice regarding culture acquisition on febrile young infants and review the outcomes of infants with and without cultures obtained.

METHODS: This study analyzed Kaiser Permanente Northern California's electronic medical record to identify all febrile, full term, previously healthy infants born between July 1, 2010, and June 30, 2013, presenting for care between 7 and 90 days of age.

RESULTS: During this 3-year study, 96 156 full-term infants were born at Kaiser Permanente Northern California. A total of 1380 infants presented for care with a fever with an incidence rate of 14.4 (95% confidence interval: 13.6–15.1) per 1000 full term births. Fifty-nine percent of infants 7 to 28 days old had a full evaluation compared with 25% of infants 29 to 60 days old and 5% of infants 61 to 90 days old. Older infants with lower febrile temperatures presenting to an office setting were less likely to have a culture. In the 30 days after fevers, 1% of infants returned with a urinary tract infection. No infants returned with bacteremia or meningitis.

CONCLUSIONS: Fever in a medical setting occurred in 1.4% of infants in this large cohort. Forty-one percent of febrile infants did not have any cultures including 24% less than 28 days. One percent returned in the following month with a urinary tract infection. There was no delayed identification of bacteremia or meningitis.

LP? not LP?
Sick ? Not sick?
Admit? Go home?
Antibiotics?

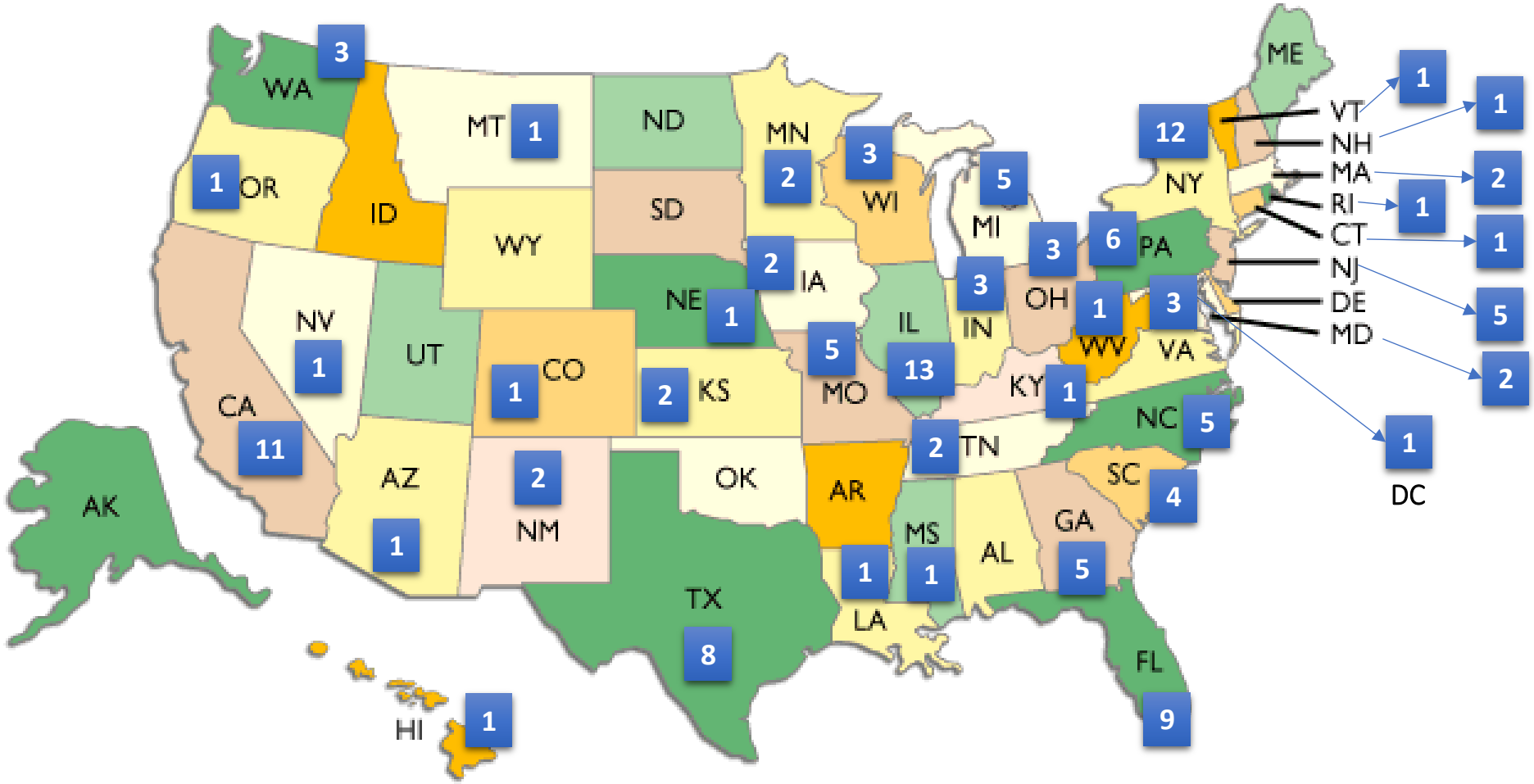
Aronson, P. L., et al. (2014). "Variation in care of the fe... emergency departments." Pediatrics **134**(4): 667-677

Greenhow TL, Hung Y, Pantell RH. Management and Ou... Previously Healthy, Full-Term, Febrile Infants Ages 7 to 90 Days. *Pediatrics.* 2016;138(6):e20160270

Why reduce variation in care?

- Universal application of evidence-based care (risk stratification)
  - Teach learners to be consumers of evidence-based care
- Decreased cost
- Decreased harm
- Care becomes more efficient
- Increased opportunity for observational research

133 Teams Participating in Project REVISE



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

QuIIN Quality Improvement Innovation Networks
A program of the American Academy of Pediatrics

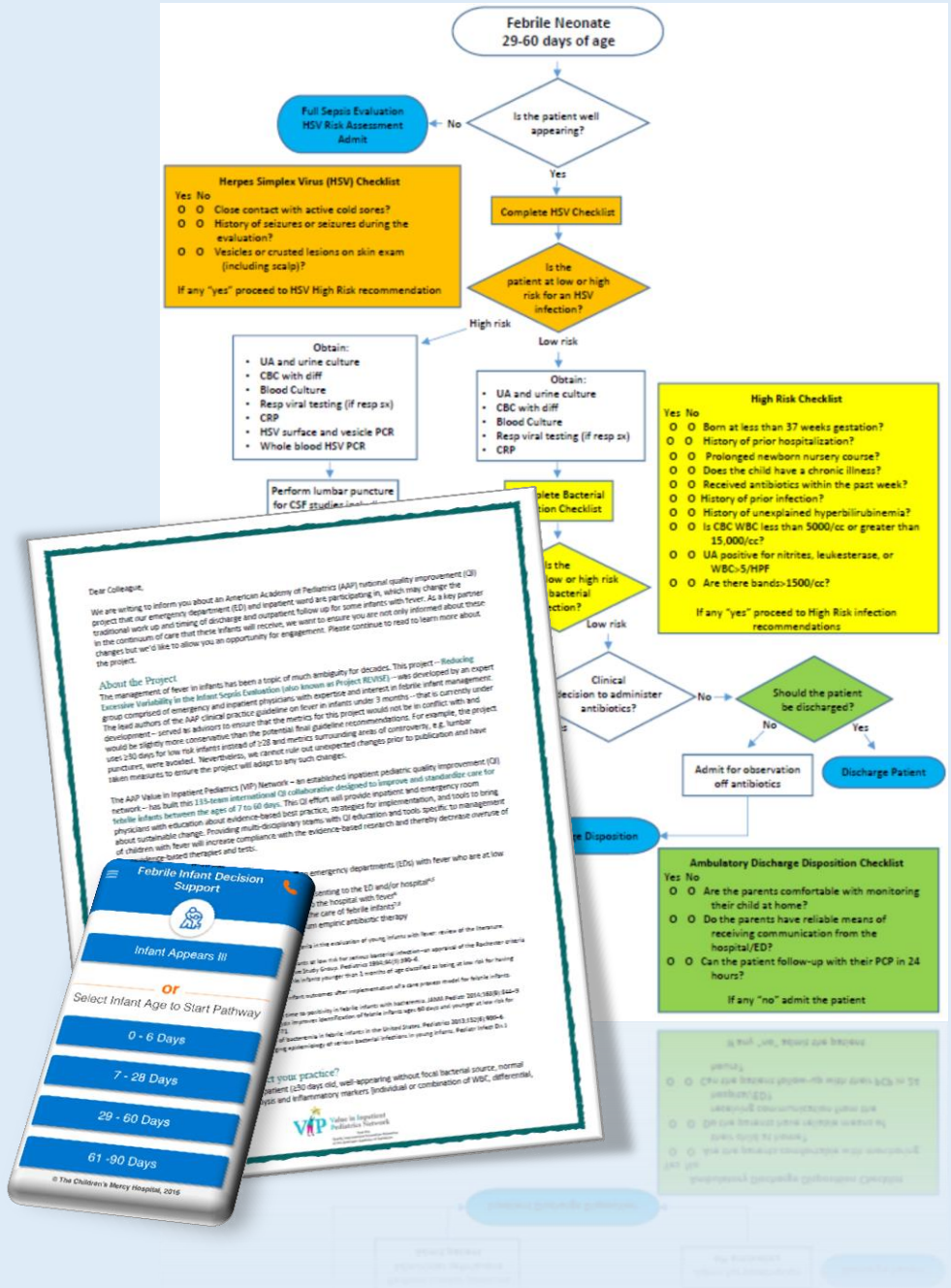
Duke Children's

Project REVISE:
Reducing Excessive Variation in Infant Sepsis Evaluation

- Decrease variation in care of febrile infants presenting to the ED and/or hospital
  - Every infant needs a urinalysis and at least one serum marker (CRP, WBC, PCT)
- Decrease use of unnecessary chest x-rays (CXR) in the care of febrile infants
- Decrease admissions for infants presenting to ED's with fever who are at low risk of bacterial infection
- Decrease length of stay for infants admitted to the hospital with fever

Change package

- Algorithms for ED care
- Ordersets
- CMPeDS App
- Outreach to community pediatricians
- QI data infrastructure



Andrew

35 days old

CC: fever and runny nose

PMHx: 38 week gestation, mother GBS+ and treated with ampicillin during labor, discharged to home with mother

ROS: no cough, good PO/UOP, no rashes

PE: T=100.4 HR=185 RR=45

Alert, vigorous, good skin color and tone, clear lungs, no murmur, benign abd, no rashes

CBC: WBC 11k, 45N 1B 35L

CRP: <0.01

UA: No LE, No Nitr, No WBC

Xris

12 days old

CC: “shaking”

Seemed to be jerking in his sleep for ~5 minutes, now less interested in eating

PMHx: 40 wk gestation, vaginal delivery, reassuring maternal serologies, discharged to home with mother

PE: T=35.6 RR=35 HR=172

Alert, vigorous, fussy but consoles

Clear lungs, no murmur

Few pustules on an erythematous base scattered over face, tiny vesicles with some crusting on top of scalp

UA clean

CBC WBC 16k: 33S 65L

Clinical Presentation of Neonatal HSV

HSV Disease	Disseminated (25%)	SEM (45%)	CNS (30%)
Onset (week)	1st (2nd)	2nd-6th	2nd-3rd
SEM findings	80%‡	100%	60-70%‡
CSF Pleocytosis	60-75%	0%*	>95%
Key Findings	Septic, Pneumonitis, ↑ALT,↓Plts, ↓ANC	Vesicles, Ulcers, Eye Inflammation (subtle in some)	Seizure, Irritability, Lethargy, Temp Instability

*SEM disease may progress to CNS or Disseminated disease

‡ Lesions appearing at some point in illness course

Non-Specific Presentation

- Fever alone
- Irritability
- Lethargy
- Feeding difficulty

Long SS et al. HSV Infection in Young Infants in Two Decades of Empiric Acyclovir Therapy. *PIDJ*. 2011;30:0-6.

- 22 year review of HSV cases at St. Christopher's
- Institutional strategy: testing and empiric acyclovir for all neonates with illness starting ≤ 21 days
- 32 HSV cases**; 50%** had a **nonspecific** presentation
- 75% with a non-specific presentation had fever

Why is (local) consensus so challenging?

Cases uncommon (1500 U.S. cases/year); very small studies

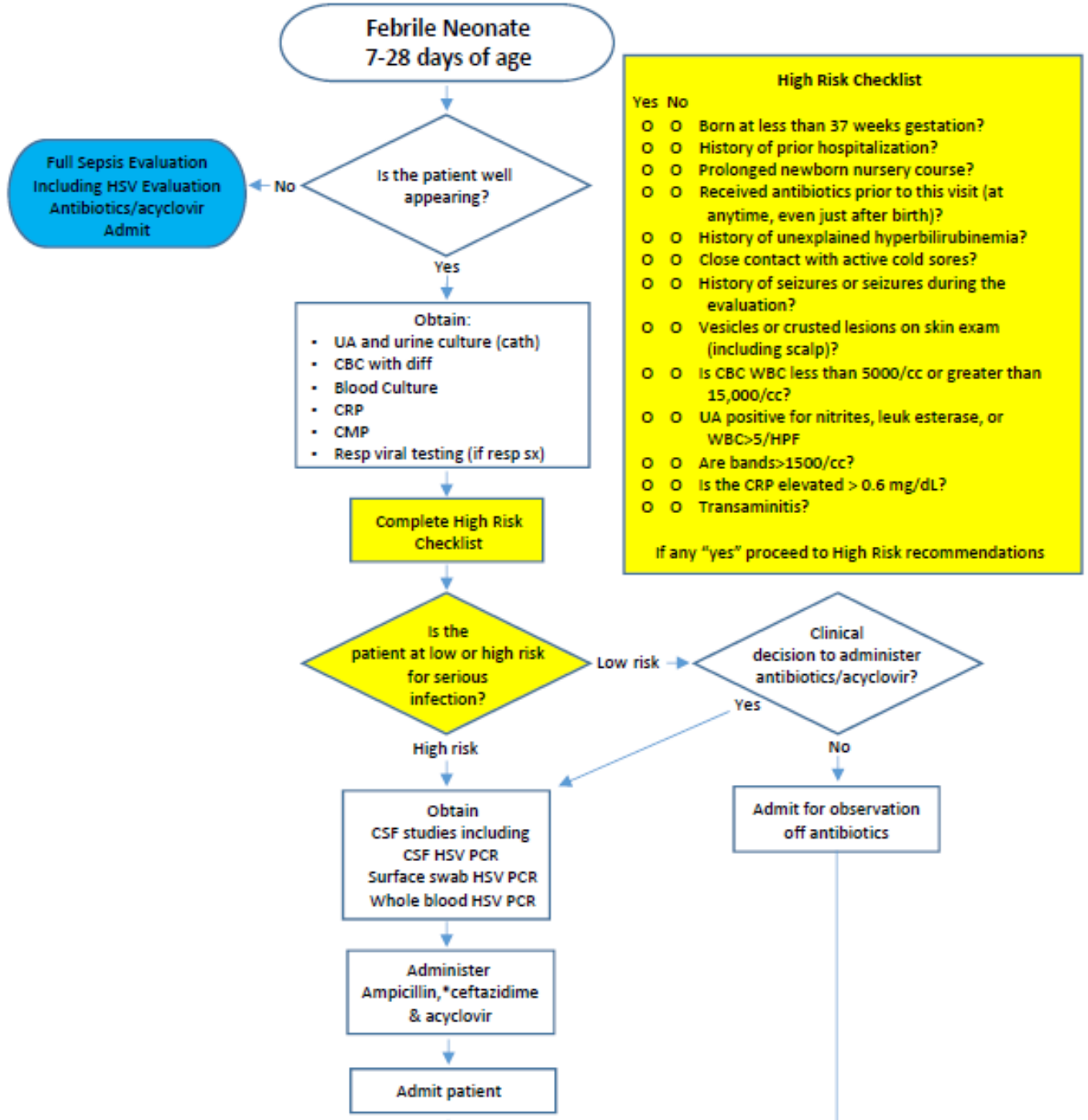
Diagnosis can be difficult early in illness due to nonspecific presentation

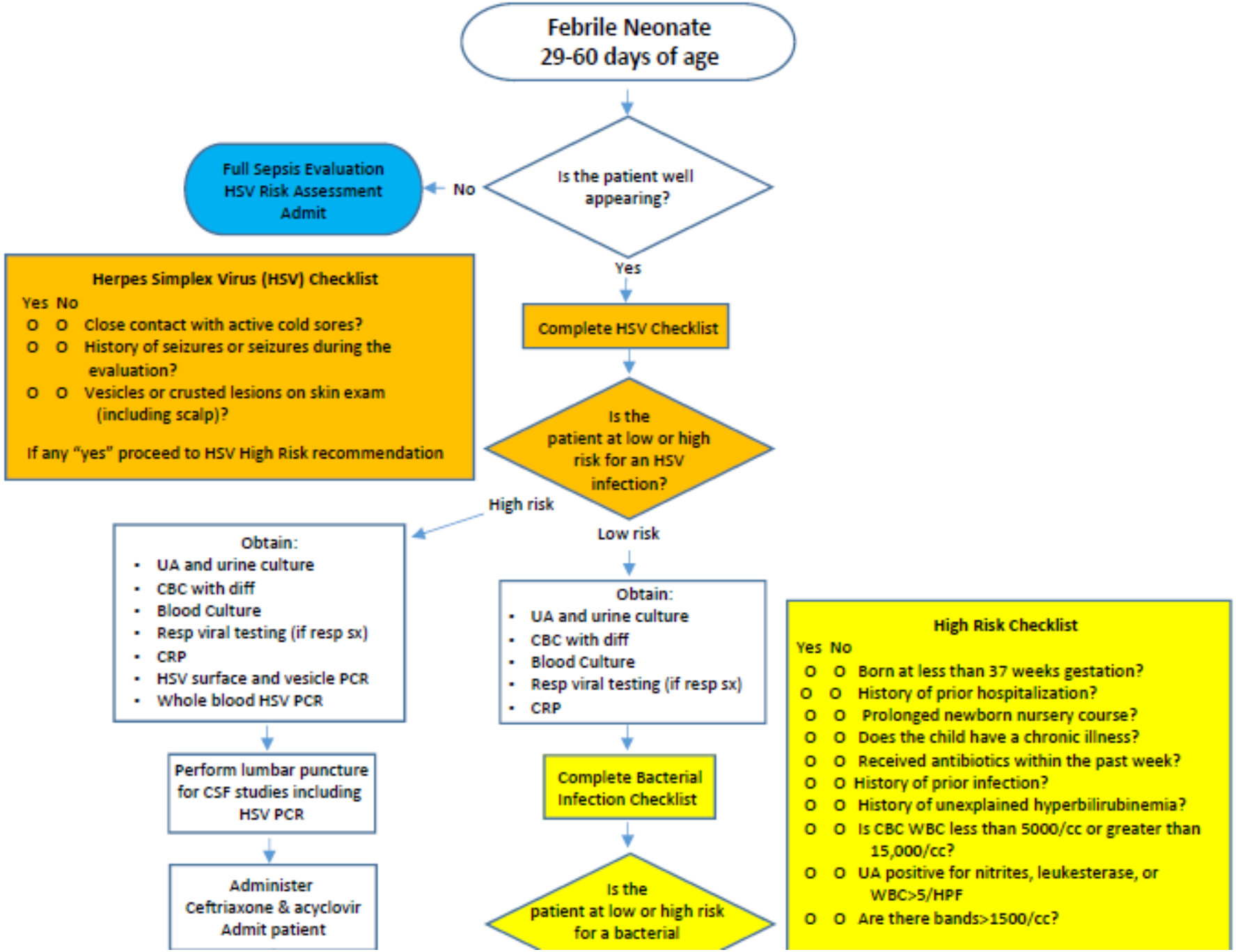
Diagnostic tests limitations (local and universal)

Test availability (local)

High morbidity and mortality; concern for liability risk, omission error

Experts don't agree; Every argument has a champion


Febrile Neonate
7-28 days of age
Is the patient well appearing?
No
Full Sepsis Evaluation
Including HSV Evaluation
Antibiotics/acyclovir
Admit
Yes
Obtain:
UA and urine culture (cath)
CBC with diff
Blood Culture
CRP
CMP
Resp viral testing (if resp sx)
Complete High Risk Checklist
High Risk Checklist
Yes No
Born at less than 37 weeks gestation?
History of prior hospitalization?
Prolonged newborn nursery course?
Received antibiotics prior to this visit (at anytime, even just after birth)?
History of unexplained hyperbilirubinemia?
Close contact with active cold sores?
History of seizures or seizures during the evaluation?
Vesicles or crusted lesions on skin exam (including scalp)?
Is CBC WBC less than 5000/cc or greater than 15,000/cc?
UA positive for nitrites, leuk esterase, or WBC>5/HPF
Are bands>1500/cc?
Is the CRP elevated > 0.6 mg/dL?
Transaminitis?
If any "yes" proceed to High Risk recommendations
Is the patient at low or high risk for serious infection?
Low risk
Clinical decision to administer antibiotics/acyclovir?
Yes
No
High risk
Obtain
CSF studies including
CSF HSV PCR
Surface swab HSV PCR
Whole blood HSV PCR
Administer
Ampicillin,*ceftazidime
& acyclovir
Admit patient
Admit for observation
off antibiotics


Febrile Neonate
29-60 days of age
Is the patient well appearing?
No
Full Sepsis Evaluation
HSV Risk Assessment
Admit
Yes
Complete HSV Checklist
Herpes Simplex Virus (HSV) Checklist
Yes No
O O Close contact with active cold sores?
O O History of seizures or seizures during the evaluation?
O O Vesicles or crusted lesions on skin exam (including scalp)?
If any "yes" proceed to HSV High Risk recommendation
Is the patient at low or high risk for an HSV infection?
High risk
Low risk
Obtain:
• UA and urine culture
• CBC with diff
• Blood Culture
• Resp viral testing (if resp sx)
• CRP
• HSV surface and vesicle PCR
• Whole blood HSV PCR
Perform lumbar puncture for CSF studies including HSV PCR
Administer Ceftriaxone & acyclovir
Admit patient
Obtain:
• UA and urine culture
• CBC with diff
• Blood Culture
• Resp viral testing (if resp sx)
• CRP
Complete Bacterial Infection Checklist
Is the patient at low or high risk for a bacterial
High Risk Checklist
Yes No
O O Born at less than 37 weeks gestation?
O O History of prior hospitalization?
O O Prolonged newborn nursery course?
O O Does the child have a chronic illness?
O O Received antibiotics within the past week?
O O History of prior infection?
O O History of unexplained hyperbilirubinemia?
O O Is CBC WBC less than 5000/cc or greater than 15,000/cc?
O O UA positive for nitrites, leukesterase, or WBC>5/HPF
O O Are there bands>1500/cc?

Charlotte

8 days old

CC: abnormal lab result

Hx: Check-up with pediatrician today for on-going jaundice

PMHx: term gestation, vaginal delivery, maternal serologies reassuring

ROS: less eager to nurse today

PE: T=100.3 HR=180 RR=35

Jaundice appearing, sleepy but arouses appropriately for age

Alex

6 weeks old

CC: referred by PCP's office, +RSV and fever

PE: T=102 RR=65 HR=185 O2=98%

Alert, vigorous, audible nasal congestion

Comfortable tachypnea, few rhonchi

Good perfusion, no murmur

PEM-CRC: 8 PEM sites, ≤ 60d, T ≥ 38.0, RSV status 1248 infants, 91% pan-cultured

TABLE 2 SBI According to Influenza Status

Variable	Influenza-Positive ($N = 123$)		Influenza-Negative ($N = 721$)		Relative Risk (95% CI)	P
	n/N	% (95% CI)	n/N	% (95% CI)		
SBI	3/119	2.5% (0.5%–7.2%)	92/690	13.3% (10.9%–16.1%)	0.19 (0.06–0.59)	<.001
UTI	3/123	2.4% (0.5%–6.9%)	77/712	10.8% (8.6%–13.3%)	0.23 (0.07–0.70)	.002
Bacteremia	0/123	0% (0%–2.4%)	16/715	2.2% (1.3%–3.6%)	0.00	.15
Meningitis	0/119	0% (0%–2.5%)	6/698	0.9% (0.3%–1.9%)	0.00	.6
Enteritis	0/3	0% (0%–56.2%)	1/60	1.7% (0.3%–8.9%)	0.00	.99

Levine et al. "Risk of Serious Bacterial Infection in Young Febrile Infants With Respiratory Syncytial Virus Infections." *Pediatrics* 2004;113:1728 –1734.
Krief et al. "Influenza Virus Infection and the Risk of Serious Bacterial Infections in Young Febrile Infants." *Pediatrics* 2009;124:30–39.

Mercedes

21 days old

CC: breast mass and fever

PE: T=100.8 HR= 195 RR=45

Alert, vigorous, no distress

Right breast with 3cm erythema and induration in upper outer quadrant, no discharge, no fluctuance

RESEARCH ARTICLE

Outcomes After Skin and Soft Tissue Infection in Infants 90 Days Old or Younger

Gabrielle Hester, MD, MS,[a] Adam L. Hersh, MD, PhD,[b] Michael Mundorff, MBA, MHSA,[c] Kent Korgenski, MS, MT,[c] Jacob Wilkes, BS,[c] Gregory Stoddard, MS,[b] Carrie L. Byington, MD,[b] Rajendu Srivastava, MD, FRCP(C), MPH[b,c]

METHODS: Retrospective study of patients ≤90 days of age who received care from the 22 emergency departments and hospitals in the Intermountain Healthcare system from July 1, 2004 to December 31, 2011, with a primary discharge diagnosis of SSTI. Concomitant bacterial infections were defined as urinary tract infection (UTI; culture-confirmed) or invasive bacterial infection (IBI; culture-confirmed bacteremia and/or meningitis). Treatment failure was defined as any unplanned change in care at hospital revisit within 14 days of discharge.

RESULTS: The study included 172 infants; 29 (17%) were febrile, and 91 (53%) had ≥1 sterile site culture performed. One case of bacteremia in a febrile infant was identified giving an overall proportion with UTI/IBI of 0.58% (95% confidence interval 0.01%–3.2%). Sixteen infants (9.3%; 95% confidence interval 5.4%–14.7%) returned for treatment failure. Perianal location ($P = .03$) and private insurance status ($P = .01$) were associated with more treatment failures compared with other locations or payer types. No patients returned for missed UTI/IBI.

CONCLUSIONS: Concomitant bacterial infections were rare in infants with SSTI, with none identified in afebrile infants. Treatment failure of SSTI leading to hospital revisit was common.

Management of Afebrile Neonates With Skin and Soft Tissue Infections in the Pediatric Emergency Department

Shervin A. Kharazmi, MD, Daniel A. Hirsh, MD,*†‡*
Harold K. Simon, MD, MBA,†‡ and Shabnam Jain, MD*†‡*

Methods: This is a retrospective cohort study of all patients aged 0 to 28 days seen in the PED for SSTIs from 2004 to 2010. The SSTIs were identified from the *International Classification of Diseases, Ninth Revision* codes of pustulosis, cellulitis, and abscess. Records were reviewed to determine the absence of fever; anatomical location; cultures of blood, urine, and cerebrospinal fluid; antibiotic usage; and return visits. Data were analyzed to compare admitted versus discharged patients with SSTI subtypes.

Results: Of the 136 neonates identified, 104 met inclusion criteria. Afebrile SSTIs included 8 pustulosis, 45 cellulitis, and 51 abscesses. Blood cultures were obtained in 13% of pustulosis, 96% of cellulitis, and 69% of abscesses. No serious bacterial infection was noted. Three blood cultures grew contaminants. Parenteral antibiotics for neonates with pustulosis, cellulitis, and abscesses were given in 13%, 87%, and 59%, respectively. Admission rates for neonates with pustulosis, cellulitis, and abscesses were 13%, 84%, and 55%, respectively. Cases of cellulitis were more likely to have blood cultures drawn (odds ratio [OR], 13.7; 95% confidence interval [CI], 3.03–62.3), receive intravenous antibiotics (OR, 5.87; 95% CI, 2.16–15.0), and be admitted to the hospital (OR, 5.62; 95% CI, 2.16–14.6) as compared with the other SSTI subtypes.