Neonatal Fever Update in 8-60d

AAP clinical practice guideline 2021 review

Faculty disclosure

- Hans-David Hartwig, MD, faculty for this educational event, has no relevant financial relationships with any ineligible companies to disclose.

Evaluation and Management of Well appearing Febrile Infants 8 to 60 days old.

- **3 new algorithms** and **21 key action statements**
- **Authors' Conclusion:** ***"Three algorithms summarize the recommendations for infants 8 to 21 days of age, 22 to 28 days of age, and 29 to 60 days of age. The recommendations in this guideline do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.***

PRESENTATION

- **Case:** A 27-day-old, full-term boy presents to the emergency department with fever. His parents report that he felt warm that evening, and they found that he had a rectal temperature of 38.2°C (100.8°F). He has an older sister at home with a cough and rhinorrhea. Overall, he has no symptoms and appears well. He has continued to feed normally and produce wet diapers. Sent in by PCP for work up.
- The parents ask you, *"Do you really think he needs any additional testing? He probably caught something from his sister, right?"*
- **What needs to be done?**

History lesson, brief

- We have been trying to optimize our approach to evaluating and managing febrile infants for more than four decades. Our goal is to identify the febrile infants with urinary tract infection, bacteremia, and bacterial meningitis (or what was referred to as serious bacterial infections) while simultaneously trying to spare them from invasive and potentially unnecessary procedures like lumbar punctures or the possible iatrogenic consequences of empiric antibiotics or hospitalization.
- Several risk stratification tools have been published over the years. These clinical decision instruments included subjective clinical criteria along with pre-determined thresholds for lab criteria like white blood cell count (WBC) and immature to total neutrophil ratio. Unfortunately, these criteria may not be appropriate in the current era. In fact, the Modified Boston and Philadelphia Criteria for invasive bacterial infections may misclassify almost one-third of infants with bacterial meningitis.

Times they are a changing

- With routine screening of pregnant women, improvements in food safety, and conjugate pneumococcal vaccines, we have seen a decrease in Group B streptococcus, Listeria, and Streptococcus pneumoniae infections in infants. Instead, there has been a shift to Gram-negative organisms being the most common culprits in bacterial infections in infants.

- Simultaneously, our ability to test for infection has advanced with the use of inflammatory markers (IM) like procalcitonin(ProCal) and C-reactive protein (CRP) as well as polymerase chain reaction (PCR) testing for rapid identification of multiple viruses and bacteria.

Inclusion exclusion criteria

Included	Excluded
Well appearing Rectal temperature ≥38°C (100.4°F) at home in past 24 hours or in clinical setting Gestational age ≥37 and <42 weeks Age 8 to 60 days Home after discharge from newborn nursery or born at home. <u>Can also include</u>: - Respiratory symptoms - Diarrhea - Otitis media - Current/recent use of antimicrobials in infants >2 weeks - Positive respiratory viral test	Preterm <37 weeks gestation <2 weeks with perinatal course complicated by maternal fever, infection, and/or antimicrobial use High suspicion of HSV Focal bacterial infection Clinical bronchiolitis Immune compromise Neonatal course complicated by surgery\infection Medically fragile or technology dependent Immunizations within 48 hours

Four Key Components of Evaluation

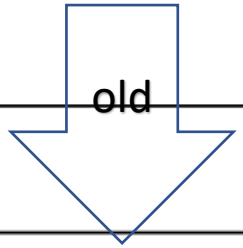
- Urine (UA and culture)
- Blood culture
- Inflammatory Markers (IM)
  - Procalcitonin >0.5 ng/mL
  - Absolute neutrophil count (ANC) > 4,000 mm^3 or >5,200 mm^3 (There are two ANC cutoffs included based on the PECARN study and Febrile Young Infant Research Collaborativestudy respectively)
  - CRP >20 mg/L or >2 mg/dL
  - Temperature > 38.5°C
- Cerebrospinal Fluid (CSF) from lumbar puncture (LP)

Algorithms At a Glance:

- There are three age groups (8-21d, 22-28d and 29-60d). All age groups get urine and blood cultures. Inflammatory markers are considered optional for the youngest group.
- The youngest group gets an LP, antibiotics and admitted (no major changes to work up on disposition)
- While the older two groups may get an LP and antibiotics and may be discharged home. (ie biggest change)

Overview of recommended work up

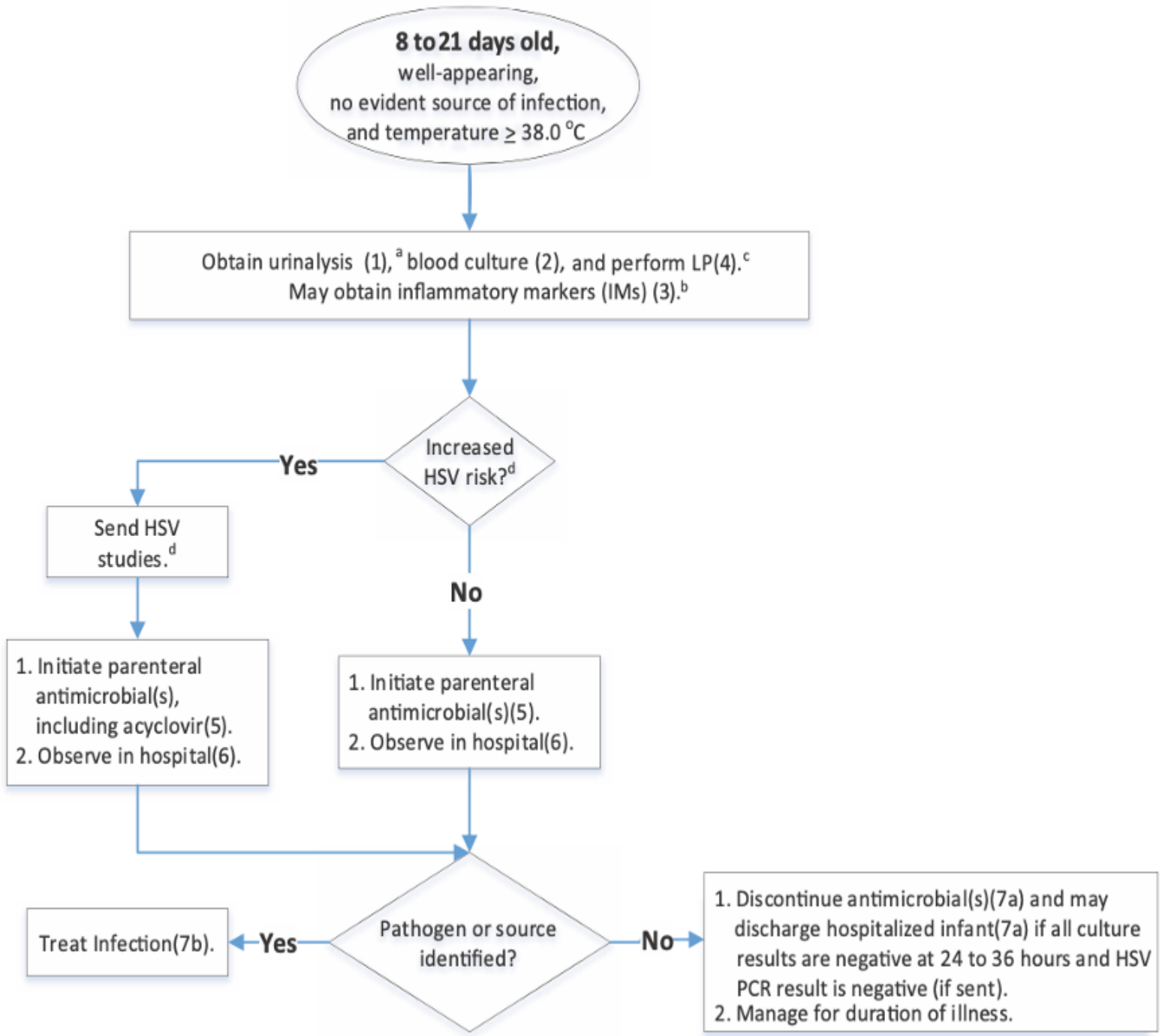
Evaluation & Management	Age		
	8 to 21 days	22 to 28 days	29 to 60 days
Urine	**Yes**		
Blood Culture	**Yes**		
Inflammatory Markers (IM)	**Optional**	**Yes**	
CSF	**Yes**	**Maybe**	
Antibiotics	**Yes**	**Maybe**	
Disposition	**Hospital**	**Hospital or Home**	



8 to 21 days

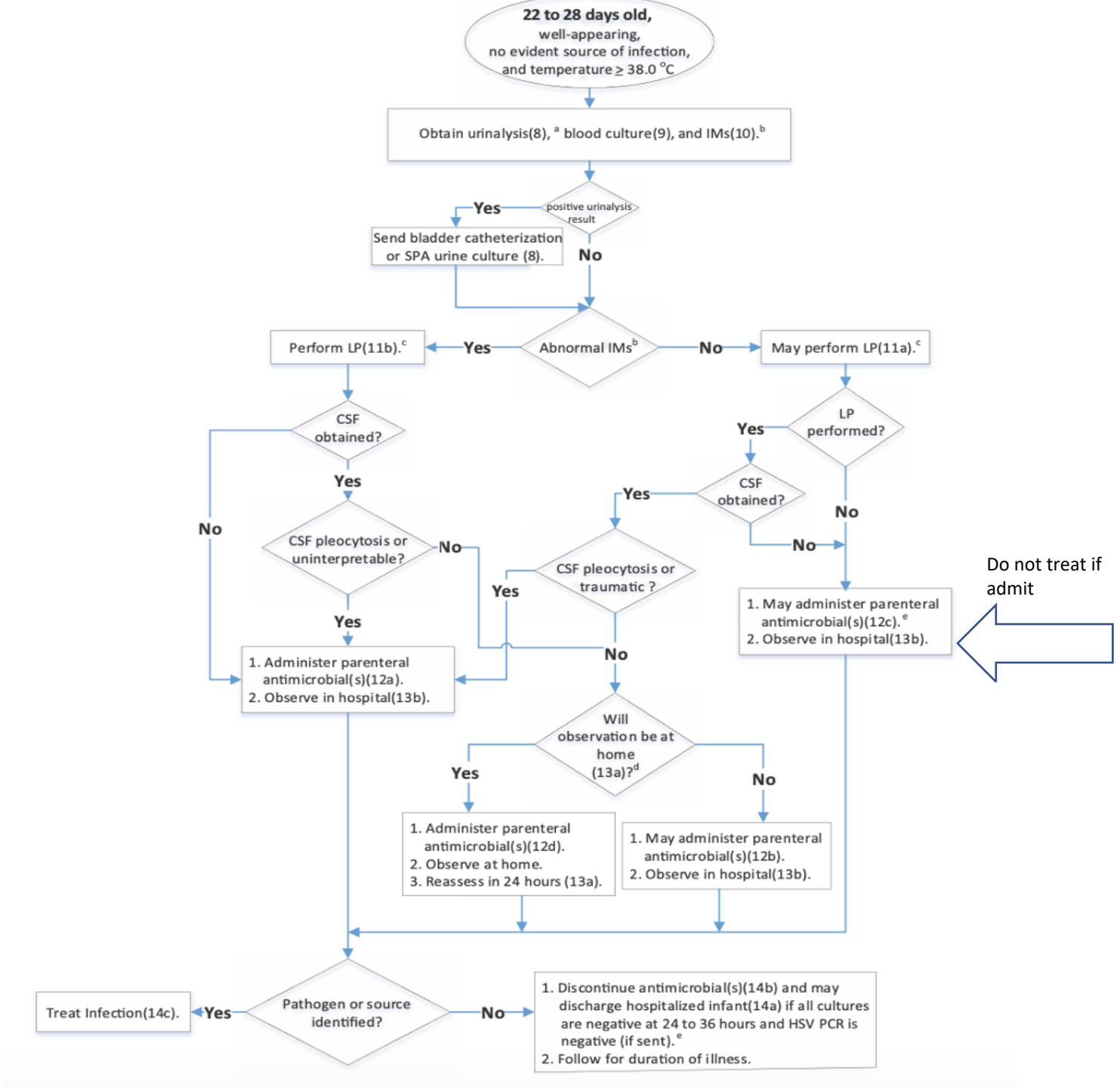
- This is a straightforward group and not a big change from previous practice. We should still be conservative with this group. These infants are all getting a full work up including urine, blood, and CSF. They are being treated with empiric antibiotics and staying in the hospital.
- The inflammatory markers are optional (Grade B, Weak Recommendation) as they do not really change decision to administer antimicrobials or disposition.
- “Before ordering a test, decide what you will do if it is (1) positive or (2) negative. If both answers are the same, don’t take the test”. Dr. Archie Cochrane
- We should be also cautious regarding herpes simplex virus (HSV) infection in this age group and may also consider adding acyclovir coverage in addition to empiric antibiotics.

CAUTION: Herpes Simplex Virus (HSV)	
Consider HSV if:	**Recommended HSV studies:**
• Maternal history of genital HSV lesions or fevers 48 hours before or after delivery • Vesicles • Seizures • Hypothermia • Mucous membrane ulcers • CSF pleocytosis without positive Gram stain • Leukopenia • Thrombocytopenia • Elevated alanine aminotransferase levels	• CSF PCR • HSV surface swabs from mouth, nasopharynx, conjunctivae, and anus for HSV culture or PCR assay • Alanine aminotransferase • Blood PCR


8 to 21 days old,
well-appearing,
no evident source of infection,
and temperature ≥ 38.0 °C
Obtain urinalysis (1),[a] blood culture (2), and perform LP(4).[c]
May obtain inflammatory markers (IMs) (3).[b]
Increased HSV risk?[d]
Yes
No
Send HSV studies.[d]
1. Initiate parenteral antimicrobial(s), including acyclovir(5).
2. Observe in hospital(6).
1. Initiate parenteral antimicrobial(s)(5).
2. Observe in hospital(6).
Pathogen or source identified?
Yes
Treat Infection(7b).
No
1. Discontinue antimicrobial(s)(7a) and may discharge hospitalized infant(7a) if all culture results are negative at 24 to 36 hours and HSV PCR result is negative (if sent).
2. Manage for duration of illness.

Infants 21 to 28 days

- This is where there is some nuance and room for shared decision making. We are still going to obtain urine and blood. Inflammatory markers can be used to guide further management.
- If any IM is abnormal, these guidelines recommend performing an LP and obtaining CSF (KAS 11b Grade C, Moderate Recommendation). However, even if all IMs are normal, the clinician can still choose to perform a LP. KAS 11a
- If the decision is made to defer LP, these patients will need to stay in the hospital. The choice of administering empiric antimicrobials in a situation where an LP is not performed is dependent on a discussion of the potential harms and potential benefits between clinician and family. While the risk of meningitis is lower in this age group, empiric treatment without CSF may result in partially treated meningitis. (Our Hospitalists would prefer no abx in this scenario.)
- A key thing to remember for this algorithm and age group is that we should not send these patients home without obtaining an interpretable CSF. If the urine studies are normal, IM are normal, CSF is normal or enterovirus positive, these patients can be discharged home after receiving a dose of parenteral antibiotics (Grade C, Moderate Recommendation) with proper anticipatory guidance and return precautions and follow up in 24 hours.
- Rocephin 50 mg/kg given IV or IM as biliary sludging risk low



IM values

ANC: abnl if >4000 , 5200 or less than 1000

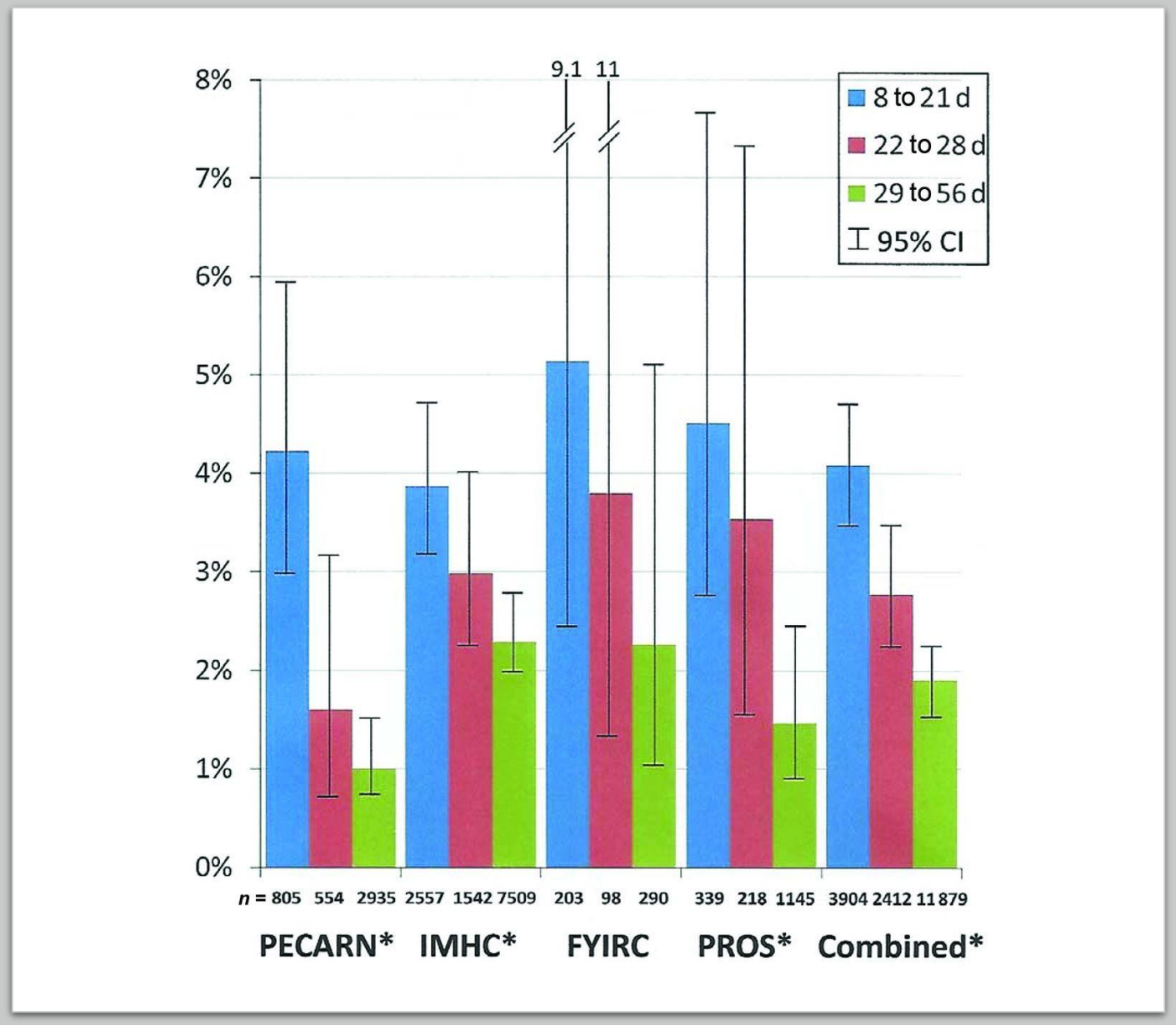
CRP: > 20mg/L

ProCal: >0.5ng/mL

Where the guidelines are basing this change

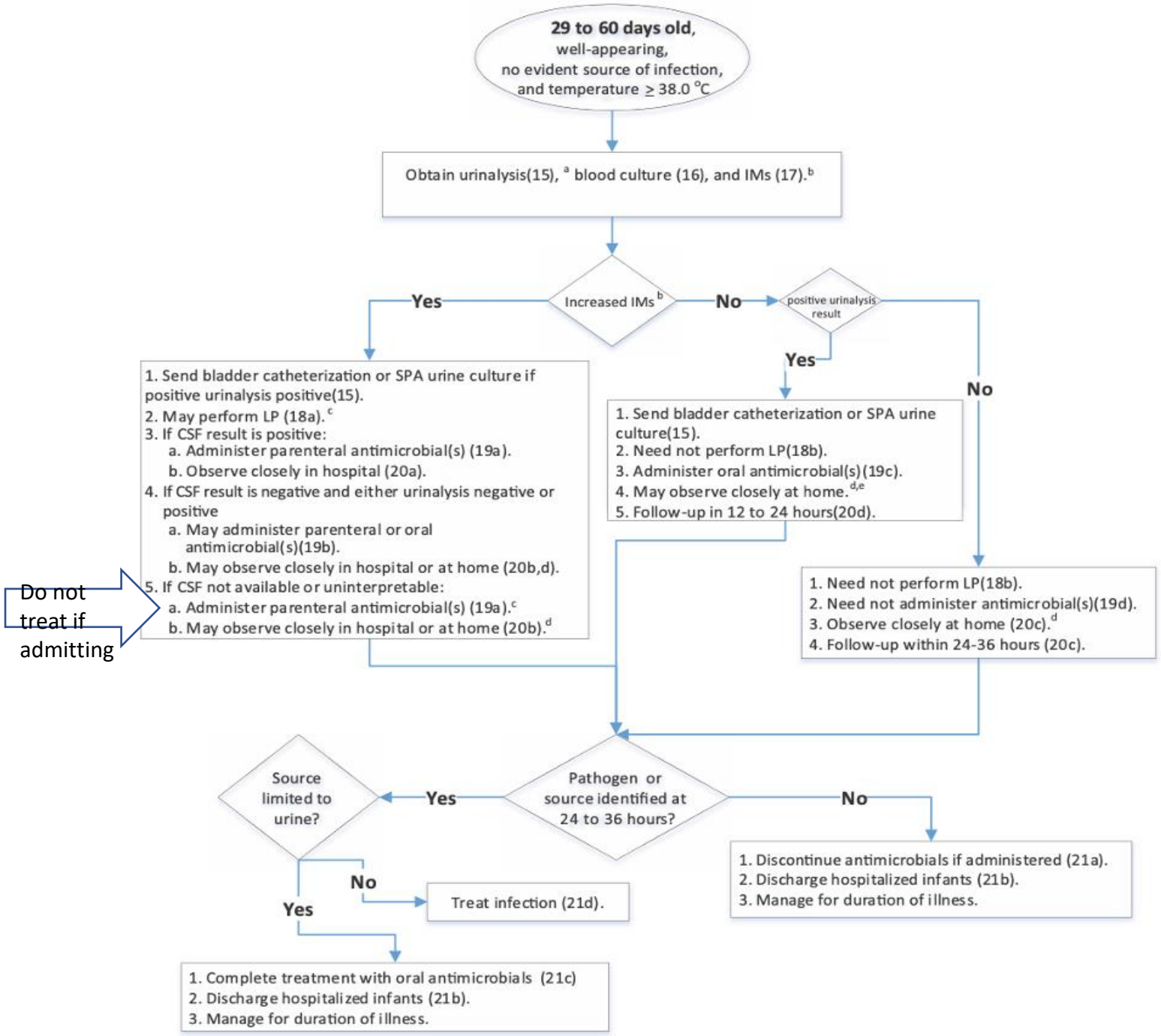
- Rate of bacteremia by age groupings.

* χ2 for trend: P < .001. Note that the 95% CIs in the combined group do not overlap. Data were adapted from reference 61; from reference 94, with detail provided by C.L.B. (personal communication, 2020); from reference 24, with detail provided by Paul Aronson (personal communication, 2020); and from reference 17, with detail provided by Matthew Pantell (personal communication, 2020). FYIRC, Febrile Young Infants Research Collaborative; IMHC, University of Utah/Intermountain Healthcare.



Infants 29 to 60 days

- This algorithm has the potential to really decrease the number of LPs and allow us to send more infants home based on the IMs. We are still going to start by obtaining urine, blood culture, and IMs. (Basically, extending high risk low risk stratification down to the 29 day old infant)
- Circumcised boys may be exempted from urine studies given their risk of urinary tract infection is <1%. In the setting of having normal IMs, LP may be deferred (Grade B, Moderate Recommendation) even with a positive urinalysis. Patients with positive urinalysis and normal IMs can be discharged home on oral antibiotics with close follow up in 12 to 24 hours.
- If urinalysis is negative and the IMs are normal, these patients may be sent home without a lumbar puncture and without antimicrobial therapy. They should be closely observed, provided with strict return precautions, and have follow up arranged within 24 to 36 hours. (lots of room for discussion)
- If the IMs are elevated, things get a bit tricky. The guidelines state that a LP may be performed (Grade C, Weak Recommendation). This is different from the previous age group where the recommendation was that LP should be performed in the setting of abnormal IMs. (lots of room for discussion base on risk tolerance, stratification). Most PEM will error on performing LP and then stratifying.
- If CSF is negative with positive or negative urinalysis, you may give them a dose of antimicrobial and still send them home. If CSF is not obtained or uninterpretable, you should give a dose of IV antimicrobial and observe in the hospital or discharge home. This requires a very careful discussion with the family about the potential harms, potential benefits, return precautions, and follow up. (Hospitalists would prefer no abx in this situation if admitting)


29 to 60 days old,
well-appearing,
no evident source of infection,
and temperature ≥ 38.0 °C
Obtain urinalysis(15), [a] blood culture (16), and IMs (17).[b]
Increased IMs [b]
Yes
No
positive urinalysis result
Yes
No
1. Send bladder catheterization or SPA urine culture if positive urinalysis positive(15).
2. May perform LP (18a).[c]
3. If CSF result is positive:
a. Administer parenteral antimicrobial(s) (19a).
b. Observe closely in hospital (20a).
4. If CSF result is negative and either urinalysis negative or positive
a. May administer parenteral or oral antimicrobial(s)(19b).
b. May observe closely in hospital or at home (20b,d).
5. If CSF not available or uninterpretable:
a. Administer parenteral antimicrobial(s) (19a).[c]
b. May observe closely in hospital or at home (20b).[d]
Do not treat if admitting
1. Send bladder catheterization or SPA urine culture(15).
2. Need not perform LP(18b).
3. Administer oral antimicrobial(s)(19c).
4. May observe closely at home.[d,e]
5. Follow-up in 12 to 24 hours(20d).
1. Need not perform LP(18b).
2. Need not administer antimicrobial(s)(19d).
3. Observe closely at home (20c).[d]
4. Follow-up within 24-36 hours (20c).
Source limited to urine?
Yes
Pathogen or source identified at 24 to 36 hours?
No
No
Yes
Treat infection (21d).
1. Discontinue antimicrobials if administered (21a).
2. Discharge hospitalized infants (21b).
3. Manage for duration of illness.
1. Complete treatment with oral antimicrobials (21c)
2. Discharge hospitalized infants (21b).
3. Manage for duration of illness.

KEY TAKEHOME POINTS:

- **1. Age Groups**: These guidelines are another step in the effort for lowering the age threshold for performing a full sepsis work up (blood, urine, CSF). We have come a long way from performing full work ups in infants up to 90 days to lowering that threshold now to 21 days. Important to note that infants less than eight days were not included in this guideline.

- What a difference a week makes. For the 22 to 28 day-old group, it is still reasonable to err on the side of being more conservative. Again, we want to emphasize that if no CSF is obtained, these patients cannot go home. For the 29 to 60 day-old group, these guidelines offer a lot more room for discussion and shared decision making about LP, antibiotics, and disposition.

- Keep in mind that the overall trend is that risk of bacteremia and bacterial meningitis tend to decline with age, but the cut offs are still arbitrary. Obviously, there is not a dichotomy between infants and risk between 28 and 29 days of age or even 60 and 61 days of age. Risk is on a spectrum and will also require clinical judgment.

KEY TAKEHOME POINTS

- **2. Stop Saying Serious Bacterial Infection (SBI):** Many studies use the term SBI, but the authors recommend that we stop using this term and be specific as to what we are describing. Urinary tract infections are much more common than bacteremia and bacterial meningitis so putting all of these in one category can affect accuracy of prediction models. Additionally, bacterial meningitis is rare so finding a large enough sample for accurate prediction is very difficult.

KEY TAKEHOME POINTS

- **3. Inflammatory Markers**: Stop using white blood count (WBC). The authors emphasize **that no individual IM is reliable for risk stratification**. We rarely use one piece of laboratory information to make a clinical decision. ie WBC with (AUC= 0.48) making WBC not recommended for use. Medical decisions take place in a clinical context.
- Most of the IMs are laboratory values but it is important to note the one that is not, temperature >38.5°C. Of the laboratory criteria, the authors favor using procalcitonin with either ANC or CRP. If procalcitonin is not available or the results do not return in a reasonable time, they recommend both ANC and CRP and temperature >38.5°C. They provide values for **area under the curve** for procalcitonin(**0.82-0.91**), CRP(**0.75-0.77**), and ANC**(0.61-0.65**).

KEY TAKEHOME POINTS

- **4. Evidence-Based Medicine (Parental and Clinician Input**): This clinical guideline really hits the mark with its consideration of all three pillars of EBM. It incorporates and acknowledges clinical judgement, scientific evidence, and the patient or family's values and preferences in its recommendations. It is emphasized that many of these decisions should be made through collaborative discussion between families and clinicians acting in the best interest of the patient.

KEY TAKEHOME POINTS

- **5. Future Directions:** Where do we go from here? These new AAP guidelines with three algorithms are like a clinical decision instrument to help clinicians risk stratify patients. There are three steps in the development and testing of clinical decision instruments. The first step has been completed with the creation and publication of these AAP algorithms.

- The next step will be to test and prospectively validate what combination of inflammatory markers will yield the most accurate prediction model for a specific infection in different clinical environments.

- The third and final step, which is often not done, is to assess the impact of these algorithms on the clinical practice in these well-appearing febrile infants. It will also be interesting to see what role viral testing, biomarkers, and genomic testing will play. From an ER perspective time in ED and numbers of LP's performed.

PRACTICE SO YOU CAN GO HOME AND SLEEP

- BOTTOM LINE: THE ALGORITHMS IN THIS AAP CLINICAL PRACTICE GUIDELINE HAVE THE POTENTIAL TO DECREASE THE NUMBER OF LUMBAR PUNCTURES, HOSPITALIZATIONS, AND ANTIBIOTIC TREATMENT IN WELL-APPEARING, FEBRILE INFANTS.
- KEEP IN MIND THAT THESE ARE GUIDELINES AND DO NOT REPLACE CLINICIAN JUDGEMENT. THEY ALSO DO NOT CLAIM TO BE THE “STANDARD OF CARE”. IT IS IMPORTANT TO CONSIDER THE RISK TOLERANCE AND AVERSION OF THE CLINICIAN AND FAMILY WHEN IMPLEMENTING THESE RECOMMENDATIONS.

CASE

- Case Resolution: You explain to the parents your concerns and performing some urine and blood testing to help me determine the next best steps. After some time passes, the urinalysis does not appear to demonstrate any signs of urinary tract infection. The procalcitonin level is <0.5 ng/mL. The ANC is <4,000 mm3. You discuss the option of a lumbar puncture with the parents who express that they really do not want that their baby to undergo that procedure. After further discussion, they agree to admission in the hospital without antibiotics for observation.

References

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- 2. Biondi EA, McCulloh R, Staggs VS, et al. Reducing Variability in Infant Sepsis Evaluation (REVISE): A National Quality Initialtive. Pediatrics. 2019;144(3):e20182201
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Kupperman's comments

- The AAP Clinical Practice Guideline on the Evaluation and Management of Well-appearing Febrile Infants 8 to 60 Days Old represent a quantum advance in the approach to this conundrum for clinicians everywhere. It reflects approximately 15 years of work by a group of investigators and clinicians representing several specialities, and was reviewed and edited by many committees of the AAP.
- As a member of the team and writing group and an investigator of this topic for 25 years, I would like to add just a few comments, some of which are already alluded to in this well-considered DFTB commentary.
- No guideline or prediction rule is meant to replace clinician judgment. These evidence-based tools are meant to empower the clinician with evidence, to be used along with their judgment and other considerations, to make the best clinical decisions for the patient and family.
- The older guidelines and prediction rules dating back to the mid 1980s did not use statistically-derived thresholds for laboratory cutoffs, and frequently used lumbar punctures (LPs) in the evaluation of these infants. As a consequence, although the sensitivity of these previous algorithms were generally high, their specificities were not. And many infants received unnecessary invasive testing, empirical antibiotics and hospitalizations.
- Other fundamental limitations of older algorithms included:
    - Enrollment of hundreds rather than thousands of infants in the studies that derived these algorithms. Therefore, the resulting point estimates of risk were not precise.
    - Different temperature thresholds for inclusion.
    - Different age cutoffs for inclusion.
    - Different WBC thresholds for defining high and low risk
    - Different methods for obtaining and different cutoffs for UA WBC
    - Differential inclusion of stool and LP WBC counts included in the protocol
- The Yale Observational Scale score has proven not to be accurate for identifying infants with invasive bacterial infections (IBI; bacteremia, bacterial meningitis)
- The WBC count has poor accuracy for identifying IBIs in these febrile infants; the absolute neutrophil count (ANC) is significantly better
- Neither the WBC nor ANC are as accurate as the C-reactive protein (CRP) or serum procalcitonin (PCT) for identifying infants with IBIs
- However, the PCT is substantially better than the CRP – serum PCT has become a fundamental biomarker for highly accurate rules that do not use the LP to risk stratify, and help maintain high sensitivity AND specificity. While misclassifying few patients who have IBIs, prediction rules using PCT also help limit the use of LPs, empirical antimicrobials and hospitalizations when not indicated.
- The two rules that have emerged as most accurate (sensitive and specific) as they include the use of PCT are the PECARN prediction rule (rounded to thresholds of ANC of 4K cells / mm3 and PCT of 0.5 ng/ml and validated, making it safer, easier, and more generalizable while maintaining its accuracy) and the Step-by-Step rule. Neither rely on LPs and neither have reported misclassified patients with bacterial meningitis.
- The role of respiratory viral testing and how they impact the two above prediction rules are under investigation. The PECARN group reported results at the 2021 PAS and SAEM meetings
- Machine learning (ML) / artificial intelligence algorithms are being investigated by some (including the PECARN group) to enhance the accuracy of current algorithms to identify young febrile infants with IBIs. Although these algorithms may enhance accuracy by increasing specificity, there must be essentially no risk for missed bacterial meningitis. And ML based rules are frequently difficult to understand and require computerized decision support to implement.
- Genomic analysis (RNA transcriptional analyses, whole genome sequencing, etc) may soon prove to be substantially better than blood cultures for identifying pathogens. In the future, as these new technologies become more accurate and efficient, they may obviate "screening algorithms" and become both the screening test and the definitive test at the same time!
- HSV infections remain of critical importance in this age range. Given that most of these infections are in the first 3 weeks of life, LPs remain necessary in these early weeks, and the PECARN and Step-by-Step rules should not be applied to infants 3 weeks and younger.
- Finally, as no research will be impactful without robust implementation, we must be thinking about how to get the evidence provided in these AAP guidelines to the clinician at the bedside to effect change. Use of computerized decision support and evidence-enhanced clinician/parent decision support will be needed and are being studied by the PECARN group.

TABLE 3
Initial Empirical Antibacterial Therapy for Well-Appearing Febrile Infants 7 to 60 Days Old
•Use of a local antibiogram, if available, can guide; and Kimberlin Dchoices. Note: If a focus of infection such as pneumonia, cellulitis, gastroenteritis, or musculoskeletal infection is identified, different regimens that cover typical microbial pathogens for the site of infection should be administered. IM, intramuscular; IV, intravenous. Adapted from Bradley JS, Nelson JD, Barnett ED, et al, eds. *2019 Nelson's Pediatric Antimicrobial Therapy*. 25th ed. Itasca, IL: American Academy of Pediatrics; 2019W, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018.

Suspected Source of Infection	8–21 d Old	22–28 d Old	29–60 d Old
UTI[a]	Ampicillin IV or IM (150 mg/kg per d divided every 8 h) and either ceftazidime IV or IM (150 mg/kg per d divided every 8 h) or gentamicin IV or IM (4 mg/kg per dose every 24 h)	Ceftriaxone IV or IM (50 mg/kg per dose every 24 h)	Ceftriaxone IV or IM (50 mg/kg/dose every 24 h). Oral medications for infants older than 28 d.[b] Cephalexin 50–100 mg/kg per d in 4 doses or cefixime 8 mg/kg per d in 1 dose
No focus identified[c]	Ampicillin IV or IM (150 mg/kg per d divided every 8 h) and either ceftazidime IV or IM (150 mg/kg per d divided every 8 h) or gentamicin IV or IM (4 mg/kg per dose every 24 h)[d]	Ceftriaxone IV or IM (50 mg/kg per dose every 24 h)	Ceftriaxone IV or IM (50 mg/kg/dose every 24 h)
Bacterial meningitis[e]	Ampicillin IV or IM (300 mg/kg per d divided every 6 h) and ceftazidime IV or IM (150 mg/kg per d divided every 8 h)	Ampicillin IV or IM (300 mg/kg per d divided every 6 h) and ceftazidime IV or IM (150 mg/kg per d divided every 8 h)	Ceftriaxone IV (100 mg/kg or d once daily or divided every 12 h) or Ceftazidime IV (150 mg/kg or d divided every 8 h) and vancomycin[f] IV (60 mg/kg or d divided every 8 h)