Febrile Infants (< 90 days): Review of ANMC and AAP Guidelines

Alaska Tribal Health Webinar Series

Dr. Emily Hogeland
Pediatric Hospitalist
Alaska Native Medical Center
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Outline

- Brief overview of epidemiology
- Walk-through of ANMC guideline for febrile infants:
  - 0-28 days
  - 29-60 days
  - 61-90 days
- Comparisons to new AAP guideline

Introduction

- Clinical management of febrile infants ≤ 3 months of age has been the topic of research and debate for many years in the pediatric community
- Wide variety in clinical management persists despite attempts to standardize work-up with various guidelines
- In 2017, shortage of cefotaxime encouraged us to revise ANMC guidelines (previously updated 2006)
  - Major revision in Feb 2021
- Principal sources: Seattle Children's and YKHC guidelines (among several other institutions), literature review, departmental consensus with input from Antimicrobial Stewardship Program, ER, and peds ID

CLINICAL PRACTICE GUIDELINE

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old

Robert H. Pantell, MD, FAAP,[a] Kenneth B. Roberts, MD, FAAP,[b] William G. Adams, MD, FAAP,[c] Benard P. Dreyer, MD, FAAP,[d] Nathan Kuppermann, MD, MPH, FAAP, FACEP,[e] Sean T. O'Leary, MD, MPH, FAAP,[f] Kymika Okechukwu, MPA,[g] Charles R. Woods Jr, MD, MS, FAAP[h] SUBCOMMITTEE ON FEBRILE INFANTS

Epidemiology

- Infants between 0-3 months of age are particularly vulnerable to serious bacterial infections (SBI - i.e. meningitis, sepsis, and UTI) and may present with vague or non-specific symptoms, making it difficult to differentiate between viral and bacterial etiologies
  - UTI: ~10%
  - Bacteremia: ~2-4% (declines with age)
  - Meningitis: 0.5-1.3% (0-28 days), 0.25% (29-60 days)
- *E. Coli* and *GBS* most common pathogens for bacteremia/meningitis; *E. Coli* most common cause of UTI
- *Listeria* now quite rare

Rate of bacteremia by age group

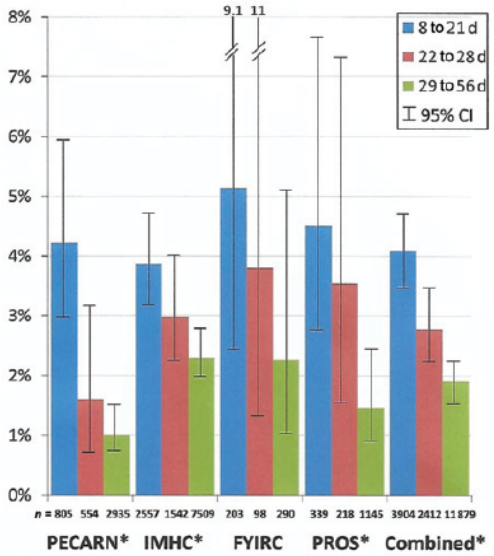
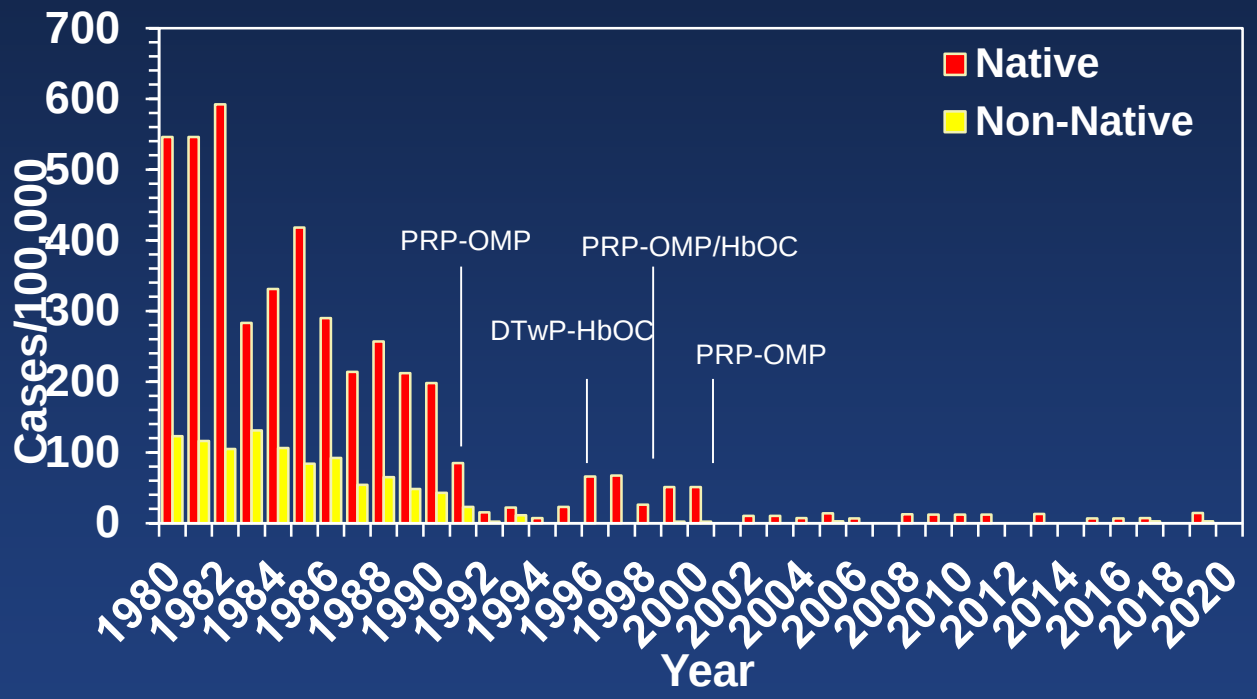


FIGURE 4 Rate of bacteremia by age groupings. * χ^2 for trend: $P < .001$. Note that the 95% CIs in the combined group do not overlap. Data were adapted from reference 61; from reference 94, with detail provided by C.L.B. (personal communication, 2020); from reference 24, with detail provided by Paul 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.

What about in Alaska?

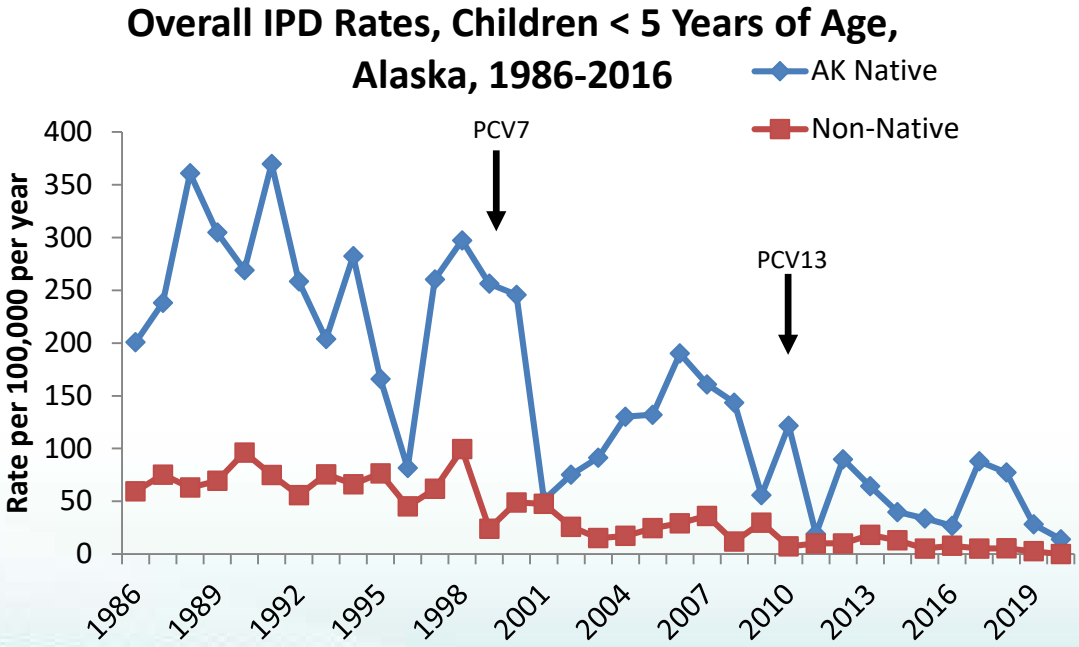
- Strong sense that rates of sepsis/meningitis are higher in the AK Native population, but limited data available
- Overall higher rates of Hib and pneumococcal disease
- Rates of invasive GBS have not been shown to be higher about AK Native children (Dr. Singleton, personal communication)

Invasive Hib Disease, Children Aged <5 Years, Alaska, 1980 - 2020



Singleton, et al. J Pediatr 2000; 137:313-20 and CDC, unpublished

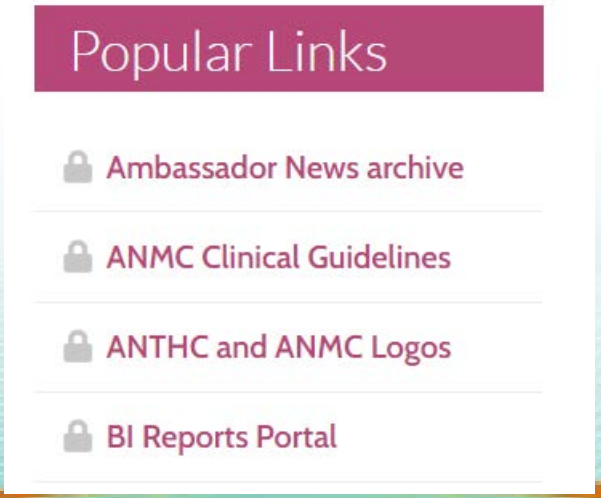
Invasive Pneumococcal Disease, Alaska Children, 1986-2020



ANMC Clinical Guideline

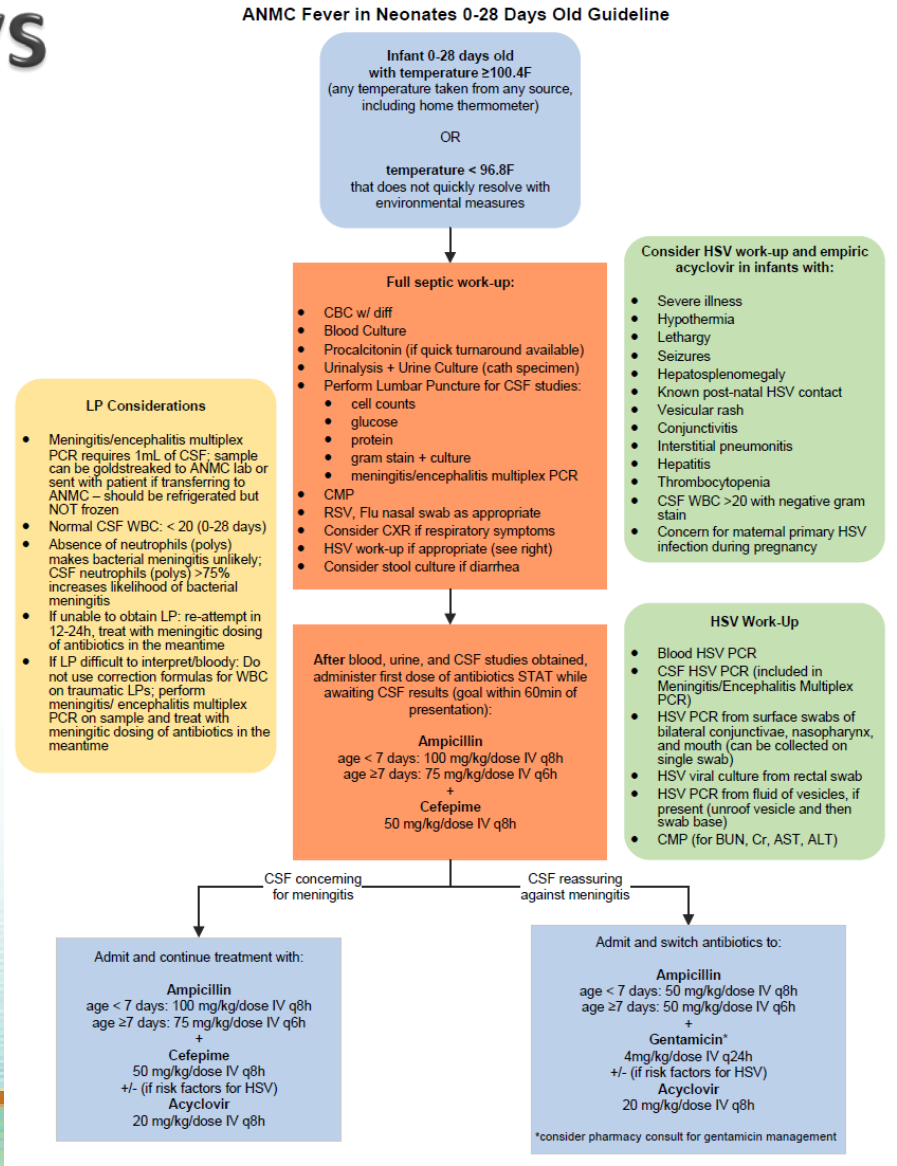
- Divided in to 3 age groups:
  - 0-28 days (presenting after initial hospital discharge)
  - 29-60 days
  - 61-90 days

anthcstaff.org:



anmc.org/clinical-guidelines

0-28 Days



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ANMC Guideline: 0-28 Days

Infant 0-28 days old
with temperature ≥100.4F
(any temperature taken from any source, including home thermometer)

OR

temperature < 96.8F
that does not quickly resolve with environmental measures

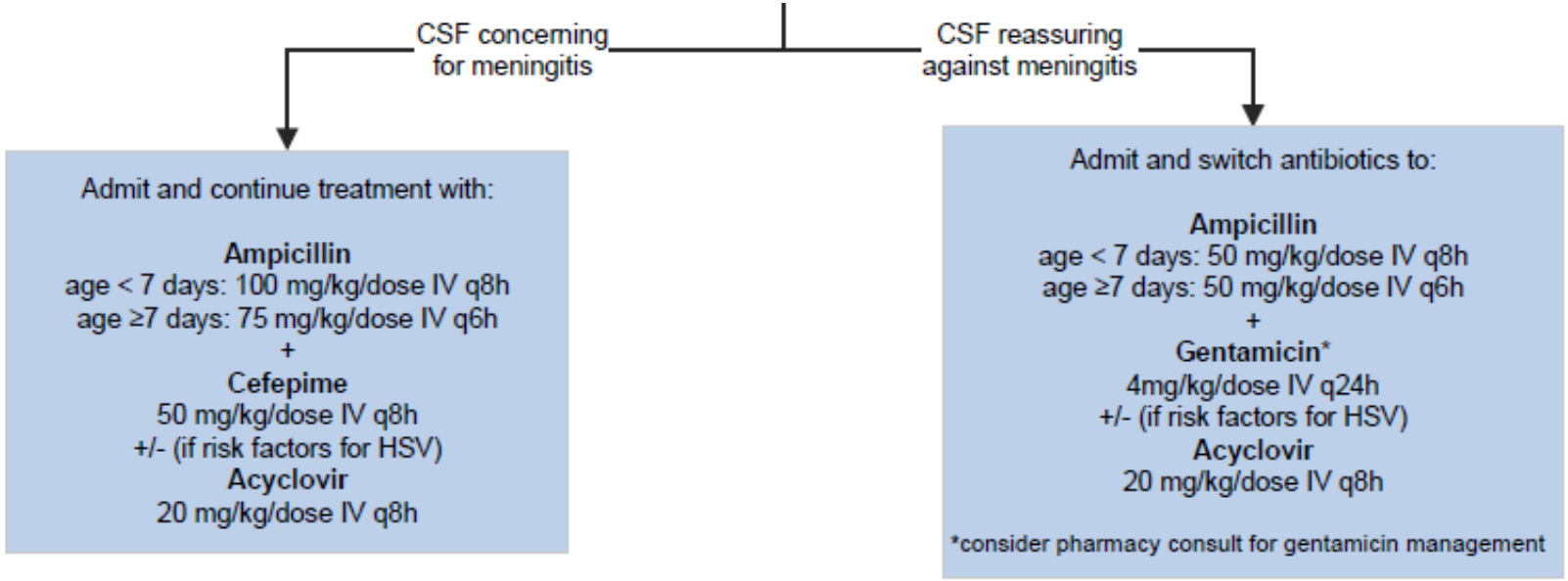
Full septic work-up:

- CBC w/ diff
- Blood Culture
- Procalcitonin (if quick turnaround available)
- Urinalysis + Urine Culture (cath specimen)
- Perform Lumbar Puncture for CSF studies:
  - cell counts
  - glucose
  - protein
  - gram stain + culture
  - meningitis/encephalitis multiplex PCR
- CMP
- RSV, Flu nasal swab as appropriate
- Consider CXR if respiratory symptoms
- HSV work-up if appropriate (see right)
- Consider stool culture if diarrhea

After blood, urine, and CSF studies obtained, administer first dose of antibiotics STAT while awaiting CSF results (goal within 60min of presentation):

Ampicillin
age < 7 days: 100 mg/kg/dose IV q8h
age ≥7 days: 75 mg/kg/dose IV q6h
+
Cefepime
50 mg/kg/dose IV q8h

ANMC Guideline: 0-28 Days



ANMC Guideline: 0-28 Days

LP Considerations

- Meningitis/encephalitis multiplex PCR requires 1mL of CSF; sample can be goldstreaked to ANMC lab or sent with patient if transferring to ANMC – should be refrigerated but NOT frozen
- Normal CSF WBC: < 20 (0-28 days)
- Absence of neutrophils (polys) makes bacterial meningitis unlikely; CSF neutrophils (polys) >75% increases likelihood of bacterial meningitis
- If unable to obtain LP: re-attempt in 12-24h, treat with meningitic dosing of antibiotics in the meantime
- If LP difficult to interpret/bloody: Do not use correction formulas for WBC on traumatic LPs; perform meningitis/ encephalitis multiplex PCR on sample and treat with meningitic dosing of antibiotics in the meantime

The FilmArray Meningitis/Encephalitis Panel tests for the presence of Ecoli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Strep agalactiae, Strep pneumoniae, CMV, Human herpesvirus 6, Human parechovirus, Varicella zoster virus, Enterovirus, Herpes simplex virus 1, Herpes simplex virus 2, and Cryptococcus neoformans/gattii nucleic acids directly from lumbar puncture collected CSF.
NOTE: Non-encapsulated strains of Neisseria meningitis and non-K1 Ecoli serotypes are not detected by this panel. Nor does this panel distinguish between latent and active CMV and HHV-6 infections. Viral shedding in the CSF often occurs in cases of zoster. VZV may not be the cause of CNS disease in these cases.
ASSAY IS NOT APPROPRIATE FOR USE AS A TEST-OF-CURE.

ANMC Guideline: 0-28 Days

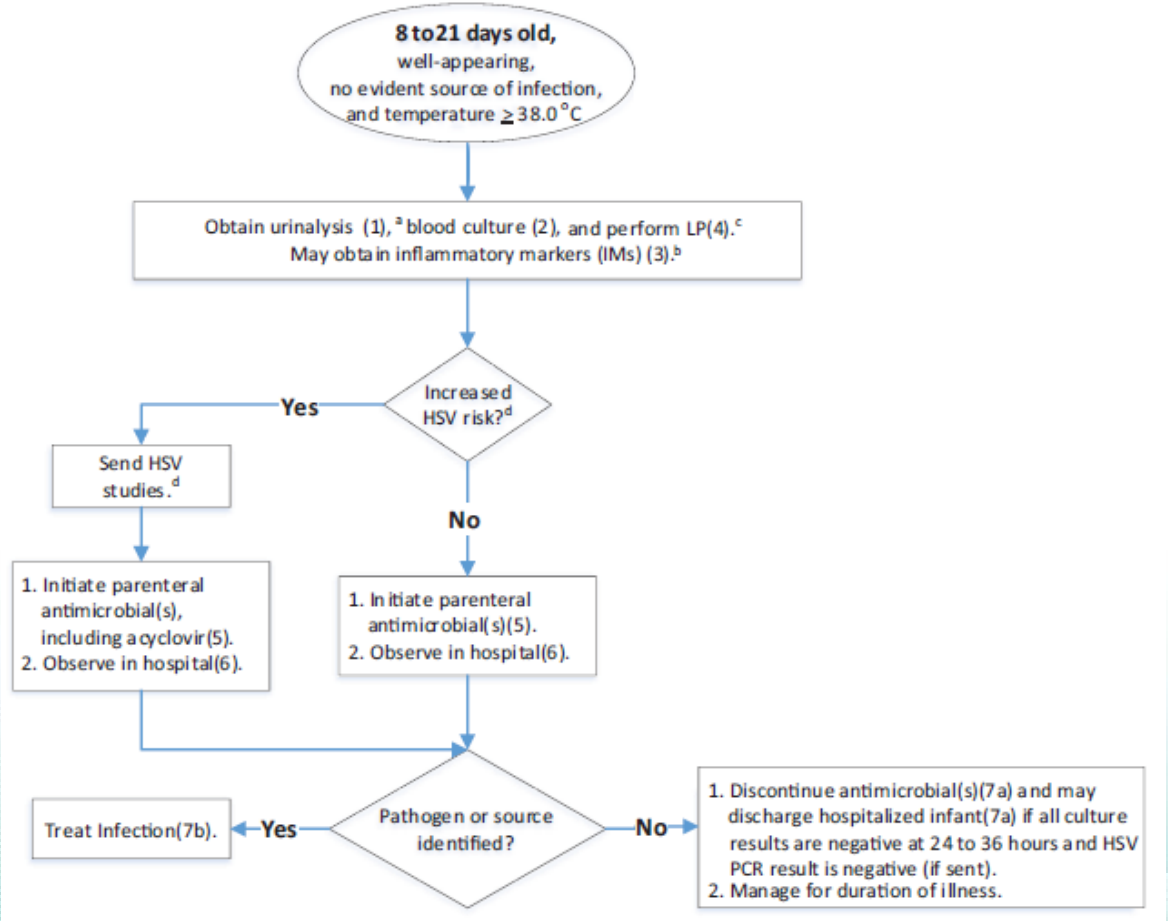
Consider HSV work-up and empiric acyclovir in infants with:

- Severe illness
- Hypothermia
- Lethargy
- Seizures
- Hepatosplenomegaly
- Known post-natal HSV contact
- Vesicular rash
- Conjunctivitis
- Interstitial pneumonitis
- Hepatitis
- Thrombocytopenia
- CSF WBC >20 with negative gram stain
- Concern for maternal primary HSV infection during pregnancy

HSV Work-Up

- Blood HSV PCR
- CSF HSV PCR (included in Meningitis/Encephalitis Multiplex PCR)
- HSV PCR from surface swabs of bilateral conjunctivae, nasopharynx, and mouth (can be collected on single swab)
- HSV viral culture from rectal swab
- HSV PCR from fluid of vesicles, if present (unroof vesicle and then swab base)
- CMP (for BUN, Cr, AST, ALT)

AAP Guideline: 8-21 Days



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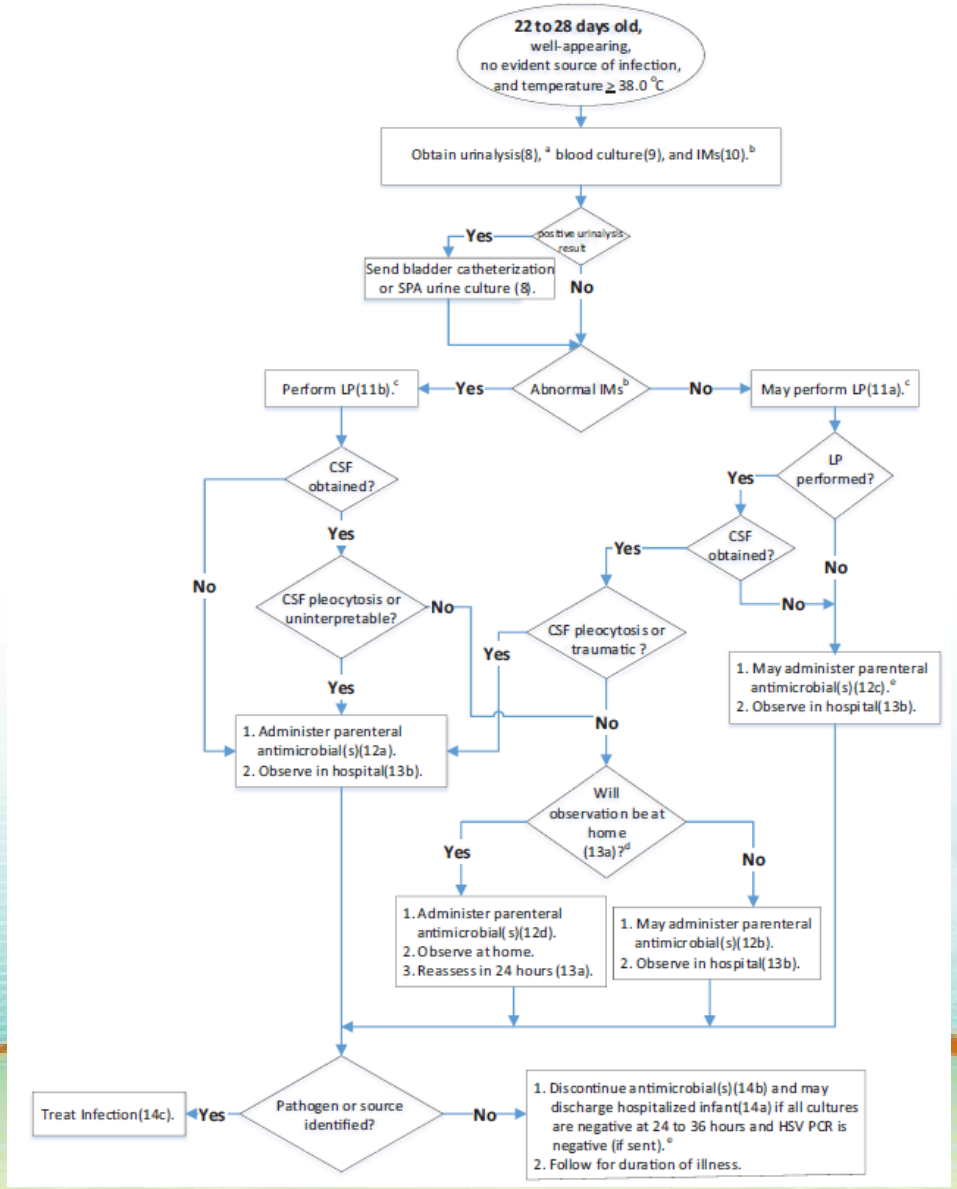
AAP Guideline: 22-28 Days



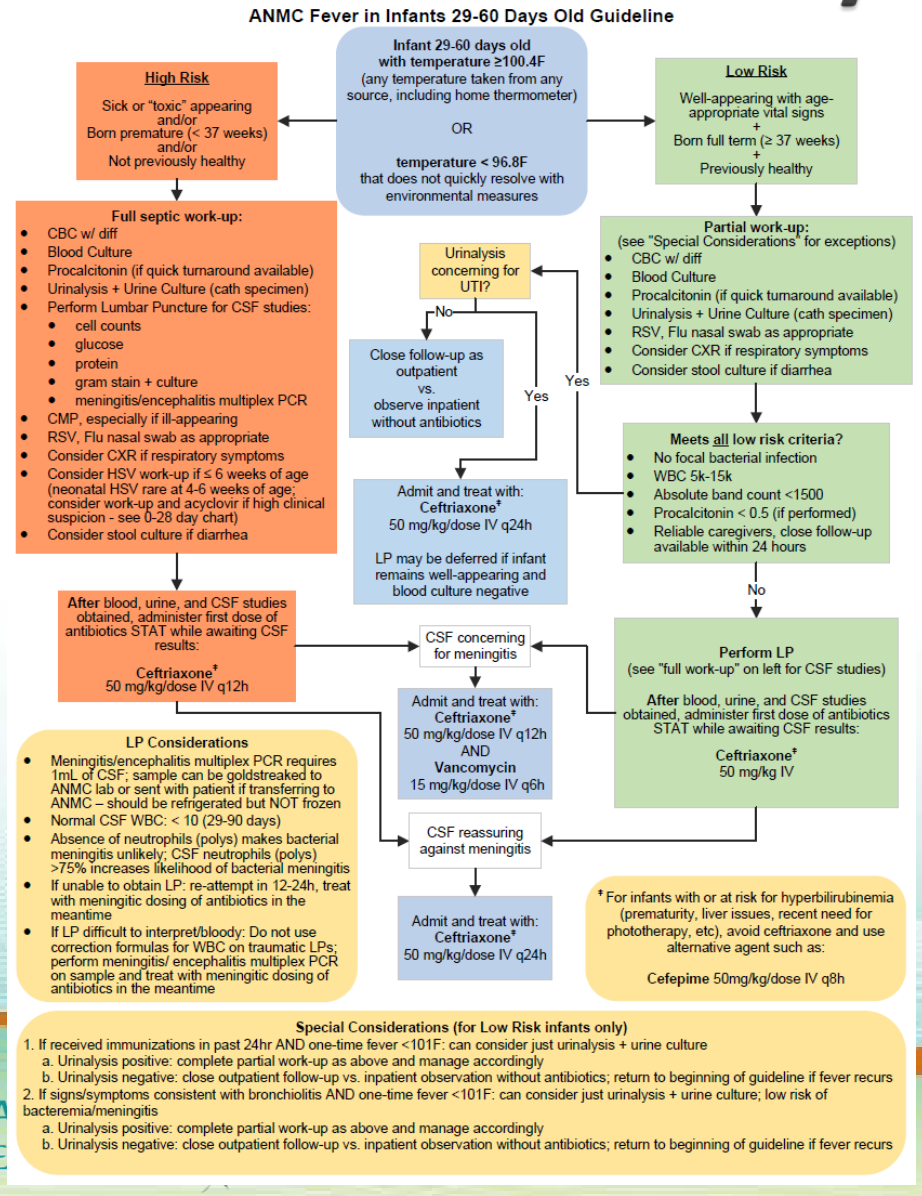
Main differences between ANMC vs AAP:

- Separate 22-28 day category
- Role for home observation (only when interpretable CSF obtained and reassuring)
- “May perform LP” if inflammatory markers normal vs. universal LP
- Option to use ceftriaxone for empiric treatment

0-28 Days – Take home points

- All febrile babies in this age group should get a full septic work-up with blood, urine, and CSF studies
- Admission on antibiotics for initial ~36 hours while cultures pending
- Minimize delays in definitive work-up (i.e. skip clinic visit if fever identified ahead of time -> straight to nearest ED or other facility that can perform necessary studies)

ANMC Guideline: 29-60 Days



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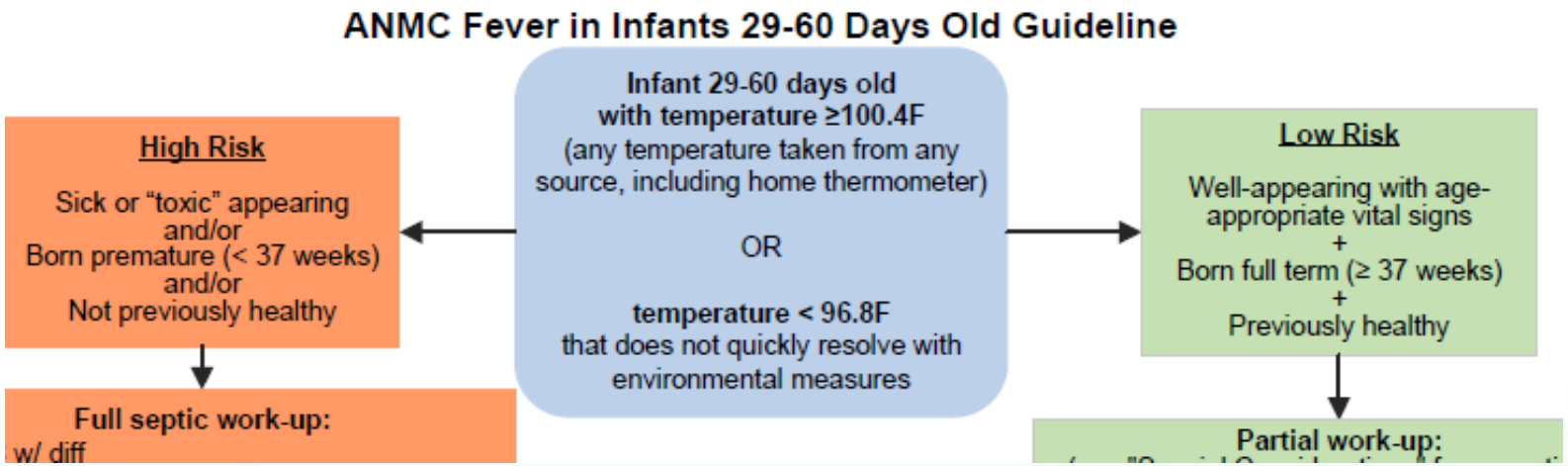
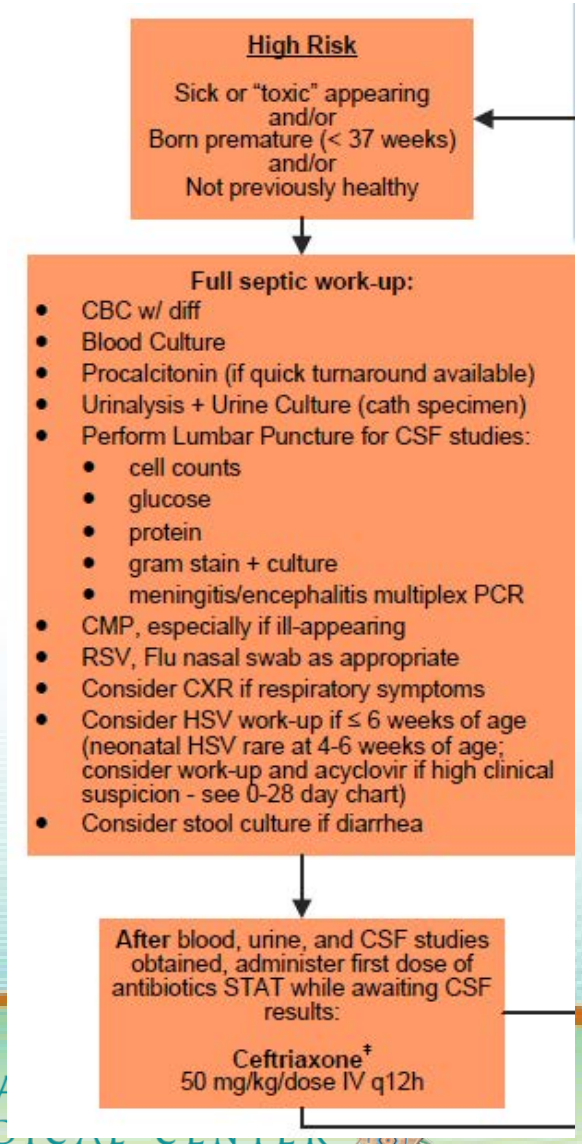
ANMC Guideline: 29-60 Days



ANMC Guideline: 29-60 Days



LP Considerations

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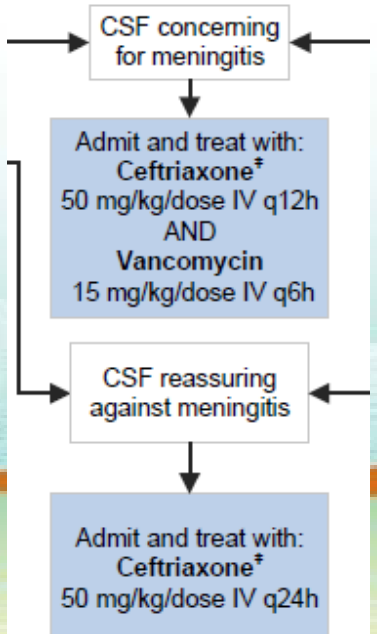
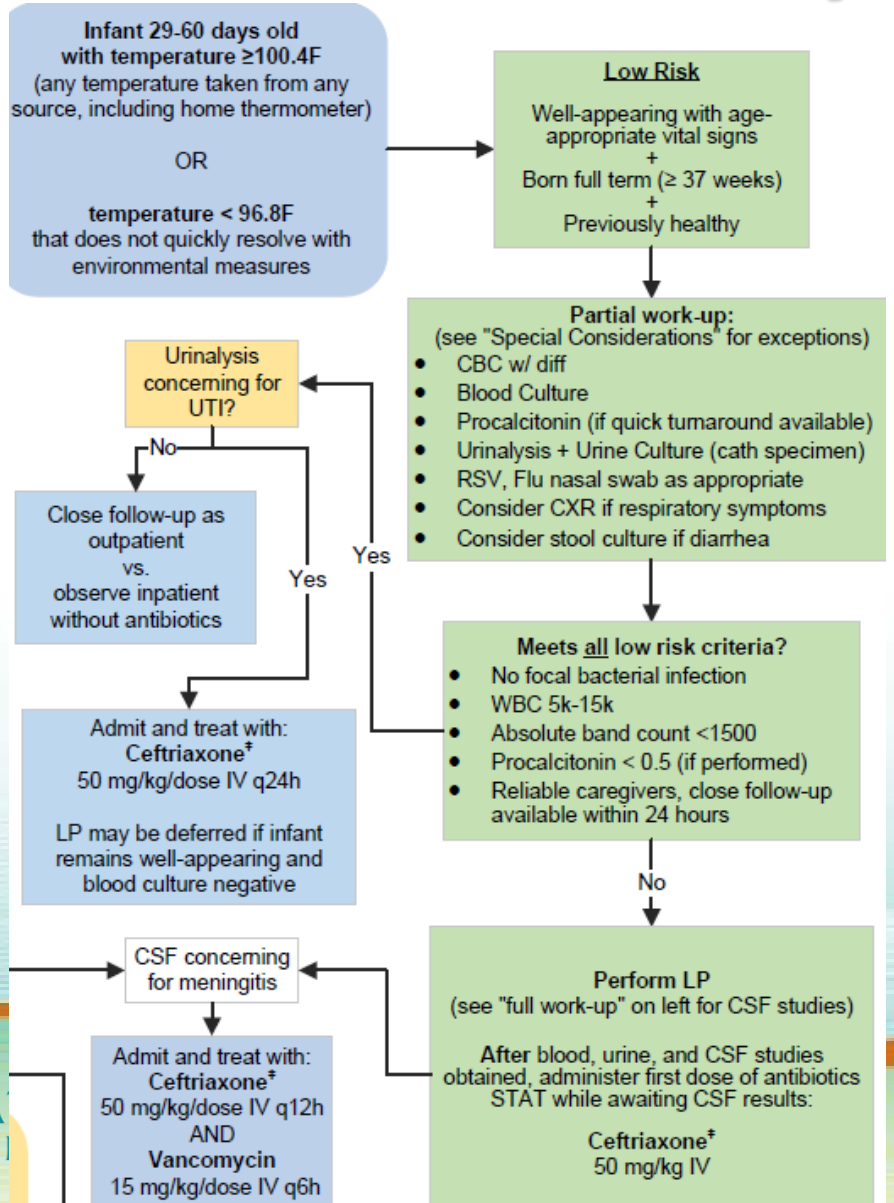
- Normal CSF WBC: < 10 (29-90 days)
- Absence of neutrophils (polys) makes bacterial meningitis unlikely; CSF neutrophils (polys) >75% increases likelihood of bacterial meningitis
- If unable to obtain LP: re-attempt in 12-24h, treat with meningitic dosing of antibiotics in the meantime
- If LP difficult to interpret/bloody: Do not use correction formulas for WBC on traumatic LPs; perform meningitis/ encephalitis multiplex PCR on sample and treat with meningitic dosing of antibiotics in the meantime



ANMC Guideline: 29-60 Days

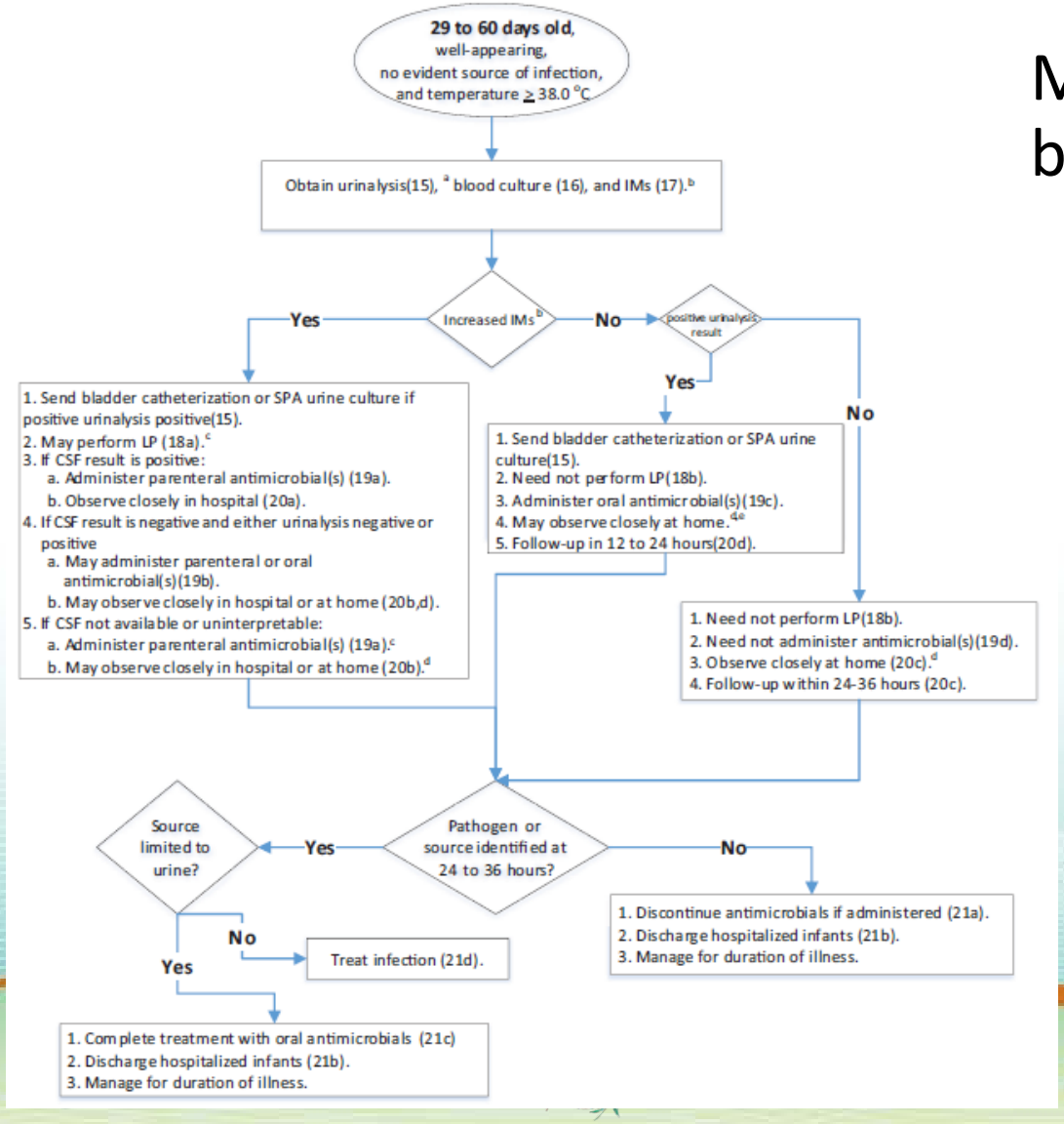


ANMC Guideline: 29-60 Days

Special Considerations (for Low Risk infants only)

1. If received immunizations in past 24hr AND one-time fever <101F: can consider just urinalysis + urine culture
   a. Urinalysis positive: complete partial work-up as above and manage accordingly
   b. Urinalysis negative: close outpatient follow-up vs. inpatient observation without antibiotics; return to beginning of guideline if fever recurs
2. If signs/symptoms consistent with bronchiolitis AND one-time fever <101F: can consider just urinalysis + urine culture; low risk of bacteremia/meningitis
   a. Urinalysis positive: complete partial work-up as above and manage accordingly
   b. Urinalysis negative: close outpatient follow-up vs. inpatient observation without antibiotics; return to beginning of guideline if fever recurs

AAP Guideline: 29-60 Days



Main differences between ANMC vs AAP:

- More detailed discussion of inflammatory markers, including fever > 38.5C (101.3F)
- “May perform LP” if elevated inflammatory markers
- Role for outpatient treatment for UTI

Inflammatory Markers

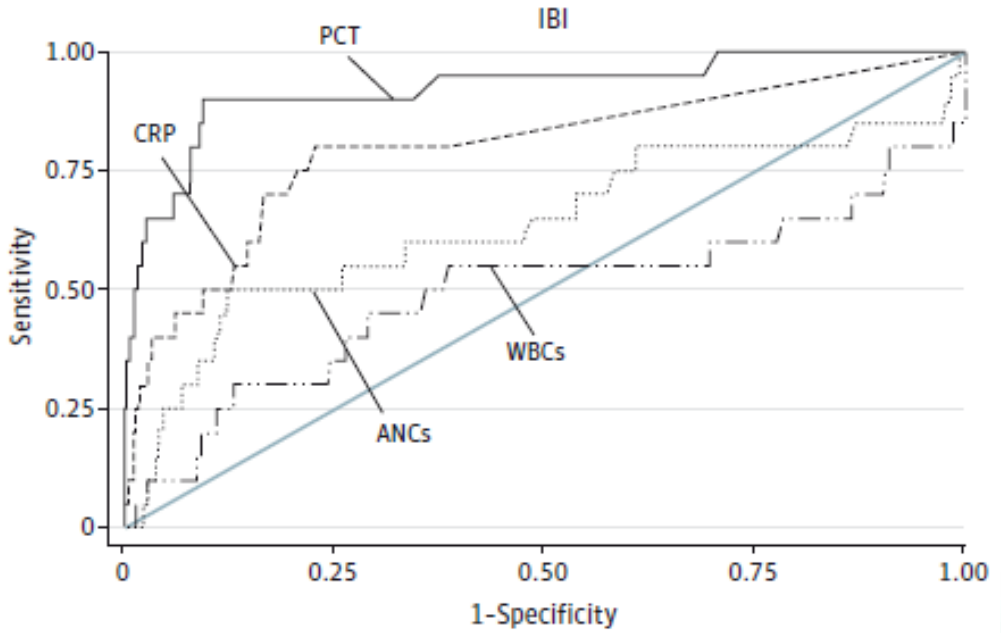
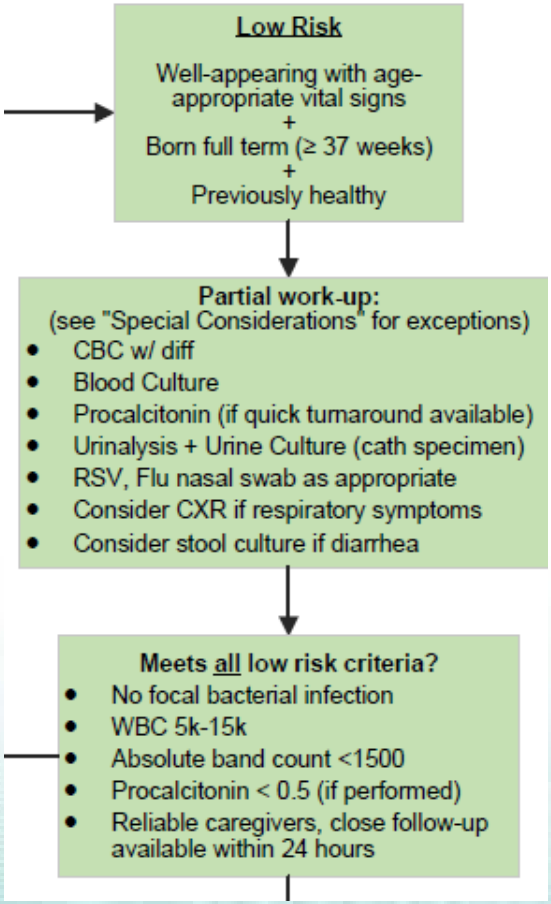


Table 4. Sensitivity, Specificity, and Likelihood Ratios (95% CIs) for Definite SBI and IBI at Various Thresholds

Biomarkers IBI	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
PCT ≥0.3 ng/mL	90 (68-99)	78 (75-80)	4.0 (3.3-4.8)	0.1 (0.03-0.4)
PCT ≥0.5 ng/mL	85 (62-97)	85 (82-87)	5.6 (4.4-7.0)	0.2 (0.06-0.5)
PCT ≥2.0 ng/mL	60 (36-81)	94 (92-95)	9.6 (6.3-14.7)	0.4 (0.2-0.7)
CRP ≥20 mg/L	75 (51-91)	75 (72-77)	3.0 (2.3-3.9)	0.3 (0.2-0.7)
CRP ≥40 mg/L	45 (23-69)	86 (84-88)	3.2 (1.9-5.3)	0.6 (0.4-0.9)

ANMC Guideline: 29-60 Days



Possible future modifications to "low risk" criteria:

- Substitute WBC criteria for ANC (1000-4000?) and delete band count criteria
- Add option for CRP < 2 mg/dL (20mg/L) if procalcitonin not available with rapid turnaround
- Consideration for fever >38.5C (101.3F)?

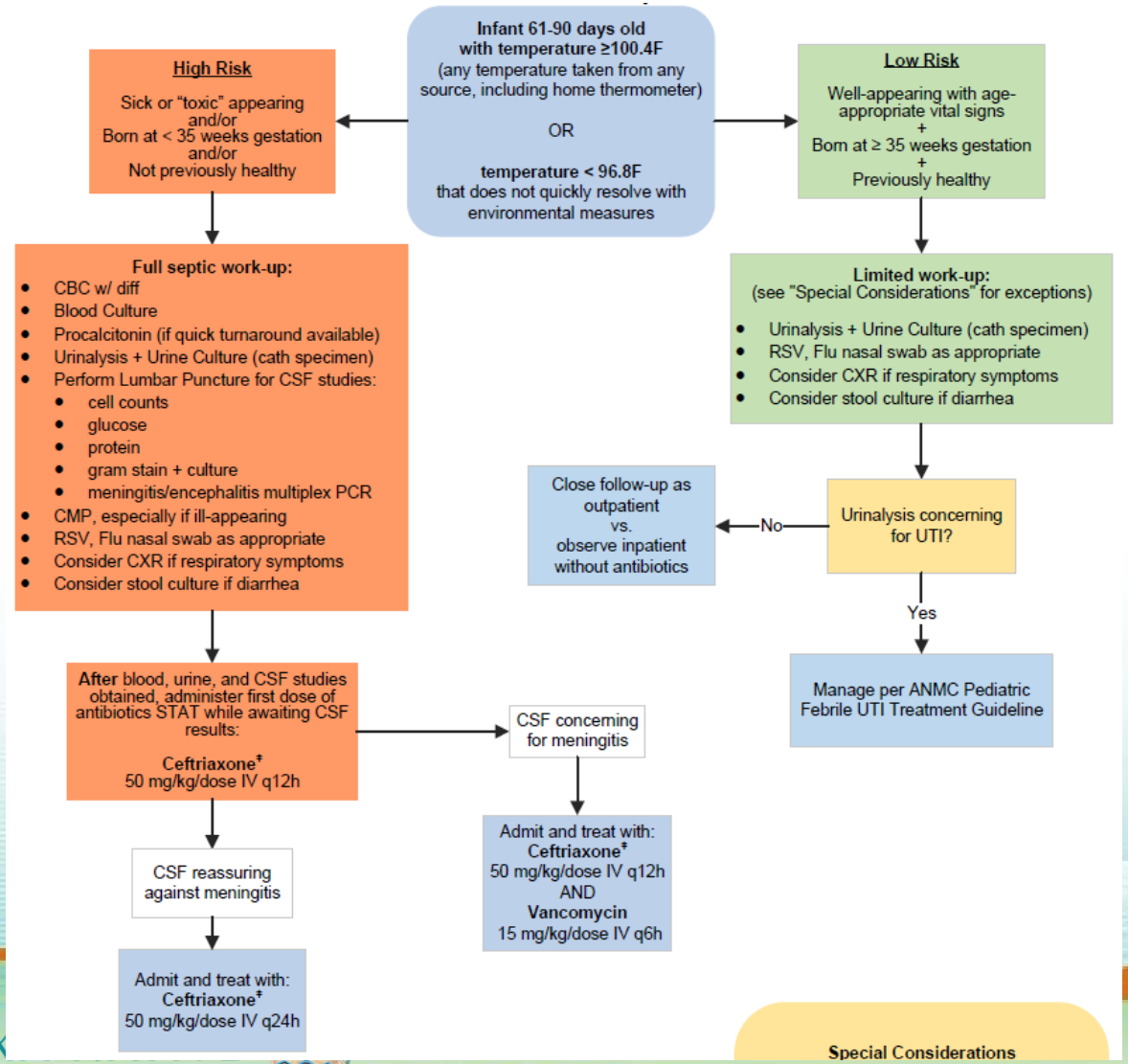
29-60 Days – Take home points

- Initial decision: term, well-appearing, and previously healthy?
- “No” to any: full work-up with blood, urine, and CSF studies; start antibiotics for initial ~36h of pending cultures
- “Yes” to all low-risk criteria: risk-stratification using lab values and other factors
- “Low risk” babies with UTI generally do not need LP
- Close follow-up important for any baby not hospitalized

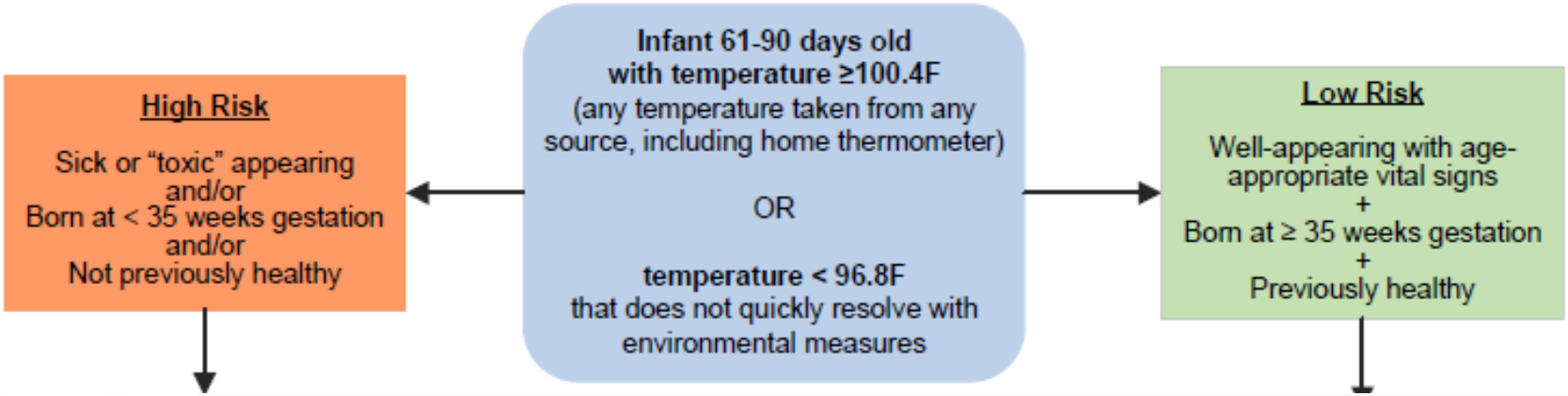
ANMC Guideline: 61-90 Days

- To include this age group or not?
- Very informal chart review of 61-90 day old febrile infants with any blood, urine, or CSF cultures at ANMC ED or inpatient peds (misses babies with work-ups done elsewhere or no work-up done) over 12-month period
- Of 18 infants, there were two cases of invasive bacterial infections (both had both sepsis + meningitis) in this age group (11%):
  - One baby who had multiple episodes of fever previously (before reaching 60 days) without complete work-up
  - An ex-26 weeker who had a prolonged NICU stay
- One UTI (6%)
- 56% were admitted, 47% got started on antibiotics
- 89% got blood cultures drawn, 83% got urine cultures, 33% underwent an LP (at least attempted)
- 33% were described as post-immunization fevers; none of these infants had a bacterial infection identified

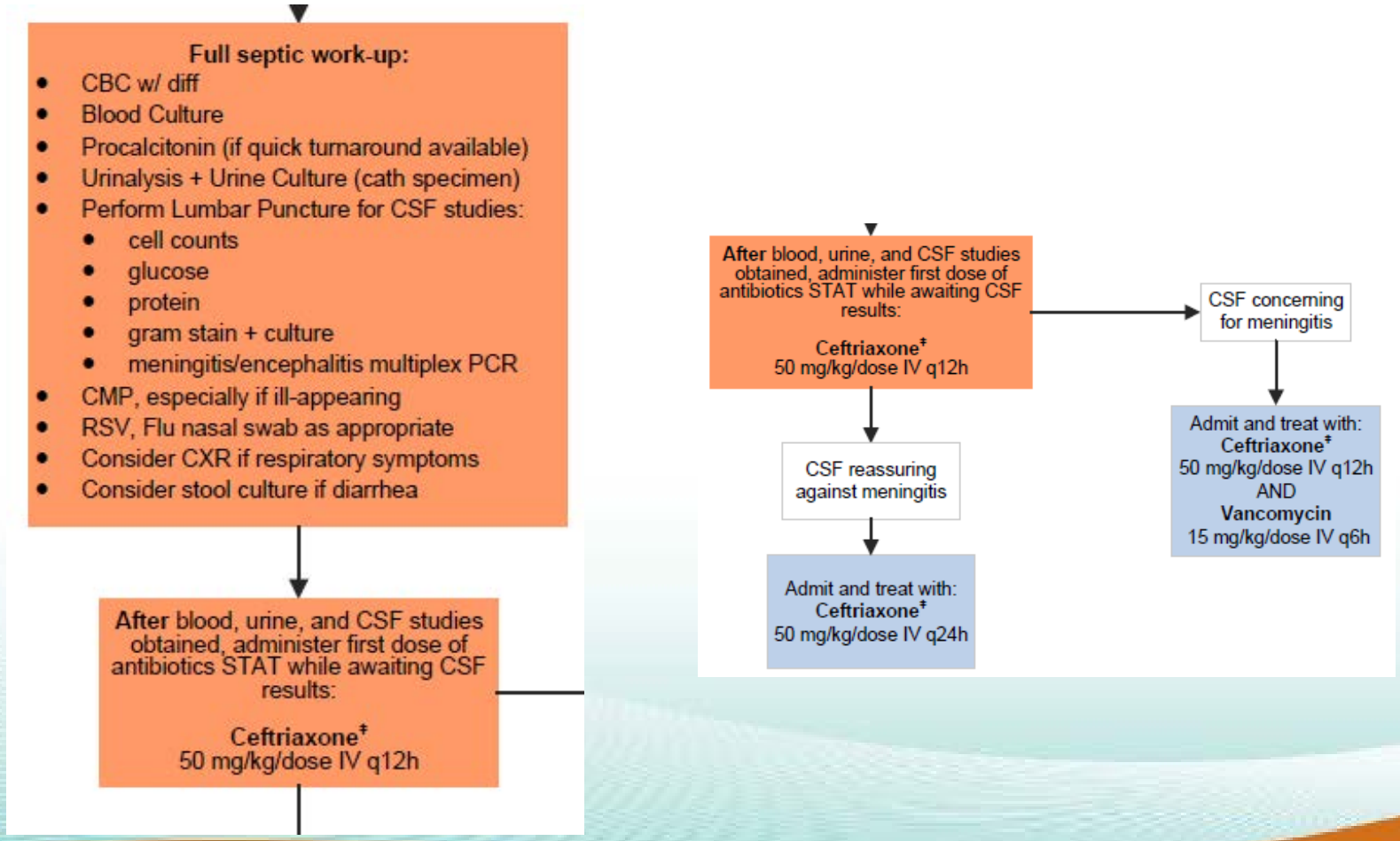
ANMC Guideline: 61-90 Days



ANMC Guideline: 61-90 Days



ANMC Guideline: 61-90 Days



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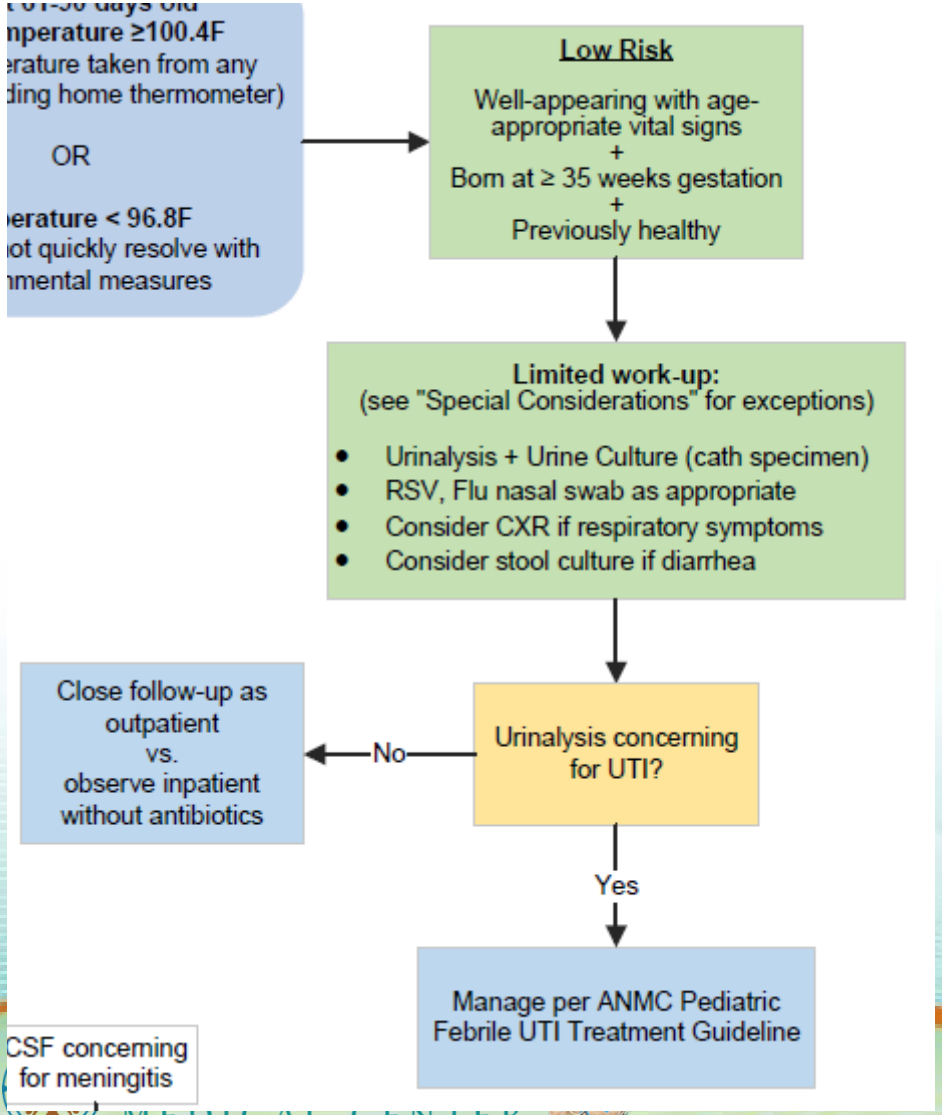
ANMC Guideline: 61-90 Days



Special Considerations
(for Low Risk infants only)

1. If received immunizations in past 24hr AND one-time fever <101F: can consider deferring any work-up, unless infant has urologic abnormality that increases risk of UTI in which case urinalysis and urine culture should be performed and managed accordingly

2. If signs/symptoms consistent with bronchiolitis AND one-time fever <101F: can consider deferring any work-up, unless infant has urologic abnormality that increases risk of UTI in which case urinalysis and urine culture should be performed and managed accordingly

61-90 Days – Take home points

- Initial decision: > 35 weeks, well-appearing, and previously healthy?
- “No” to any: full work-up with blood, urine, and CSF studies; start antibiotics for initial ~36h of pending cultures
- “Yes” to all low-risk criteria: do just do urine studies + other targeted testing

FAQ's

- Infants presenting with a focal source of infection (i.e. acute otitis media, pneumonia, omphalitis, cellulitis, osteomyelitis) may require targeted antibiotic therapy instead of, or in addition to, the standard antibiotics outlined in these guidelines
  - AAP recommends that acute otitis media does NOT count as an exclusion the guideline
- We do not recommend routine use of respiratory viral PCR panels, as bacterial infections may be overlooked if a fever is entirely ascribed to the presence of a virus, which may or may not be clinically significant
  - Very limited data on role of COVID; would generally not use COVID + swab as exemption to guideline

We're here 24/7

- Consults: ANMC Operator 907 563 2662
- Transfers: ANMC Transfer Center 907 729 2337
- TigerText: ANMC On-Call Pediatrics
  - If likely transfer, please call transfer center instead

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