Approach to the Febrile Infant: How to Diagnose and Manage Bacterial Infections in Young Infants

Roger Baxter Memorial Infectious Disease Symposium
January 27th, 2020

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Objectives

- Febrile infants 7 – 90 days
  - Risk of bacterial infection
  - Evaluation
  - Empiric therapy
  - Need to perform a lumbar puncture in infants with a positive urinalysis
  - Treatment of bacteremic UTI

Definition of Fever and SBI

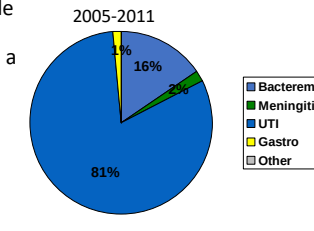
- Definition of fever
  - ≥ 100.4 º Fahrenheit (38.0 º Celsius) rectally
- Serious bacterial infection (SBI) includes
  - Urinary tract infections (UTIs)
  - Bacteremia and
  - Bacterial meningitis
- Many experts now prefer the term invasive bacterial infection (IBI) which includes only bacteremia and bacterial meningitis

Case #1

- You are the microbiology lab technician processing blood cultures. You note that the majority of cultures are negative. You begin to wonder what is the risk for positive cultures in febrile infants ≤ 90 days.

Historical Epidemiology

- 7 – 12.6% of febrile infants less than three months had a SBI
- Historically, bacteremia in absence of infection in other locations was common



TL Greenhow, et al. PIDJ 2013

SBIs in Full-Term, Previously Well, Febrile

- 13% UTI
- 2% bacteremia
  - Gram negative organisms accounted for the majority (89/130, 68%) of bacterial pathogens
  - There were no cases of *Listeria* or meningococcal infection
- 1% of those tested meningitis (0.4% overall)

TL Greenhow, et al. PIDJ 2013

Case #1

- You next begin to wonder about the evaluations performed on febrile infants as not all infants have blood, urine and cerebral spinal fluid (CSF) collected.
- One sample that you processed is on a 22 day old full-term, previously well male with fevers that began that afternoon and he has a sick older brother at home. Infant is eating well. Vital signs are normal for age, he is well appearing and has no focus on exam.
- What are the next steps?

PROS Study

- 1995-1998
- Consecutive sample of 3066 infants ≤3 months with temp ≥38.0

- 1975 (64%) managed outside the hospital
- 1666 (54%) had urine tested
- 726 (24%) had NO blood, urine, or CSF cultures obtained
- 45.7% of infants ≤30 days had complete work-up for SBI and hospitalization

Pantell RH et al. JAMA 2004

PROS Study

- Bacteremia: 2.4% of infants with blood cultures
- Bacterial meningitis: 0.5% of the entire sample of infants
- 2 infants not treated initially included:
  - 26-day-old infant who appeared well, WBC count of 13,000/µL, and had a blood culture positive for group B streptococci
  - 4-week old infant who appeared well, WBC count of 15,300/µL with 8% bands, and had pneumococcal meningitis

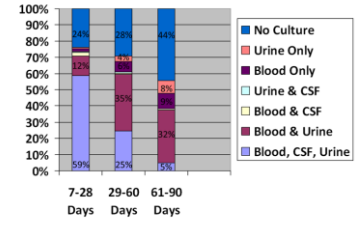
Pantell RH et al. JAMA 2004

Kaiser Permanente Study

- 3 years
- 96,156 full-term infants born
- 1380 infants presented for care with a fever
  - Incidence rate of 14.4 per 1000 full term births
- Less likely to have a urine, blood, and/or CSF culture
  - Older infants
  - Lower febrile temperatures
  - Presented to an office setting

Greenhow et al. Pediatrics 2016

Kaiser Permanente Study



Greenhow et al. Pediatrics 2016

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The Untested: Reasons and Outcomes

- Providers reasons for not testing differed by age
  - Infants 7-28 days
    - Environmental reasons for fever
  - Infants 29-90 days
    - Viral symptoms
    - Recent immunization
- Outcomes of untested infants
  - In the 30 days after a fever, 5 of 429 infants (1.2%) who didn't have cultures returned febrile with a UTI
  - No cases of bacteremia or meningitis in this group

Greenhow et al. Pediatrics 2016

Clinical Practice - Neonates

- **Diagnosis of fever**
- **Neonates evaluated in 36 pediatric EDs in the 2010 PHIS database**
- **2253 met study criteria**

	Overall (n = 2253)	
	%	95% CI
Blood + urine + CSF culture[a]	72.9	71.1–74.7
Blood + urine culture	7.3	6.2–8.4
Blood culture only	1.1	0.7–1.6
Urine culture only	0.9	0.6–1.4
CSF culture only	1.7	1.3–2.4
Other cultures or combinations	3.6	2.9–4.5
No cultures	12.5	11.2–13.9
Chest radiograph	32.8	30.9–34.7

[a] Recommended testing for neonatal fever.

Jain, et al Pediatrics 2014

Clinical Practice - ED

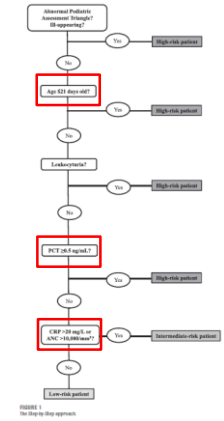
- **Retrospective cohort study of infants < 90 days of age with a diagnosis code of fever presenting to 1 of 37 pediatric EDs**
- **35,070 ED visits**
- **Significant inter-hospital variation was seen**

	Overall Median (IQR)[a]	≤28 d Median (IQR)[a]	29–56 d Median (IQR)[a]	57–89 d Median (IQR)[a]
Testing[b]				
Laboratory testing[c]				
Urine + Blood + CSF	43.0 (33.8–49.6)	72.0 (66.2–76.5)	47.2 (38.5–58.8)	11.8 (8.1–19.0)
Urine + Blood	26.4 (21.8–33.5)	5.8 (4.4–9.3)	25.0 (20.0–34.3)	39.9 (34.6–47.9)
Urine only	5.4 (3.0–8.1)	0.9 (0.7–2.0)	2.3 (1.6–4.7)	12.6 (5.8–19.0)
Other combinations of Urine, Blood, CSF	5.6 (4.3–6.8)	4.8 (3.6–6.6)	5.0 (4.0–7.1)	6.2 (5.2–7.5)
None	18.2 (13.7–22.9)	14.6 (9.1–18.7)	14.8 (10.3–18.5)	23.5 (19.7–30.8)

Aronson, et al. Pediatrics 2014

Step-By-Step Approach with PCT

- Developed by a European group of pediatric ED physicians
- Primary objective was to identify a low risk group of infants who could be safely managed as outpatients without lumbar puncture nor empirical antibiotic treatment



Gomez, et al. Pediatrics 2016

Case #1

- A complete blood count (CBC), blood culture, urinalysis, urine culture, and cerebrospinal fluid (CSF) analysis and culture are obtained
- The CBC is abnormal with a WBC count of 15,100 x 10^9 cells per liter
- The urinalysis is normal without leukocyte esterase or WBC / hpf
- CSF analysis is normal

Historical Low-Risk Criteria

	Age (d)	Lab criteria
Rochester	≤60	• WBC 5,000-15,000/mm^3 • Absolute band count ≤1500/mm^3 • UA ≤10 WBC/hpf
Pittsburgh	≤60	• WBC 5,000-15,000/mm^3 • Absolute band count ≤1500/mm^3 • CSF <10 WBC/mm^3 0-28 days, < 5 WBC/mm^3 29-60 days with negative GS • Enhanced UA with WBC <10 WBC/hpf with negative GS

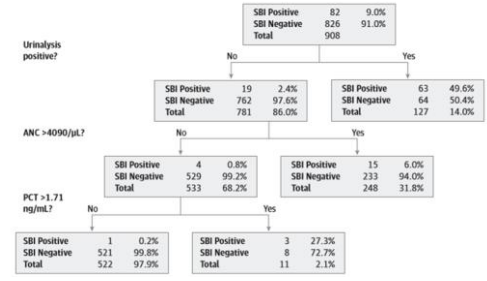
Adapted from M Neuman

Historical Low-Risk Criteria

	Age (d)	Lab criteria
Philadelphia	29-56	• WBC <15,000/mm^3 • Band: total neut (I:T) ratio <0.2 • UA <10 WBC/hpf • CSF <8 WBC/mm^3
Boston	28-89	• WBC <20,000/mm^3 • UA <10 WBC/hpf • CSF <10 WBC/mm^3
Milwaukee	28-56	• WBC <15,000/mm^3 • Band: total neut (I:T) ratio <0.2 • UA <5-10 WBC/hpf with negative GS, LE and nitrite • CSF <10 WBC/mm^3

Adapted from M Neuman

PECARN Recursive Partitioning with PCT



Kuppermann et al. Jama Peds 2019

Question

- Which empiric antibiotics should febrile infants receive:
  - ampicillin + gentamicin or
  - 3rd generation cephalosporin +/- ampicillin?

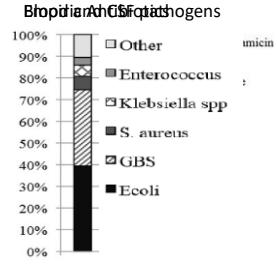
Bacteremia - Age

Pathogen	7-28 Days N (%)	29-60 Days N (%)	61-90 Days N (%)	Total N (%)
E. coli	25 (51)	27 (64)	20 (80)	72 (62)
GBS	14 (29)	5 (12)	1 (4)	20 (17)
S. aureus	3 (6)	3 (7)	1 (4)	7 (6)
Salmonella sp.	1 (2)	1 (2)	1 (4)	3 (3)
Klebsiella sp.	1 (2)	2 (5)	0 (0)	3 (3)
S. pneumoniae	0 (0)	1 (2)	2 (8)	3 (3)
Other	5 (10)	3 (7)	0 (0)	8 (7)
Total	49	42	25	116 (100)

TL Greenhow, et al. PIDJ 2013

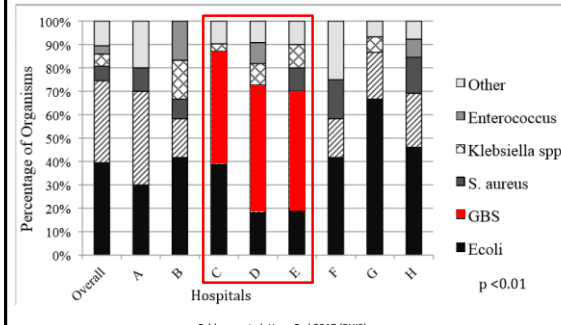
PHIS Study

- Infants <90 days old without substantial comorbidities evaluated in the ED of 8 US children's hospitals between 7/1/12 – 6/30/14 with positive urine, blood, or CSF culture



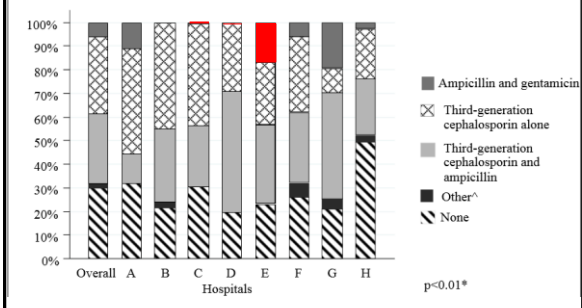
Feldman, et al. Hosp Ped 2017 (PHIS)

Figure 3: Bacterial Epidemiology across Hospitals by Source
3A: Blood and CSF pathogens (n=114)*



Feldman, et al. Hosp Ped 2017 (PHIS)

Figure 2: Empiric Antibiotics by Hospital



Feldman, et al. Hosp Ped 2017 (PHIS)

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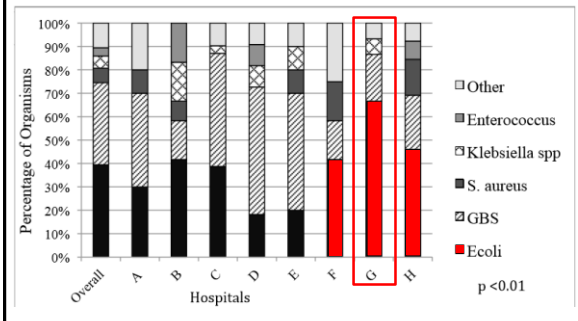

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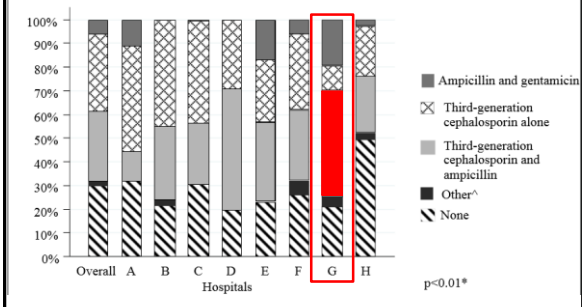

Feldman, et al. Hosp Ped 2017 (PHIS)

Febrile Young Infant Research Collaborative

- Infants ≤60 days old with IBI evaluated in the ED of 1 of 11 children's hospitals between 7/1/11 – 6/30/16

Infants ≤28 d of age

Pathogens	Total n (%) (n = 234*)	Bacteremia without meningitis n (%) (n = 175*)	Bacterial meningitis† n (%) (n = 59)
E coli	72 (30.8)	62 (35.4)	10 (16.9)
GBS	71 (30.3)	41 (23.4)	30 (50.8)
S aureus	29 (12.4)	26 (14.9)	3 (5.1)
Enterococcus spp	17 (7.3)	16 (9.1)	1 (1.7)
Klebsiella spp	13 (5.6)	11 (6.3)	2 (3.4)
Other Gram negative‡	9 (3.8)	8 (4.6)	1 (1.7)
Group A streptococcus	8 (3.4)	8 (4.6)	0
Other Gram positive‡	7 (3.0)	1 (0.6)	6 (10.2)
Enterobacter spp	5 (2.1)	4 (2.3)	1 (1.7)
L monocytogenes	4 (1.7)	0	4 (6.8)
Salmonella spp	2 (0.9)	1 (0.6)	1 (1.7)
S pneumoniae	0	0	0

Woll, et al. J Ped 2018 (Febrile Young Infant Research Collaborative)

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S pneumoniae	0	0	0

Infants ≤28 d of age‡

Antimicrobial(s)	Total n (%)‡	Bacteremia without meningitis n (%)	Bacterial meningitis† n/n(%)
Individual			
Ampicillin	152/229 (66.4)	105/173 (60.7)	47/56 (83.9)
Third-generation cephalosporin	202/229 (88.2)	151/173 (87.3)	51/56 (91.1)
Combination			
Ampicillin/gentamicin	217/228 (95.2)§	170/172 (98.8)	47/56 (83.9)§
Ampicillin/third-generation cephalosporin	224/230 (97.4)	168/174 (96.6)	56/56 (100)
Vancomycin/ampicillin/gentamicin	227/230 (98.7)§	172/174 (98.9)	55/56 (98.2)§
Vancomycin/third-generation cephalosporin	225/227 (99.1)	171/173 (98.8)	54/54 (100)

Woll, et al. J Ped 2018 (Febrile Young Infant Research Collaborative)

Febrile Young Infant Research Collaborative

Infants 29–60 d of age

Pathogens	Total n (%) (n = 296*)	Bacteremia without meningitis n (%) (n = 178*)	Bacterial Meningitis† n (%) (n = 30)
GBS	91 (44.3)	73 (41.0)	18 (60.0)
E coli	64 (30.8)	57 (32.0)	7 (23.2)
S aureus	14 (6.7)	14 (7.9)	0
Enterococcus spp	12 (5.8)	11 (6.2)	1 (3.3)
Other Gram negative‡	7 (3.4)	4 (2.2)	3 (10.0)
Enterobacter spp	6 (2.9)	6 (3.4)	0
S pneumoniae	6 (2.9)	5 (2.8)	1 (3.3)
Salmonella spp	4 (1.9)	4 (2.2)	0
Group A streptococcus	3 (1.4)	3 (1.7)	0
Other Gram positive‡	2 (1.0)	2 (1.1)	0
Klebsiella spp	1 (0.5)	1 (0.6)	0
L monocytogenes	0	0	0

Infants 29–60 d of age‡

Antimicrobial(s)	Total n (%)‡	Bacteremia without meningitis n (%)	Bacterial meningitis† n/n(%)
Individual			
Ampicillin	114/200 (77.0)	128/171 (74.9)	26/29 (89.7)
Third-generation cephalosporin	186/206 (90.3)	158/176 (89.8)	28/30 (93.3)
Combination			
Ampicillin/gentamicin	194/200 (97.0)§	168/171 (98.3)	26/29 (89.7)§
Ampicillin/third-generation cephalosporin	198/206 (96.1)	169/176 (96.0)	29/30 (96.7)
Vancomycin/ampicillin/gentamicin	202/204 (99.0)§	173/175 (98.9)	29/29 (100)§
Vancomycin/third-generation cephalosporin	199/205 (97.1)	170/175 (97.1)	29/30 (96.7)

Woll, et al. J Ped 2018 (Febrile Young Infant Research Collaborative)

Empiric Therapy

Age	Pathogens	Antibiotics	Comments
0-6 days	GBS *E. coli* Listeria	Ampicilin + Gentamicin	Do not use amp + gent without cefotaxime if GNR bacterial meningitis suspected
7-28 days	*E. coli* GBS *Staph aureus* Other gram neg rods *Enterococcus*	Ampicilin + Gentamicin OR Cefotaxime	Do not use amp + gent without cefotaxime if bacterial meningitis suspected
29-90 days	As above + *Strep pneumoniae*	Ampicillin + Gentamicin OR Ceftriaxone	Use ceftriaxone + vancomycin if bacterial meningitis suspected

TL Greenhow, JB Cantey. Hosp Peds 2017

How long to treat pending cultures?

- Multicenter, retrospective, cross-sectional evaluation of blood culture time to positivity
- 392 pathogenic blood cultures were included from 17 hospital systems
- 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% and 99% had become positive, respectively

Biondi et al JAMA Ped 2014

Case #2

- Later that same day…
- A 40 day old full-term, previously well female infant presents to the ED with fever to 101.3 ºF (38.5 ºC).
- Mother reports she is feeding well and there are no sick contacts
- On exam she appears well. Exam is non-focal.
- Blood and urine studies are obtained.
- The urinalysis is positive for 50 WBC/HPF and large leukocyte esterase.

How to Diagnose a UTI?

- 27,000 infants (median age 1.7 months) were studied, 7.8% had a UTI
- Optimal WBC cut-points were
  - 3 WBC/HPF in dilute urine
  - 6 WBC/HPF in concentrated urine
- For dipstick analysis, positive LE has excellent test characteristics regardless of urine concentration

- 13,030 febrile infants identified, 12% had a UTI
- The combined urinalysis NPV was 99.2% and was significantly greater than the dipstick NPV of 98.7%
- The dipstick PPV was significantly greater than combined urinalysis (66.8% vs 51.2%)

Chaudhari, et al. Ped 2016, Byington et al. Ped 2014

How to Diagnose a UTI?

- 245 infants with bacteremic UTI and 115 infants with negative urine cultures < 3 months from 8 healthcare delivery systems
  - The sensitivity of leukocyte esterase was 97.6% and pyuria (>3 white blood cells/high-power field) was 96%
  - In infants with negative urine cultures, leukocyte esterase specificity was 93.9% and of pyuria was 91.3%
- 1181 children diagnosed with UTI
  - Pyuria (≥5 white blood cells per high-powered field or ≥10 white blood cells per cubic millimeter) was present in 1031 (87%) children and absent in 150 (13%)
  - Children with *Enterococcus* species, *Klebsiella* species, and *Pseudomonas aeruginosa* were significantly less likely to exhibit pyuria than children with *Escherichia coli*
  - Children with these organisms were also less likely to have a positive leukocyte esterase on dipstick urinalysis

Schroeder et al. Ped 2015, Shaikh N et al. Ped 2016

How to Diagnose a UTI?

- Febrile infants ≤60 days old at 26 EDs in PECARN
  - 4147 infants analyzed
  - 289 (7.0%) had UTIs with colony counts ≥50 000 CFUs/mL, including 27 (9.3%) with bacteremia
  - For these UTIs, a positive UA exhibited
    - Sensitivity of 0.94 (95% confidence interval [CI]: 0.91–0.97), regardless of bacteremia
      - 1.00 (95% CI: 0.87–1.00) with bacteremia
      - 0.94 (95% CI: 0.90–0.96) without bacteremia.
    - Specificity was 0.91 (95% CI: 0.90–0.91) in all groups

Tzimenatos et al. Ped 2018 (PECARN)

UA (-) vs. UA (+) UTIs

- Of 20,570 well-appearing febrile infants 7-60 days
  - 2,407 (12.1%) were treated for UTI, of whom 2,298 (95.5%) had an initial UA performed
  - UAs were negative in 337 / 2,298 (14.7%) treated subjects
  - Compared to UA (+) infants, UA (-) infants were
    - More likely to have respiratory symptoms
    - Less likely to have abnormal inflammatory markers

Schroeder et al. Hosp Ped 2019

Case #2

- Given the positive urinalysis you are concerned for a UTI
- A lumbar puncture has not been performed

Question

- What is the prevalence of bacterial meningitis in febrile infants 29–60 days with positive urinalysis?

Background

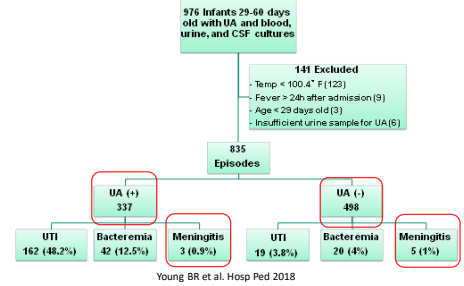
- All risk stratification algorithms use positive urinalysis as 'high risk' criteria
  - Rochester
  - Pittsburgh
  - Philadelphia
  - Boston
  - Step-by-Step
  - PECARN
- Many have begun to question the risk of bacterial meningitis and the need for lumbar puncture in infants 29-60 days

Risk of Meningitis in Infants with UTI

- Study population PEM CRC 2010
  - Urine cultures with bacterial growth in infants aged 29-60 days in the ED, 1995-2006
- Outcome
  - Bacterial meningitis (definite or probable)
    - n= 5/1609; 0.3% (95% CI: 0.1–0.7)
  - Definite bacterial meningitis
    - n=2/1609; 0.1% (95% C:I 0–0.4)
- Study population PEM CRC 2017
  - Infants aged ≤60 days in the ED between 2005-2013 with CSF culture obtained and +UTI
- Outcome
  - Concomitant bacterial meningitis
    - 0-28 days of age: n=7/803; 0.9% (95% CI: 0.4–1.8)
    - 29-60 days of age: n=2/934; 0.2%; (95% CI: 0–0.7)

Schnadower et al. Pediatrics 2010, Thomson et al. PIDJ 2017

Prevalence of Bacterial Meningitis Among Infants with Abnormal UA



Young BR et al. Hosp Ped 2018

Infants with Abnormal UA Treated Without LP

- 341 febrile infants (345 episodes) 29-60 days with positive urinalyses treated with antibiotics without lumbar puncture
  - Zero cases of missed bacterial meningitis (95% CI: 0%-1.1%)
  - Zero cases of severe sequelae (95% CI: 0%-1.1%)
    - Severe sequelae: Sepsis, seizure, neurologic deficit, intubation, PICU admission, death

Young BR et al. Hosp Ped 2018

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Meta-Analysis Abnormal UA / UTI and Bacterial Meningitis

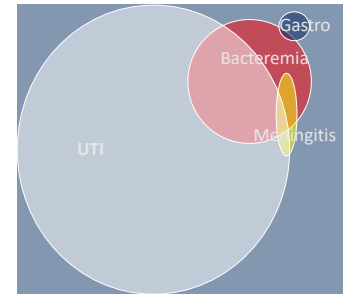
- 3 prospective and 17 retrospective cohort studies
- The pooled prevalence of concomitant bacterial meningitis in infants with UTI was 0.25% (95% CI, 0.09%-0.70%)
  - LP needed in order to diagnose 1 case of bacterial meningitis is 400 infants (95% CI, 143-1111).
  - Comparable prevalence (0.2-0.3%) reported in other cohorts of infants aged 29 – 90 days.
- Rates of sterile pleocytosis ranged from 0% - 29%

Nugent J et al. JPed 2019

Case #2

- She is admitted to the hospital and started on ceftriaxone. She appears well.
- On the second day, both blood and urine are growing gram negative rods.
- A lumbar puncture is performed. CSF is reassuring.

Infections With Multiple Sources



TL Greenhow, et al. PIDJ 2013

Question

- What is the appropriate therapy of a bacteremic UTI?
  - Subjects were infants < 3 months treated at 13 healthcare institutions with bacteremic UTI

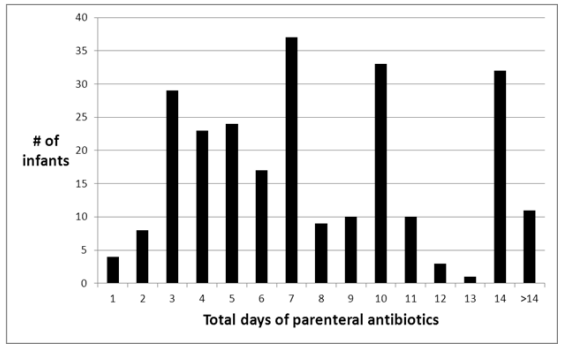
Schroeder et al. Arch Dis Child 2014

Bacteremic UTI

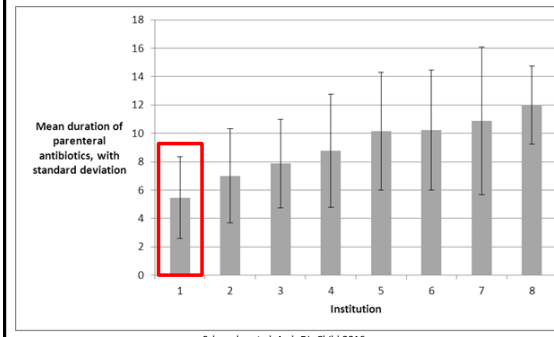
- **276 infants**
  - **25 infants excluded**
  - **19 (7%) were treated for meningitis [7 (2.5%) with positive CSF cultures]**
    - **Received a mean ± SD of 20.6 ± 2.7 days of parenteral antibiotics**

Variable	*Result*
Age in days, median (IQR)	35 (17 - 58)
Male gender (%)	148 (59)
Febrile >38°C (%)	238 (94.8)
Comorbidity* (%)	10 (4)
Ill appearance (%)	19 (7.6)
Hospitalized (%)	242 (96.4)
Organism (%)**	
Escherichia coli	203 (89.6)
Enterobacter spp	8 (3.2)
Klebsiella spp	7 (2.8)
Group B Streptococcus	4 (1.6)
Enterococcus spp	3 (1.2)
Staphylococcus aureus	1 (0.4)
Citrobacter	1 (0.4)
Klebsiella+Pseudomonas	1 (0.4)
Group A Streptococcus	1 (0.4)

Schroeder et al. Arch Dis Child 2016



Schroeder et al. Arch Dis Child 2016



Schroeder et al. Arch Dis Child 2016

Bacteremic UTI

- Predictors of longer IV course
  - Younger age
  - Repeat positive blood culture
  - Non- *E. coli* pathogen
- 6 infants had recurrent UTI
  - No difference in the parenteral antibiotic duration between infants with and without a recurrence (8.2 vs 7.8 days, P=0.81)
- No infants had a recurrent bacteremic UTI

Schroeder et al. Arch Dis Child 2016

Bacteremic UTI

- Multicenter retrospective ≤60 days old infants with growth of a pathogen in blood and urine cultures at 11 children's hospitals between 2011 - 2016
  - Short-course parenteral antibiotic duration was defined as ≤7 days and long-course defined as >7 days
- 115 infants with bacteremic UTI
  - 58 (50%) infants received short-course parenteral antibiotics

Desai et al. Peds 2019

Bacteremic UTI

- Infants who received long-course parenteral antibiotics were more likely to be
  - Ill appearing and
  - Have growth of a non–*Escherichia coli* organism
- There was no difference in adjusted 30-day UTI recurrence between the long- and short-course groups or 30-day all-cause reutilization

Outcome	Short-Course IV/SH Antibiotics (n = 58)	Long-Course IV/SH Antibiotics (n = 57)	Adjusted Relative Risk (95% CI)*	Percent Adjusted Risk Difference (95% CI)*	Adjusted Mean Difference (95% CI)*
Recurrent UTI, n (%)	0 (0)	4 (7)	1.9 (0.3 to 11.6)	3 (−0.8 to 10.7)	–
Recurrent UTI with same organism, n (%)	0 (0)	2 (4)	1.1 (0.1 to 9.4)	0.2 (−7.0 to 6.8)	–
All-cause reutilization, n (%)	6 (10)	8 (14)	1.2 (0.4 to 3.9)	3 (−14.9 to 20.6)	–
LOS, d, adjusted mean (95% CI)	4.8 (4.4 to 5.3)	10.9 (10.7 to 11.0)	–	–	6 (4.8 to 6.0)

Desai et al. Peds 2019

Bacteremic UTI

- Recommend IV therapy until
  - Infant is afebrile
  - Repeat blood culture is negative 24 hours
  - ID and susceptibilities known for urine pathogen

Schroeder et al. Arch Dis Child 2016, Riordan Arch Dis Child 2015

Updates on Cases #1 and #2

- Case #1
  - The infant becomes afebrile after the first night
  - Blood, urine and CSF cultures are negative at 24 hours and he is sent home
- Case #2
  - The blood and urine grow *E. coli*
  - She is afebrile after hospital day # 2
  - CSF culture remains negative
  - She is sent home on hospital day #3 on oral cephalexin

Conclusions

- *E. coli* is the most common cause of UTI, bacteremia and meningitis in young, previously well infants
- Empiric ampicillin + gentamicin for febrile infants without suspected meningitis
- No higher risk for meningitis in infants 29-60 days with a positive UA (but higher rates of bacteremia)
- It not testing for meningitis, don't treat for meningitis
- Short course IV therapy for bacteremic UTI