University of Iowa Stead Family Children's Hospital

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Well-Appearing Febrile Infant Management Guideline

Objective

This document was created by a multidisciplinary effort among pediatric providers with the goal of providing condition/disease-specific care recommendations based on best available scientific evidence and/or consensus-based institutional recommendations. It is intended to decrease the complexity of medical decision making, reduce practice variation and improve the quality and safety of delivered care. These recommendations are intended to be utilized for the management of infants presenting with fever. This guideline does not replace the clinical judgment of the treating physician allowing deviation depending on unique clinical scenarios.

Definition

Infants between 8 to 60 days of life who are presenting with a fever, which is defined as an elevation of central temperature to 38°C or higher, are at potential risk of presenting with an invasive bacterial infection (IBI)[1]. Risk is related to age at time of presentation, with the highest risk carried by infants in the first few weeks of life. Therefore, for febrile infants who are otherwise well-appearing this guide is stratified based on the following age classifications:

Infants appearing moderately to severely ill are at higher risk for IBI and therefore are excluded from this guideline. While a consensus definition or measure to adequately define well-appearing versus ill-appearing has not been established, for the purposes of this guideline ill appearance is defined as:

- Clinical presentation characterized by lethargy, evidence of poor perfusion, cyanosis, hypoventilation or hyperventilation
- Significant abnormalities in vital signs

Acknowledging that the distinction between "well" and "ill" may not be so easily defined, it is at the discretion of the treating physician to determine whether an infant meets the objective definition of well-appearing.

Parental report of fever at home, regardless of the measurement technique used, is to be believed and the infant should be further evaluated[2]. There is mixed evidence as to whether the clinician should rely on the ability of a parent to detect a fever in the infant population without a thermometer. Whether the clinician accepts the report as sole evidence of fever is an individual decision[3,4].

It should be recognized that parents and practitioners have different levels of risk aversion and thresholds for treatment should be incorporated into shared decision-making.

Inclusion Criteria

Infants 8 to 60 days of age who:

- Are at home after discharge from a newborn nursery or were born at home
- Are evaluated in the UIHC emergency department, UIHC Quick/Urgent Care clinics or other UIHC ambulatory clinics
- Have a documented temperature of greater than or equal to 38.0°C within the last 24 hours measured by any route either by a healthcare worker or by parental report
- Have a gestational age between 37 and 42 weeks

Exclusion Criteria

Infants <7 days or >60 days of age, or any infant without a fever either on exam or by history. The following populations merit additional consideration specific to their condition and are intended to be excluded from the algorithms:

- Preterm infants (<37 weeks' gestation)
- Infants <2 weeks of age whose prenatal courses were complicated by maternal fever, infection and/or antimicrobial use
- Febrile infants with high suspicion for herpes simplex virus (HSV) infection (e.g. vesicles or other risk factors detailed in Table 2)
- Infants with a focal bacterial infection (e.g. cellulitis, omphalitis, septic arthritis, osteomyelitis) whose infection should be managed according to accepted disease-specific standards
- Infants with clinical bronchiolitis with or without positive test results for respiratory syncytial virus (RSV). A review by Ralston et al of 11 studies of bronchiolitis found no cases of meningitis, and researchers in 8 studies reported no cases of bacteremia.
- Infants with documented or suspected immune compromise
- Infants whose neonatal course was complicated by surgery or infection
- Infants with congenital or chromosomal abnormalities
- Medically fragile infants requiring some form of technology or ongoing therapeutic intervention to sustain life
- Infants who have received immunizations within the last 48 hours. The incidence of postimmunization fevers ≥38°C is estimated to be >40% within the first 48 hours

Management of Well Appearing Febrile Infants

Well Appearing Infants 8-21 Days Old

Evaluation

1. Sterile urine specimen obtained via catheterization or suprapubic aspirate sent for:
    a. Urinalysis with microscopy, **and**
    b. Urine culture
        - Urine culture will be **discontinued** if the urinalysis result is **not** abnormal, with abnormal defined as:
        i. Presence of any leukocyte esterase, and/or
        ii. >5 WBC per high power field

        - Parents opposed to catheterization should be offered a choice of suprapubic aspiration and informed of higher rate of ambiguous/false-positive culture results obtained from bagged or voided specimens

2. Blood culture

3. Blood for baseline labs:
    a. Renal function
    b. Inflammatory markers (CBC with differential and CRP)
    c. Hepatic function panel

4. CSF via lumbar puncture should be obtained and sent for:
    a. Cell counts with differential
    b. CSF protein and glucose
    c. Routine Gram stain and bacterial culture
    d. Meningitis/encephalitis PCR panel

        - The presence of CSF pleocytosis for age (defined in **Table 1**) should raise suspicion for HSV and warrant addition of acyclovir to the empiric antimicrobial regimen

5. Evaluation for HSV should be considered based on the presence of risk factor(s) (see **Table 2**). Additional diagnostic studies specific for the evaluation of HSV disease (**Table 3**) are:
    a. HSV surface swabs for PCR from: conjunctivae, mouth, nasopharynx and rectum
    b. Swab for PCR from an unroofed vesicle (if present)
    c. HSV blood PCR
    d. If not already performed, CSF for cell counts, protein, glucose and meningitis/encephalitis PCR panel

Table 1: Physiologic Range of CSF Values in Infants Without IBI, Viral Meningoencephalitis or Traumatic CSF

	Age (days)	**Range**
WBC (per mm^3)	1-28	0-18
	29-60	0-8.5
Protein (mg/dL)	1-28	15.8-131
	29-60	5.5-105.5
Glucose (mg/dL)	1-28	30-61
	29-60	20.6-65.6
RBC (per mm^3)	1-28	0-236
	29-60	0-64.5

Table 2: Risk Factors for Perinatal HSV

Maternal Factors	**Infant Factors**
Maternal history of genital HSV lesions 48 hours before to 48 hours after delivery	Seizures
Maternal history of fever 48 hours before to 48 hours after delivery	Hypothermia (<36.4°C)
	Mucous membrane ulcers and/or vesicular rash
	CSF pleocytosis in the absence of a positive Gram stain
	Leukopenia[5], WBC count less than: 1-4 weeks of life: 5000 per mm^3 1-24 months of life: 6000 per mm^3
	Thrombocytopenia (<150,000 per mm^3)[6]
	Elevated ALT >50 U/L (at least 1.5x ULN for age)[7]

Table 3: Diagnostic Testing for HSV Disease of the Newborn

Surface swabs of mouth, nasopharynx, conjunctivae and anus for PCR	LAB2467
Swab for PCR from an unroofed vesicle (if present)	LAB2467
Blood for PCR	LAB7879
CSF for PCR (AKA meningitis/encephalitis panel)	LAB8514
ALT	LAB132

Treatment

1. Empiric antibiotics at meningitic dosing (see **Table 4**) **should** be started in **all** infants following evaluation

    a. In the absence of CSF pleocytosis, dosing can be adjusted based on the suspected source of infection (see **Table 5**)

2. **All** infants will be monitored **in-house** while awaiting bacterial culture results

3. Definitive antimicrobial therapy should be targeted at pathogen(s) identified in urine, blood and/or CSF with duration of therapy consistent with the nature of the disease, responsible organism and the infant's response to treatment

4. Parenteral antimicrobial agents may be discontinued when the following criteria are met:
    a. Culture results are negative for 24-36 hours of incubation or *only* positive for contaminants
    b. Meningitis/encephalitis panel is negative for all bacterial targets
    c. The infant continues to appear clinically well or is improving
    d. If CSF is positive for Enterovirus, antimicrobial agents can be discontinued or held if:
        - There is absence of significant CSF pleocytosis with a neutrophil predominance, and/or
        - There is no reason to suspect a concomitant bacterial infection, such as with abnormal inflammatory markers

Table 4: Empiric Antimicrobial Dosing for Infants 8-21 Days of Life

Antimicrobial Agent	**Dose***
Ampicillin	75 mg/kg/***dose*** IV/IM Q6h (total 300 mg/kg/***day***)
Ceftazidime	50 mg/kg/***dose*** IV/IM Q8h (total 150 mg/kg/***day***)
Acyclovir (if concerned for HSV, **Table 2**)	20 mg/kg/***dose*** IV Q8h (total 60 mg/kg/***day***)

*Consider the need for dose adjustment based on results of baseline renal function testing

Table 5: Empiric Therapy for Infants 8-21 Days of Life Based on Suspected Source of Infection

Suspected Source of Infection	**Antimicrobial**
UTI (based on abnormal UA)	1. Ampicillin 50 mg/kg/***dose*** IV/IM Q8h (total 150 mg/kg/***day***), **AND** 2. Ceftazidime 50 mg/kg/***dose*** IV/IM Q8h (total 150 mg/kg/***day***), **OR** Gentamicin 4 mg/kg/***dose*** IV Q24h
No Focus Identified (possible bacteremia)	1. Ampicillin 50 mg/kg/***dose*** IV/IM Q8h (total 150 mg/kg/***day***), **AND EITHER** 2. Ceftazidime 50 mg/kg/***dose*** IV/IM Q8h (total 150 mg/kg/***day***), **OR** Gentamicin 4 mg/kg/***dose*** IV Q24h
Bacterial Meningitis (based on CSF pleocytosis)	1. Ampicillin 75 mg/kg/***dose*** IV/IM Q6h (total 300 mg/kg/***day***), **AND** 2. Ceftazidime 50 mg/kg/***dose*** IV/IM Q8h (total 150 mg/kg/***day***)
Concern for HSV (see **Table 2**)	Add Acyclovir 20 mg/kg/***dose*** IV Q8h (total 60 mg/kg/***day***)

Summary of Evaluation and Management of Well-Appearing Febrile Infants 8-21 Days Old

8-21 Days of Life				
Urinalysis	**Inflammatory Markers**	**Lumbar Puncture**	**Antibiotics**	**Disposition**
Positive or negative	Not indicated (but can be performed)	Perform LP	IV antibiotics	Admit

Well Appearing Infants 22-28 Days Old

Evaluation

1. Sterile urine specimen obtained via catheterization or suprapubic aspirate sent for:
    a. Urinalysis with microscopy, **and**
    b. Urine culture
        - Urine culture will be **discontinued** if the urinalysis result is **not** abnormal, with abnormal defined as:
            i. Presence of any leukocyte esterase, and/or
            ii. >5 WBC per high power field

        - A urine specimen may be obtained via bag or spontaneous or stimulated void and sent **ONLY** for urinalysis with microscopy; *if* urinalysis is abnormal a sterile urine specimen obtained via catheterization or suprapubic aspirate should be sent for culture

        - Parents opposed to catheterization should be offered a choice of suprapubic aspiration and informed of higher rate of ambiguous/false-positive culture results obtained from bagged or voided specimens

        - Technique for collecting urine via bladder stimulation involves[8]:
            i. Clean the genital area with warm water and soap
            ii. One provider holds the child under the armpits with legs dangling
            iii. Physician provider applies bladder stimulation by gently tapping the suprapubic area at a frequency of 100 taps per minute for 30 seconds, followed by massaging the lumbar paravertebral area in the lower back for 30 seconds. Both maneuvers are repeated until micturition started or for a maximum of 3 minutes
            iv. A third provider collects a midstream urine sample is collected in a sterile container

2. Blood culture

3. Blood for baseline labs:
    a. Renal function
    b. Inflammatory markers (CBC with differential and CRP)
    c. Hepatic function panel

4. Assess baseline markers of inflammation and if abnormal an LP **should** be performed. Abnormal markers of inflammation are defined as:
    a. Temperature > 38.5°C, or
    b. Absolute neutrophil count > 5200 cells/mm^3 or <1000 cells/mm^3, or
    c. CRP > 2.0 mg/dL

5. CSF via lumbar puncture **should** be obtained if markers of inflammation are abnormal and fluid sent for:
    a. Cell counts with differential
    b. CSF protein and glucose
    c. Routine Gram stain and bacterial culture
    d. Meningitis/encephalitis PCR panel

        - The presence of CSF pleocytosis for age (defined in **Table 6**) should raise suspicion for HSV and warrant additional testing (see **Table 7**) and addition of acyclovir (see **Table 8)** to the empiric antimicrobial regimen.

        - Clinicians *may* obtain CSF for analysis if all the following criteria are met:
            i. Urinalysis is negative or positive,
            ii. Inflammatory markers are normal

iii. Blood and urine cultures have been obtained
iv. Infant is hospitalized

5. Evaluation for HSV should be considered based on the presence of risk factor(s) (see **Table 8**). Additional diagnostic studies specific for the evaluation of HSV disease (**Table 7**) are:
    a. HSV surface swabs for PCR from: conjunctivae, mouth, nasopharynx and rectum
    b. Swab for PCR from an unroofed vesicle (if present)
    c. HSV blood PCR
    d. If not already performed, CSF for cell counts, protein, glucose and meningitis/encephalitis PCR panel

Table 6: Physiologic Range of CSF Values in Infants Without IBI, Viral Meningoencephalitis or Traumatic CSF

	Age (days)	**Range**
WBC (per mm^3)	1-28	0-18
	29-60	0-8.5
Protein (mg/dL)	1-28	15.8-131
	29-60	5.5-105.5
Glucose (mg/dL)	1-28	30-61
	29-60	20.6-65.6
RBC (per mm^3)	1-28	0-236
	29-60	0-64.5

Table 7: Diagnostic Testing for HSV Disease of the Newborn

Surface swabs of mouth, nasopharynx, conjunctivae and anus for PCR	LAB2467
Swab for PCR from an unroofed vesicle (if present)	LAB2467
Blood for PCR	LAB7879
CSF for PCR (AKA meningitis/encephalitis panel)	LAB8514
ALT	LAB132

Table 8: Risk Factors for Perinatal HSV

Maternal Factors	**Infant Factors**
Maternal history of genital HSV lesions 48 hours before to 48 hours after delivery	Seizures
Maternal history of fever 48 hours before to 48 hours after delivery	Hypothermia (<36.4°C)
	Mucous membrane ulcers and/or vesicular rash
	CSF pleocytosis in the absence of a positive Gram stain
	Leukopenia[5], WBC count less than: 1-4 weeks of life: 5000 per mm^3 1-24 months of life: 6000 per mm^3
	Thrombocytopenia (<150,000 per mm^3)[6]
	Elevated ALT >50U/L (at least 1.5x ULN for age)[7]

Treatment

1. Clinicians **should** administer parenteral antimicrobial therapy and manage infants **in-house** if any of the following apply:
    a. CSF analysis demonstrates pleocytosis, or
    b. Urinalysis result is abnormal

    c. Clinicians **may** administer parenteral antimicrobial therapy and manage infants **in-house** if all the following apply
        i. CSF analysis is normal, and
        ii. Urinalysis is normal, and
        iii. Any inflammatory marker is abnormal

        - **If no CSF was obtained and the decision is made to administer antibiotics a discussion between the ED and admitting providers will be held to ensure agreement about appropriateness of withholding LP *and* initiation of antibiotics**

2. Selection of empiric antimicrobial therapy will be dependent on the suspected source of infection (**Table 9**)
    a. Empiric antibiotics at meningitic dosing should be started in **all** infants where an LP is performed or required
    b. In the absence of CSF pleocytosis, dosing can be adjusted based on the suspected source of infection

        - Any infant in whom CSF was not obtained or is uninterpretable should be managed **in-house**

3. Infants **may** be discharged home if all the following criteria are met:
    a. Urinalysis is normal
    b. Inflammatory markers obtained are normal
    c. CSF analysis is normal or enterovirus-positive
    d. Instructions on indications for re-evaluation are provided, including:
        i. Change in general appearance, particularly dusky color or respiratory distress
        ii. Change in behavior including lethargy, irritability, inconsolable crying, difficulty in consoling/comforting
        iii. Difficulty feeding
        iv. Vomiting
        v. Decreased urine output
    e. Plan for re-evaluation in 24 hours is established
    f. Plan in place in case of clinical change, including communication between family and providers and access to emergency medical care

        - A dose of ceftriaxone **should** be administered for infants who will be managed at home

4. Parenteral antimicrobial agents may be discontinued when the following criteria are met:
    a. Culture results are negative for 24-36 hours of incubation or *only* positive for contaminants
    b. Meningitis/encephalitis panel is negative for all bacterial targets (if CSF was obtained)
    c. The infant is clinically well or improving
    d. There are no other sources of bacterial infection, such as otitis media

5. Definitive antimicrobial therapy should be targeted at pathogen(s) identified in urine, blood and/or CSF with duration of therapy consistent with the nature of the disease, responsible organism and the infant's response to treatment.

Table 9: Initial Empiric Therapy for Infants 22-28 Days of Life

Suspected Source of Infection	
UTI (based on abnormal UA)	Ceftriaxone 50 mg/kg/***dose*** IV/IM Q24h
No Focus Identified (possible bacteremia)	Ceftriaxone 50 mg/kg/***dose*** IV/IM Q24h
Bacterial Meningitis (based on CSF pleocytosis)	1. Ampicillin 75 mg/kg/**dose** IV/IM Q6h (total 300 mg/kg/**day**), **AND** 2. Ceftriaxone 50 mg/kg/**dose** IV/IM Q12h (total 100 mg/kg/**day**)
Concern for HSV (see **Table 8**)	Add Acyclovir 20 mg/kg/***dose*** IV Q8h (total 60 mg/kg/***day***)

Summary of Evaluation and Management of Well-Appearing Febrile Infants 22-28 Days Old

22-28 Days of Life				
Urinalysis	**Inflammatory Markers**	**Lumbar Puncture**	**Antibiotics**	**Disposition**
Negative	Negative	LP *may* be performed	LP *not* performed --> option to admit off antibiotics*	Observe in hospital
			LP performed --> may give IV antibiotics (required if CSF abnormal)	May discharge home if CSF normal and ceftriaxone x1 given
Positive	Negative	LP *may* be performed*	IV antibiotics*	Admit
Positive or negative	Positive	Perform LP	IV antibiotics	Admit

***Opportunity for shared decision making if no CSF is obtained and the decision is made to administer antibiotics**

<u>Well Appearing Infants 29-60 Days Old</u>

Evaluation

1. A urine specimen should be obtained by either:
    - Bag, spontaneous void or stimulated void (non-sterile sample), or
    - Bladder catheterization or suprapubic aspirate (sterile sample)

    a) If urine is obtained via bag, spontaneous void or stimulated void, send specimen **ONLY** for urinalysis with microscopy
        i. *If* urinalysis is abnormal obtain a **sterile** specimen via bladder catheterization or suprapubic aspirate to send for urine culture (do NOT send non-sterile sample for culture)
        ii. Abnormal urinalysis is defined as:
            1. Presence of any leukocyte esterase, and/or
            2. >5 WBC per high power field

    b) If urine is obtained via bladder catheterization or suprapubic aspirate and urinalysis is **abnormal**, send sample for urine culture

    - Urine culture will be **discontinued** if the urinalysis result is **not** abnormal

    - Technique for collecting urine via bladder stimulation involves[8]:
        i. Clean the genital area with warm water and soap
        ii. One person holds the child under the armpits with legs dangling
        iii. Physician provider applies bladder stimulation by gently tapping the suprapubic area at a frequency of 100 taps per minute for 30 seconds, followed by massaging the lumbar paravertebral area in the lower back for 30 seconds. Both maneuvers are repeated until micturition started or for a maximum of 3 minutes

iv. A third person collects a midstream urine sample in a sterile container

2. Blood culture

3. Blood for baseline labs:
    a. Renal function
    b. Inflammatory markers (CBC with differential and CRP)
    c. Hepatic function panel

4. Assess baseline markers of inflammation and if abnormal an LP **may** be performed. Abnormal markers of inflammation are defined as:
    a. Temperature > 38.5°C
    b. Absolute neutrophil count > 5200 cells/mm^3 or <1000 cells/mm^3
    c. CRP > 2.0 mg/dL

        - Individual values that are exceedingly high or low or several inflammatory markers are abnormal should be considered in decision-making, because they, in all likelihood, increase the risk of bacterial meningitis

4. CSF via lumbar puncture **may** be obtained if markers of inflammation are abnormal and fluid sent for:
    a. Cell counts with differential
    b. CSF protein and glucose
    c. Routine Gram stain and bacterial culture
    d. Meningitis/encephalitis PCR panel

        - CSF need **NOT** be obtained if all inflammatory markers are normal

5. Although uncommon in this age group, evaluation for HSV should be considered based on the presence of risk factor(s) (see **Table 10**). Additional diagnostic studies specific for the evaluation of HSV disease (**Table 7**) are:
    a. HSV surface swabs for PCR from: conjunctivae, mouth, nasopharynx and rectum
    b. Swab for PCR from an unroofed vesicle
    c. HSV blood PCR
    d. If not already performed, CSF for cell counts, protein, glucose and meningitis/encephalitis PCR panel

Table 10: Risk Factors for Perinatal HSV

Maternal Factors	**Infant Factors**
Maternal history of genital HSV lesions 48 hours before to 48 hours after delivery	Seizures
Maternal history of fever 48 hours before to 48 hours after delivery	Hypothermia (<36.4°C)
	Mucous membrane ulcers and/or vesicular rash
	CSF pleocytosis in the absence of a positive Gram stain
	Leukopenia[5], WBC count less than: 1-4 weeks of life: 5000 per mm^3 1-24 months of life: 6000 per mm^3
	Thrombocytopenia (<150,000 per mm^3)[6]
	Elevated ALT >50 U/L (at least 1.5x ULN for age)[7]

Table 11: Diagnostic Testing for HSV Disease of the Newborn

Surface swabs of mouth, nasopharynx, conjunctivae and anus for PCR	LAB2467
Swab for PCR from an unroofed vesicle (if present)	LAB2467
Blood for PCR	LAB7879
CSF for PCR (AKA meningitis/encephalitis panel)	LAB8514
ALT	LAB132

Treatment

1. Antimicrobial Therapy
    a. Parenteral antimicrobial therapy **should** be initiated if CSF analysis shows pleocytosis

        - Parenteral antimicrobial therapy **may** be initiated if:
            i. CSF analysis is normal (if obtained), AND
            ii. Any inflammatory marker is abnormal

        - **If no CSF was obtained and the decision is made to administer antibiotics a discussion between the ED and admitting providers will be held to ensure agreement about appropriateness of withholding LP *and* initiation of antibiotics**

    b. Enteral antimicrobial therapy should be initiated if:
        i. CSF analysis is normal (if obtained),
        ii. Urinalysis result is abnormal, AND
        iii. No inflammatory marker is abnormal

    c. Antimicrobial therapy need NOT be initiated while awaiting culture results if:
        i. CSF analysis, if obtained, is normal or enterovirus-positive
        ii. Urinalysis is negative, AND
        iii. No inflammatory marker is abnormal

Table 12: Initial Empiric Therapy for Infants 29-60 Days of Life

Suspected Source of Infection	
UTI (based on abnormal UA)	Oral medications for infants older than 28 days ▪ Cephalexin 33 mg/kg/***dose*** PO TID (total 100 mg/kg/***day***) (preferred), **OR** ▪ Cefixime 4 mg/kg/***dose*** PO BID (total 8 mg/kg/***day***) (alternative)
No Focus Identified (possible bacteremia)	Ceftriaxone 50 mg/kg/***dose*** IV/IM Q24h
Bacterial Meningitis (based on CSF pleocytosis)	1. Ceftriaxone 50 mg/kg/***dose*** IV/IM divided Q12h (total 100 mg/kg/***day***), **AND** 2. Vancomycin 20 mg/kg IV load once, **AND** 3. Vancomycin 15 mg/kg/***dose*** IV Q8h (for PMA <44 weeks), (total 45 mg/kg/***day***), **OR** 4. Vancomycin 15 mg/kg/***dose*** IV Q6h (for PMA ≥44 weeks), (total 60 mg/kg/***day***)
Concern for HSV (see **Table 10**)	Add Acyclovir 20 mg/kg/***dose*** IV Q8h (total 60 mg/kg/***day***)

2. Disposition
    a. Infants **should** be hospitalized if CSF (if obtained) is abnormal
        i. Infants without interpretable CSF may be managed at home without antimicrobial treatment if:
            1. Urinalysis is negative
            2. All inflammatory markers obtained are normal,
            3. Parents can return promptly if there is a change in the infant's condition, AND

4. Plan for re-evaluation in 24 hours is established

b. Infants **may** be hospitalized if any inflammatory marker is abnormal

c. Infants **should** be managed at home if:
   i. CSF analysis, if obtained, is normal
   ii. Urinalysis is negative
   iii. All inflammatory markers are normal
   iv. Instructions on indications for re-evaluation are provided, including:
      1. Change in general appearance, particularly dusky color or respiratory distress
      2. Behavior change including lethargy, irritability, inconsolable crying, difficulty in consoling/comforting
      3. Difficulty feeding
      4. Vomiting
      5. Decreased urine output
   v. Plan for re-evaluation in 24-36 hours is established
   vi. Plan in place in case of clinical change, including communication between family and providers and access to emergency medical care

3. Definitive Management
   a. Antimicrobial agents should be discontinued when
      i. All bacterial cultures are negative at 24-36 hours
      ii. Infant is clinically well or improving, AND
      iii. There is no other infection requiring treatment

   b. Clinicians should discharge hospitalized patients with positive urine culture results if:
      i. Blood culture is negative
      ii. CSF culture, if obtained, is negative
      iii. Infant is clinically well or improving, AND
      iv. There are no other reasons for hospitalization

Summary of Evaluation and Management of Well-Appearing Febrile Infants 29-60 Days Old

29-60 Days of Life				
Urinalysis	**Inflammatory Markers**	**Lumbar Puncture**	**Antibiotics**	**Disposition**
Negative	Negative	No LP	No antibiotics	Observe closely at home, follow up in 24 hours
Positive	Negative	No LP	Oral antibiotics	Observe closely at home, follow up in 24 hours
Positive or negative	Positive	May perform LP, then:		
		If CSF is negative:	IV or oral antibiotics (if UA abnormal)	May observe in hospital or home
		If CSF is positive:	IV antibiotics	Admit
		If CSF is not obtained or uninterpretable:*	IV antibiotics*	May observe in hospital or home

***Opportunity for shared decision making if no CSF is obtained and the decision is made to administer antibiotics**

Abbreviations

IBI: invasive bacterial infection
UIHC: University of Iowa Hospitals and Clinics
HSV: herpes simplex virus
RSV: respiratory syncytial virus
WBC: white blood cell
CBC: complete blood count
CRP: C-reactive protein
CSF: cerebrospinal fluid
PCR: polymerase chain reaction
RBC: red blood cell
ULN: upper limit of normal
ALT: alanine transaminase
IV: intravenous
IM: intramuscular
UTI: urinary tract infection
UA: urinalysis
LP: lumbar puncture
ED: emergency department
PMA: post-menstrual age

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Management of Well-Appearing Febrile Neonates 8- to 21-day old

ᵻ Well-appearing, no evident source of infection, and temperature ≥ 38ºC

Obtain CBC with differential, CRP, CMP, Blood Culture, UA with microscopy, Urine Culture ⁜
CSF for cell count with differential, CSF protein and glucose, Gram stain and bacterial culture and Meningitis PCR

Increased HSV risk?*

Yes

Obtain the following labs:
- CSF Meningitis/Encephalitis PCR (M/E PCR)
- HSV surface swabs of the conjunctivae, mouth, nasopharynx and rectum for PCR
- HSV PCR swab from unroofed vesicle (if any)
- HSV blood PCR

Start Acyclovir 20 mg/kg IV Q8h

No

Start IV antibiotics at MENINGITIC doses. Observe in hospital

Pathogen or Source Identified?

UTI (abnormal UA) **OR** No Focus Identified (possible bacteremia)

1. Ampicillin 50 mg/kg IV/IM Q8h, **AND EITHER**
2. Ceftazidime 50 mg/kg IV/IM Q8h, **OR**
3. Gentamicin 4mg/kg IV Q24h

No

Bacterial Meningitis (based on CSF pleocytosis)

Meningitic Dose
1. Ampicillin 75 mg/kg IV/IM Q6h, **AND**
2. Ceftazidime 50 mg/kg/day IV/IM Q8h

Clinicians should discontinue parenteral antimicrobial agents and discharge hospitalized patients when ALL the following criteria are met:
1. Culture results are negative for 24 to 36 hours or only positive for contaminants
2. Meningitis/Encephalitis PCR panel is negative for all targets
3. The infant continues to appear clinically well or is improving (e.g., fever, feeding)
4. If the CSF is positive for Enterovirus, and there is
   A. absence of CSF pleocytosis with neutrophil predominance and/or
   B. there is no reason to suspect a concomitant bacterial infection, such as with abnormal inflammatory markers

⁜ **How to Obtain Urine Specimen?**
Obtain Urine Specimen by Catheterization or Suprapubic Aspiration for Urinalysis and Urine Culture.
For 8-21 days of age, urine specimen should be sterile. Do NOT send bagged specimens for culture. Discontinue Urine Culture if UA is not abnormal i.e. any LE and/or >5WBC per high power field.

*** Consider HSV if any of the following are present**
- Maternal history of genital HSV lesions or fevers from 48 hours before to 48 hours after delivery
- Seizures
- Hypothermia (≤36.4ºC)
- Mucous membrane ulcers and/or vesicular rash
- CSF pleocytosis (WBC>18) in the absence of BOTH a positive Gram stain and a positive M/E PCR for bacterial pathogens
- Leukopenia <5 000/mm^3
- Platelets <150 000/mm^3
- ALT >50 U/L

ᵻ Exclusion Criteria
1. Preterm infants (<37 weeks' gestation)
2. Infants <2 wks of age whose perinatal courses were complicated by maternal fever, infection, and/or antibiotics use
3. Febrile infants with high suspicion of HSV infection
4. Infants with a focal bacterial infection
5. Infants with clinical bronchiolitis
6. Infants with immune compromise
7. Infants whose neonatal course was complicated by surgery or infection
8. Infants with congenital or chromosomal abnormalities
9. Medically fragile infants requiring technology or ongoing therapeutic intervention to sustain life
10. Infants who received immunizations within last 48hrs

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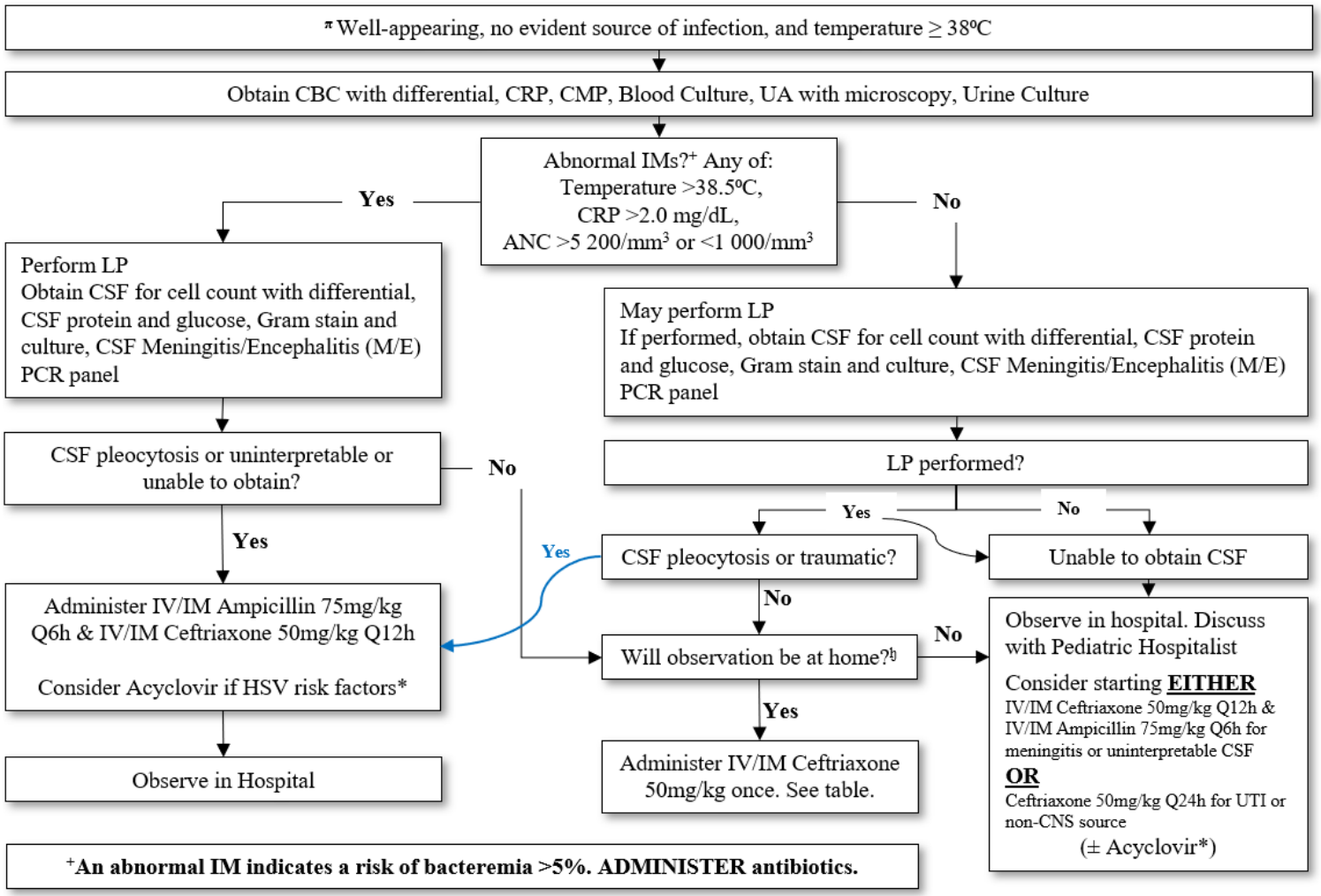
Management of Well-Appearing Febrile Neonates 22- to 28-day old



⁺An abnormal IM indicates a risk of bacteremia >5%. ADMINISTER antibiotics.

ᵬ Clinicians may manage infants at home if ALL the following criteria are met:

Labs:	Teaching:	Follow-up:
1. UA is normal 2. No IM obtained is abnormal 3. CSF analysis is normal or entero-virus positive	Verbal teaching and written instructions have been provided for monitoring throughout the period of time at home for the following: 1. change in general appearance, particularly a dusky color, or respiratory or other distress; 2. behavior change, including lethargy, irritability, inconsolable crying, difficulty in consoling/comforting, or other evidence of distress; 3. difficulty feeding; 4. vomiting; and 5. decreased urine output	1. Follow-up plans for reevaluation in 24 hours have been developed and are in place. 2. Plans have been developed and are in place in case of change in clinical status, including means of communication between family and providers and access to emergency medical care.

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Management of Well-Appearing Febrile Infant 29- to 60-day old

ᵠ Well-appearing, no evident source of infection, and temperature ≥ 38ºC

Obtain CBC with differential, CRP, CMP, Blood Culture, UA with microscopy, Urine Culture

Abnormal IMs? Any of:
Temperature >38.5ºC,
CRP >2.0 mg/dL,
ANC >5 200/mm^3 or <1 000/mm^3

Yes

May perform LP

Individual IM values that are exceedingly high/low, or several abnormal IMs should be considered in decision-making

If CSF result is abnormal:

a) Administer parenteral antimicrobials¥
b) Observe in hospital

If CSF result is negative and either urinalysis is negative or abnormal:

a) May admit for observation (if IM abnormal): may administer parenteral antimicrobials¥. Discuss with Pediatric Hospitalist
b) May observe at home: administer oral antimicrobials¥ if UA is abnormal

If CSF not available or uninterpretable:
Admit for observation and administer parenteral antimicrobials¥ after discussion with pediatric hospitalist

No

Abnormal Urinalysis?
(>5WBC per high power field and/or any LE)

Yes

1. Need not perform LP
2. Administer oral antimicrobials¥
3. May observe at home
4. Follow up in 12-24 hrs

No

1. Need not perform LP
2. Need not administer antimicrobials
3. Observe at home
4. Follow-up within 24 hrs

Pathogen or Source Identified at 24 to 36 hrs?

No

1. Discontinue antimicrobials if administered
2. Discharge hospitalized infants
3. Manage for duration of illness

Yes

Source of infection limited to urine?

No

Treat infection

Yes

1. Complete treatment with oral antimicrobials
2. Discharge hospitalized infants
3. Manage for duration of illness

¥ Antimicrobials

	Parenteral	Oral
Meningitis OR Uninterpretable CSF findings	Ceftriaxone 50 mg/kg Q12h AND Vancomycin loading dose 20 mg/kg. Subsequent Vancomycin doses: < 44 wks PMA: 15 mg/kg Q8h ≥ 44 wks PMA: 15 mg/kg Q6h	
UTI or non-CNS source	Ceftriaxone 50mg/kg Q24h	Cephalexin 33 mg/kg TID for 10 days
HSV infection*	Acyclovir 20 mg/kg Q8h	

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