Fever Without a Source Clinical Guideline

Definition

For the purpose of this pathway, Fever Without a Source (FWS) is defined as an acute febrile illness with temperature of 38°C (100.4°F) or greater taken rectally and no identifiable source of infection following a thorough history and physical examination in patients under 6 months of age. Patients with serious and/or life-threatening infection, especially young infants, may present with hypothermia (below 36°C or 96.8°F) and may be treated using this pathway. Approximately 12% of infants under 30 days of age and 9% of infants 30-90 days of age will have a serious bacterial infection (SBI), such as bacteremia, meningitis, or urinary tract infection (UTI). Because the clinical exam alone is unable to reliably predict serious bacterial illness in young infants, providers must rely on a combination of history, exam, diagnostic tests, and risk factors to reduce morbidity and mortality in this patient population.

Epidemiology

The most common cause of fever without localizing signs is a viral infection. The key point of evaluation is distinguishing which young infants have a serious bacterial infection and using a standardized assessment to stratify risks for these infections in young infants.

Most studies used to stratify risk for serious bacterial infection in neonates have defined a fever as a rectal temperature of 38°C (100.4°F) or greater. In our recommendations we use a cutoff of 38°C for evaluation of infants < 3 months for fever and a cutoff of 39°C (102.2°F) for older children.

While viral infections are the most common cause of fever in young infants, neonates less than 28 days have a particularly higher risk of invasive bacterial infection (up to 14%).[1,2] This document aims to provide a risk-stratified method of distinguishing low risk vs high risk of invasive bacterial infection based on age, clinical appearance, and specific risk factors for certain bacterial infections. These pathways should not be used for the ill appearing young infant who by definition is considered higher risk for invasive bacterial infection.[3,4]

Etiology

Neonates are most commonly infected via perinatal vertical transmission or postnatal exposure to organisms. Perinatal vertical transmission usually manifests within 48 to 72 hours after birth. Early-onset sepsis is defined as occurring within the first week of life and late-onset sepsis occurs beyond 7 days of age. Group B *Streptococcus* used to be the predominant pathogen in neonatal sepsis in the 1970s but with GBS screening and intrapartum antibiotic prophylaxis, there has been an approximate 80% reduction in Group B *Streptococcal* infection rates. Recent studies demonstrate that Escherichia coli is now the most common organism to cause bacteremia; it is the leading or second most common cause of bacterial meningitis in infants 1 to 60 days of age.[26,46-49] Now, gram-negative pathogens are the cause of infection in about 80% of young infants. *Escherichia coli* and *Klebsiella pneumoniae* are noted to be the most common gram-negative pathogens and *Staphylococcus aureus*, Group B *Streptococcus*, and *Enterococcus* spp. as the most common gram-positive pathogens. The shift from Gram-positive to Gram-negative predominance has implications for the choice of tests, interpretation of values for decision-making, and the selection of antimicrobial drugs. The majority of bacterial infections in this patient population are identified as urinary tract infections.

Guideline Eligibility Criteria

0-60 days:
Non-toxic with temperature ≥ 38°C (100.4°F) measured in Emergency Department OR reported measurement at home.

2-6 months:
Non-toxic with temperature > 39°C (102.2°F) OR < 36°C (96.8°F) measured in Emergency Department OR reported measurement at home.

Guideline Exclusion Criteria

-Toxic appearing
-No fever
-Born < 37 weeks gestational age
-High suspicion for HSV (vesicles or seizures)
-Documented or suspected immune compromise
-Neonatal course complicated by surgery or infection
-Congenital/chromosomal abnormality
-Medically fragile (ie, technology to sustain life)
-Received immunizations in the past 48 hrs

Additional exclusion criteria for Age 0-21 Days:
-All above AND Infants <2 weeks of age whose perinatal courses were complicated by maternal fever, infection, and/or antimicrobial use

Differential Diagnosis

Fever in the young infant most often raises the concern for underlying infection. Other causes of fever, such as environmental or toxin exposure should be sought in the history.

Etiologic causes of infection in the infant less than 90 days of age is a dynamic subject. Changes in pediatric medical practice over the past 20 years such as the use of new immunizations have had an impact on the epidemiology of various infections. These include the routine use of rotavirus vaccine, influenza vaccination of mothers, pneumococcal, Haemophilus influenza and varicella vaccines. In addition, widespread Group B streptococcal screening and intrapartum maternal antibiotic therapy has had an impact on the prevalence of Group B streptococcal infections. Ages, appearance, comorbidities, prematurity < 37 weeks gestation, height of fever, history of specific exposures to antibiotics are all risk factors for the presence of infection. [7,8]

The etiologies for infectious causes of the febrile infant less than 90 days old include:

Viral Infections

- These infections are the most common cause of fever in young infants. Studies of febrile young infants, including neonates, support an identifiable viral etiology in 17-35% of patients. [5,6]
- Acquisition may be vertical from the mother in utero, during the birth process or exposure after birth to close family members and community
- Viurses can cause increased morbidity in young infants due to specific deficiencies in their functional immune system.
- Viruses that are important agents include HSV, Enterovirus, CMV, Varicella, RSV, Influenza, and Adenovirus.

Bacterial Infections

- Invasive and serious bacterial infections in infants include urinary tract infections, blood stream infections, pneumonia, meningitis, omphalitis, skin and soft tissues infections, bone and joint infections, and gastroenteritis.
- These agents account for 10-14% of infections in the young febrile infant. [5,6]
- Invasive bacterial infection can be caused by Gram negatives such as E coli, Enterobacter, Klebsiella, Salmonella and Gram positives such as Group B streptococci, S. aureus, S. epidermidis, Listeria, Enterococcus. [9,10]
- E coli is the most common bacterial infection in the young febrile infant and is the primary cause of UTI in this age group. [9,10]

The prevalence of Group B streptococcus (GBS) is decreasing with the advent of widespread maternal screening and intrapartum prophylaxis for this infection. S. aureus is important in skin and soft tissue infection; S epidermidis may play a role in pre-term infants. [9,10]

Recommendations

Evidence Supports	Evidence Lacking/Inconclusive	Evidence Against
Narrow antibiotic coverage for patients 0-28 days with low risk of meningitis.	Patients 0-28 days: Ampicillin and Gentamicin as a first line therapy with Cefotaxime/Cefepime and Ampicillin used in patients with high suspicion of meningitis. Antibiotic choices are also based on local susceptibilities.	Necessity of lumbar puncture in patients greater than 28 days of age.
Cohort patients 0-28 days into subgroups that should have HSV workup or not.	Monitoring cultures for 36 hours.	
Cohort patient 29-60 days into subgroups by risk of SBI.		
Not getting LP in patients 29-60 days at low risk of SBI.		
Patients 28-60 days: Use of ceftriaxone to as outpatient management in patients at low risk for SBI and HSV.		

Diagnostic Evaluation

Clinical presentation

1. Fever (>38◦C or 100.4◦F rectally) without clinically identifiable source in infants age 0-60 days of life

-OR-

2. Hypothermia[1] (<36◦C) without clinically identifiable source in infants age 0-60 days of life
   Applies to temperature measured in Emergency Department or reported from home

Laboratory Tests

Laboratory tests, though some may be non-specific, can provide evidence towards a potential serious bacterial infection (SBI) or other viral pathology as the fever source, prompting further evaluation and treatment

1. Complete blood count (CBC)
   a. Leukocytosis or leukopenia defined as white blood cell (WBC) count >15,000/mm^3 or <5,000/mm^3)
   b. Increased immature cells (presence of bands or "left shift")
   c. Thrombocytopenia (Platelet count <100,000/mm^3) can be seen in severe sepsis or secondary to a viral process
2. Complete metabolic panel
   a. In patients with severe sepsis, acidosis, electrolyte disturbances, elevation in serum creatinine, hypoalbuminemia and transaminitis can be seen
   b. Transaminitis can also be seen with certain viral infections such as disseminated Herpes simplex virus
   c. If dosing ceftriaxone in patient under 28 days of life, consider screening total bilirubin due to risk of bilirubin displacement
3. Urinalysis with Micro
   a. Pyuria (>5 WBC per HPF via standard method and/or positive leukocyte esterase) provides evidence of urinary tract inflammation, most commonly from acute cystitis or pyelonephritis
   b. Nitrites can indicate presence of certain gram negative bacteria within the urine, though generally have a low sensitivity for diagnosis of cystitis or pyelonephritis specifically
4. Cerebrospinal fluid (CSF) analysis
   a. CSF pleocytosis (increased WBC count) according to age specific norms indicates inflammatory process most commonly seen with infectious etiologies such as meningitis or meningoencephalitis

Normal CSF WBC values based on age	
0-28 days	0-22/mm^3
≥ 29 days	0-7/mm^3

b. Increased protein can be seen in the setting of meningitis or meningoencephalitis

Normal CSF protein values based on age	
0-30 days	<100 mg/dL
> 30 days	15-45 mg/dL

c. Glucose can be decreased in acute bacterial meningitis

Normal CSF Glucose values based on age	
0-28 days	34-119 mg/dL
≥ 29 days	40-80 mg/dL

d. Gram stain can provide evidence of bacterial pathogens present in CNS

5. Cultures
    a. Cultures of blood, urine and CSF should be obtained to rule out presence of bacterial pathogen
    b. Stool culture can be considered in patient where significant diarrhea is present to rule out bacterial pathogen. Fecal WBCs can be seen in significant colitis as well as other non-infectious sources.
6. Molecular diagnostics
    a. Herpes simplex virus – if concerned for acute HSV disease, following workup should be obtained for complete evaluation
        i. HSV PCR blood
        ii. HSV PCR CSF (can be included in Biofire – see section d.)
        iii. HSV surface cultures
    b. Enterovirus PCR in CSF can provide etiology of pleocytosis in the absence of positive bacterial culture (can be included in Biofire – see section d.)
    c. Rapid viral testing for Influenza and RSV, when taken in context of correlating clinical symptoms and community prevalence can provide evidence of a fever source in the absence of suspected SBI.
    d. PCR panels (Respiratory pathogen panel, Biofire of CSF) provide rapid PCR testing for a variety of bacterial and viral pathogens and can be helpful in identifying fever source in cases where positive results would affect clinical management and potential outcomes such as
        i. Antibiotic pretreatment where bacterial culture may not be reliable
        ii. Initiation of antimicrobials (HSV encephalitis, mycoplasma pneumonia, pertussis, etc)

Imaging

Chest X-Ray can be considered if concerned for an acute lower respiratory tract infection based on clinical symptoms.

Fever Without a Source: Age 0-21 Day Pathway

Evidence Based Outcome Center

EXCLUSION CRITERIA

-Toxic appearing
-No fever
-Born < 37 weeks gestational age
-High suspicion for HSV (vesicles or seizures)
-Infants <2 weeks of age whose perinatal courses were complicated by maternal fever, infection, and/or antimicrobial use
-Documented or suspected immune compromise
-Neonatal course complicated by surgery or infection
-Congenital/chromosomal abnormality
-Medically fragile (ie, technology to sustain life)
-Received immunizations in the past 48 hrs

INCLUSION CRITERIA

Non-toxic with temperature ≥ 38°C (100.4°F) measured in Emergency Department OR reported measurement at home.

- Focal bacterial infection (other than otitis media) OR
- Temperature <36°C (96.8°F) OR
- Clinical Bronchiolitis OR
- Clinically ill or concern for invasive bacterial infection

YES → **Manage OFF-PATHWAY**

NO

Order labs:
- ☑ Complete Blood Count (CBC) with differential
- ☑ Blood Culture
- ☑ Complete Metabolic Panel (CMP)
- ☑ UA
- ☑ Cerebrospinal Fluid (Hold Tube # 4)
  - ☑ Gram stain
  - ☑ Culture
  - ☑ Cell count with differential
  - ☑ Glucose
  - ☑ Protein
  - ☑ Meningitis/ Encephalitis PCR panel
- ❑ Stool culture (If patient has diarrhea)
- ❑ CRP, procalcitonin (may obtain)

UA Positive? 1

YES → Send urine culture via bladder catheterization

NO

! ALERT
Patient Toxic/Septic Appearance
Full Sepsis Workup & treat as appropriate.
(LINK TO SEPSIS PATHWAY/GUIDELINE)

Abnormal UA Values 1
- Positive LE (leukocyte esterase)
- Positive Nitrites
- > 5wbc/hpf on microscopy

Abnormal CSF Values 2
- ≥ 15 wbc/mm^3
- Positive Gram Stain

Herpes Simplex Virus (HSV) work-up indicated?

YES →

Order labs:
- ☑ Herpes Simplex 1&2 Subtype by PCR of blood
- ☑ Herpes Simplex 1&2 Subtype by PCR of CSF
- ☑ Herpes Simplex 1&2 Subtype by PCR of surface cultures
  - ☑ Conjunctiva
  - ☑ Throat
  - ☑ Nasopharynx
  - ☑ Rectum
  - ☑ Vesicle (if present)

Add Acyclovir

NO

Patient Age: 0-7 Days
1. Administer Ampicillin and Gentamicin

Patient Age: 8-21 Days
1. Administer Ceftriaxone (Use Cefepime if contraindicated)

CSF pleocytosis, traumatic, or not interpretable? 2

YES →

Patient Age: 0-7 Days

Change antibiotic treatment:
1. Confirm meningitic dose of Ampicillin (Redose if needed)
2. Add Cefepime
3. Discontinue Gentamicin
4. Consider HSV workup and Acyclovir therapy

Patient Age: 8-21 Days

Change antibiotic treatment:
1. Confirm meningitic dose of Ceftriaxone (Redose if needed)
2. Add Ampicillin and confirm meningitic dosing
3. Consider HSV workup and Acyclovir therapy

NO

ADMIT TO INPATIENT

Pathogen or source identified?

YES → 1. Treat Infection

NO → 1. Discontinue antimicrobials and may discharge if infant is well-appearing and all culture results are negative at 24-36 hours.
2. Manage for duration of illness.

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Fever Without a Source: Age 22-28 Day Pathway

Evidence Based Outcome Center

INCLUSION CRITERIA

Non-toxic with temperature ≥ 38°C (100.4°F) measured in Emergency Department OR reported measurement at home.

EXCLUSION CRITERIA

-Toxic appearing
-No fever
-Born < 37 weeks gestational age
-High suspicion for HSV (vesicles or seizures)
-Documented or suspected immune compromise
-Neonatal course complicated by surgery or infection
-Congenital/chromosomal abnormality
-Medically fragile (ie, technology to sustain life)
-Received immunizations in the past 48 hrs

- Focal bacterial infection (other than otitis media) OR
- Temperature <36°C (96.5°F) OR
- Clinical Bronchiolitis OR
- Clinically ill or concern for invasive bacterial infection

YES → Manage OFF-PATHWAY

NO

Order labs:
- ☑ CBC with differential
- ☑ Blood culture
- ☑ UA
- ☑ Procalcitonin
- ☑ CMP
- ❑ CRP
- ❑ Stool culture (If patient has diarrhea)

UA Positive? 2
- NO
- YES → Send urine culture via bladder catheterization

Meets ANY abnormal Inflammatory markers? 1
- NO → Shared decision making (SDM) about LP
- YES → Perform LP

LP Performed?
- NO → 1. ADMIT TO INPATIENT 2. Prefer observing off antibiotics, consider discussion with PCRS but may administer Ceftriaxone (use Cefepime if contraindicated)
- YES → CSF obtained?

CSF obtained?
- NO → 1. ADMIT TO INPATIENT 2. Prefer observing off antibiotics, consider discussion with PCRS but may administer Ceftriaxone (use Cefepime if contraindicated)
- YES → CSF pleocytosis, traumatic, or not interpretable? 3

CSF pleocytosis, traumatic, or not interpretable? 3
- YES → UA Positive? 2
- NO → UA Positive? 2

UA Positive? 2
- YES → 1. Administer Cefazolin 2. ADMIT TO INPATIENT
- NO → SDM about disposition; Observe at home?

SDM about disposition; Observe at home?
- YES → 1. Administer Ceftriaxone (If contraindications, will need to consider using Cefepime and admitting to inpatient) 2. OBSERVE AT HOME and follow up in 24 hrs
- NO → 1. ADMIT TO INPATIENT 2. If abnormal IM, may administer Ceftriaxone (use Cefepime if contraindicated). If normal IM, prefer observing off antibiotics and consider discussion with PCRS but may administer Ceftriaxone.

CSF obtained?
- NO → 1. Administer Ceftriaxone at meningitic dosing (use Cefepime if contraindicated) 2. Add Ampicillin and confirm meningitic dosing 3. Consider HSV work-up and Acyclovir therapy 3. ADMIT TO INPATIENT
- YES → CSF pleocytosis, traumatic, or not interpretable? 3

CSF pleocytosis, traumatic, or not interpretable? 3
- NO → 1. Administer Ceftriaxone at meningitic dosing (use Cefepime if contraindicated) 2. Add Ampicillin and confirm meningitic dosing 3. Consider HSV work-up and Acyclovir therapy 3. ADMIT TO INPATIENT
- YES → 1. Administer Ceftriaxone at meningitic dosing (use Cefepime if contraindicated) 2. Add Ampicillin and confirm meningitic dosing 3. Consider HSV work-up and Acyclovir therapy 3. ADMIT TO INPATIENT

Pathogen or source identified?
- YES → 1. Treat Infection
- NO → 1. Discontinue antimicrobials (if started) and may discharge if infant is well-appearing and all culture results are negative at 24-36 hours. 2. Manage for duration of illness.

! ALERT

Patient Toxic/Septic Appearance
Full Sepsis Workup & treat as appropriate.
(LINK TO SEPSIS PATHWAY/GUIDELINE)

Abnormal Inflammatory Markers (IM) 1
- Temperature > 38.5°C (101.3°F)
- Procalcitonin >0.5 ng/mL
- CRP >2.0 mg/dL
- ANC >4000 cells/mm^3

Abnormal UA Values 2
- Positive LE (leukocyte esterase)
- Positive Nitrites
- > 5wbc/hpf on microscopy

Abnormal CSF Values 3
- ≥ 15 wbc/mm^3
- Positive Gram Stain

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Fever Without a Source: Age 29-60 Day Pathway

EXCLUSION CRITERIA

-Toxic appearing
-No fever
-Born < 37 weeks gestational age
-High suspicion for HSV (vesicles or seizures)
-Documented or suspected immune compromise
-Neonatal course complicated by surgery or infection
-Congenital/chromosomal abnormality
-Medically fragile (ie, technology to sustain life)
-Received immunizations in the past 48 hrs

INCLUSION CRITERIA

Non-toxic with temperature ≥ 38°C (100.4°F) measured in Emergency Department OR reported measurement at home.

- Focal bacterial infection (other than otitis media) **OR**
- Temperature <36°C (96.8°F) **OR**
- Clinical Bronchiolitis **OR**
- Clinically ill or concern for invasive bacterial infection

YES → Manage OFF-PATHWAY

NO →

Order labs:
- ☑ CBC with differential
- ☑ Blood culture
- ☑ UA
- ☑ Procalcitonin
- ❑ CMP
- ❑ CRP
- ❑ Stool culture (If patient has diarrhea)

Abnormal UA Values (1)
- Positive LE (leukocyte esterase)
- Positive Nitrites
- > 5wbc/hpf on microscopy

Abnormal CSF Values (2)
- ≥ 9 wbc/mm^3
- Positive Gram Stain

Abnormal Inflammatory Markers (IM) (3)
- Temperature > 38.5°C (101.3°F)
- Procalcitonin >0.5 ng/mL
- CRP >2.0 mg/dL
- ANC >4000 cells/mm^3

Meets ANY abnormal Inflammatory markers? (3)

YES → UA Positive? (1)

NO → UA Positive? (1)

YES → 1. Send urine culture via bladder catheterization
2. Do not need to perform LP
3. Administer oral Cephalexin
4. OBSERVE AT HOME and follow-up in 24 hrs

NO → 1. Do not need to perform LP
2. Do not need to administer antibiotics
3. OBSERVE AT HOME and follow-up in 24 hrs

UA Positive? (1)

YES → Send urine culture via bladder catheterization

NO → May perform LP

YES → CSF pleocytosis, traumatic, or not interpretable? (2)

YES → 1. Administer Ceftriaxone and Vancomycin at meningitic dosing
2. ADMIT TO INPATIENT

NO → UA Positive? (1)

YES → SDM about disposition; Observe at home?

YES → 1. May Administer Ceftriaxone
2. OBSERVE AT HOME and follow-up in 24 hrs

NO → 1. ADMINT TO INPATIENT
2. Prefer observing off antibiotics, consider discussion with PCRS but may administer Ceftriaxone.

NO → 1. If negative CSF results, administer oral Cephalexin. If no CSF results, administer Ceftriaxone followed by oral Cephalexin.
2. May OBSERVE AT HOME and follow-up in 24 hrs.

YES → SDM about disposition; Observe at home?

NO → 1. Administer Cefazolin
2. ADMIT TO INPATIENT

NO → 1. Treat Infection

YES → Pathogen or source identified?

NO → 1. Discontinue antimicrobials (if started) and may discharge if infant is well-appearing and all culture results are negative at 24-36 hours.
2. Manage for duration of illness.

! ALERT

Patient Toxic/Septic Appearance
Full Sepsis Workup & treat as appropriate.
(LINK TO SEPSIS PATHWAY/GUIDELINE)

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Fever Without a Source: Age 2-6 Months Pathway

Evidence Based Outcome Center

EXCLUSION CRITERIA

Toxic appearing
No fever
Born < 37 weeks gestational age

INCLUSION CRITERIA

Non-toxic with temperature > 39°C (102.2°F) OR < 36°C (96.8°F) measured in Emergency Department OR reported measurement at home.

! ALERT

Patient Toxic/Septic Appearance

Full Sepsis Workup & treat as appropriate.
(LINK TO SEPSIS PATHWAY/GUIDELINE)

Defined Focal Bacterial Infection: Cellulitis, abscess, pneumonia, osteomyelitis, bacterial arthritis, omphalitis, meningitis

YES → **Manage OFF-Pathway**

Consider Alternate Management Pathway
- Community Acquired Pneumonia
- Urinary Tract Infection
- Acute Osteomyelitis

Prolonged fever >5 days: Consider Kawasaki Disease or MIS-C

NO

Defined Viral Syndrome
- Croup
- Bronchiolitis
- Stomatitis
- Influenza
- Varicella

YES → Treat with Supportive Care

NO

Patient received 2 or more doses of Pneumococcal Conjugate Vaccine (PCV)

NO → **Continue UTI Assessment**

Order labs:
☐ Complete Blood count with differential

CBC with Differential
> 15,000/mm^3
OR
< 5,000/mm^3

NO

YES

Order Blood Culture

After UTI Assessment is Complete
Empiric antibiotic treatment:
Ceftriaxone

YES

Influenza/ Bronchiolitis

YES → **Meets Low Risk UTI Criteria?**

NO

Order labs:
☐ Urinalysis with Micro
☐ UA: Catheter or Suprapubic

YES

UA positive?

YES → **UTI Management Guideline**

NO

NO

ED Discharge Criteria

- ☑ Tolerating liquids
- ☑ Reliable PCP or ED follow-up
- ☑ PCP and Caregiver comfortable with discharge
- ☑ Good social support
- ☑ Education complete

NO → **ADMIT TO INPATIENT**

YES → **DISCHARGE Home Follow-up in 24 hours**

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Fever Without a Source
Risk Factors for UTI and Screening Recommendations
Evidence Based Outcome Center

> 2 months – Not Toilet Trained

Probability of UTI > 1%:
2 or more risk factors

Female Risk Factors*
Non-black
T ≥ 39°C
Fever ≥ 2 days
No apparent source of fever
Age < 12 months

*Recommend screening if prior history of UTI, fever ≥ 2 days

Probability of UTI > 1%:
Uncircumcised
OR
Circumcised with 3 or more Risk Factors

Male Risk Factors*
Non-black
T ≥ 39°C
Fever ≥ 2 days
No apparent source of fever
Age < 6 months

Toilet Trained – 18 years

All Patients
Symptoms referable to urinary tract
Prior history of UTI, fever ≥ 2 days
Prolonged fever (≥ 5 days)

Recommend screening for any of the above factors

Fever without a source Pathway
0-21Days | 22-28Days | 29-60 Days | 2-6 Months

DCMC Positive Urinalysis (UA) Definition: The presence of Leukocyte Esterase *or* Nitrites *or* microscopic analysis results positive for leukocytes *or* bacteria is suggestive of an active UTI. When more than one of these findings is present at the same time, the sensitivity and specificity increase significantly.

Dell Children's and Seton Family of Hospitals does not currently perform an enhanced urinalysis on urine specimens routinely. The following criteria are guide in diagnosing a UTI in young children using the standard method of collection and processing.

Diagnostic	Interpretation
Nitrites	• Poor sensitivity: Conversion of nitrates to nitrites by bacteria takes approximately 4 hours and not all bacteria reduce nitrate levels combined with frequency of infants voiding. • Helpful when positive. Few false positives and high specificity.
Leukocyte Esterase	• Positive leukocyte esterase is suggestive of a UTI. However, children may have WBC present in their urine in conditions other than a UTI (e.g. Kawasaki Disease)
White Blood Cells (WBC) - Pyuria	Positive if: • ≥ 5 WBC per HBF via standard method Pyuria is absent in approximately 10% of children with a UTI
Bacteriuria	Presence of bacteriuria alone in the absence of other findings does not define a UTI.

Culture			
Method	Definite*	Indeterminant†	Contaminant
Suprapubic	Any growth		Growth of non-pathogens, Mixed culture
Catheter	≥ 50,000 CFU/ML	≥ 10,000 CFU/ML	Growth of non-pathogens, Mixed culture, < 10,000 CFU/ml

* If also with presence of pyuria or bacteriuria
† Consider obtaining repeat specimen
Mixed Culture = uropathogen + non-pathogen or two uropathogens
Bag UA specimens should never be sent for urine culture. Only catheter or suprapubic methods are appropriate for culture collection in this age.

Uropathogens		
Gram Negative	Gram Positive	Non-pathogens
Escherichia coli (~80%)	Staphylococcus saprophyticus	Lactobacillus
Klebsiella	Enterococcus	Coagulase-negative Staph
Proteus	Staphylococcus aureus	Corynebacterium
Enterobacter		
Citrobacter		

Fever without a source Pathways
0-21Days | 22-28Days | 29-60 Days | 2-6 Months

Patients with any of the following conditions should be considered for a Herpes Simplex Virus work up and empiric treatment:
Historical and Clinical Features
Severe illness / Hypothermia / Lethargy
Seizures
Hepatosplenomegaly
Postnatal HSV contact
Vesicular rash
Conjunctivitis
Interstitial pneumonitis
Laboratory Findings
Thrombocytopenia
CSF pleocytosis without clear bacterial infection
Transaminitis

Herpes Simplex Virus work-up consist of the following labs:

- ☑ Herpes Simplex 1&2 Subtype by PCR of blood
- ☑ Herpes Simplex 1&2 Subtype by PCR of CSF
- ☑ Herpes Simplex 1&2 Subtype by PCR of surface cultures
  - ☑ Conjunctiva
  - ☑ Throat
  - ☑ Nasopharynx
  - ☑ Rectum
  - ☑ Vesicle (if present)

Fever without a source Pathway

0-21Days | **22-28Days** | **29-60 Days** | **2-6 Months**

Contraindications for Ceftriaxone in patients < 28 days of age:

Gestational age < 37 weeks
Postnatal age < 7 days
Patient expected to or receiving calcium containing IV products
Total bilirubin > 10mg/dL (See risk factors for hyperbilirubinemia)

Risk factors for hyperbilirubinemia	
ABO incompatibility	Albumin < 3g/dL
HDN	Dehydration
Lethargy	Weight loss
Temperature instability	Poor feeding
Sepsis	Irritability
Acidosis	Jaundice

Fever Without a Source
Antimicrobial and Antiviral Dose Recommendations

Evidence Based Outcome Center

Recommended Doses for Antimicrobials		
Drug[a,b,c,d,e,f]	**Dose**	**Duration[e] (for rule out period)[f]**
Ampicillin	NON-MENINGITIC 0-7 days of age: 50 mg/kg/DOSE IV or IM q8h MENINGITIC 0-7 days of age: 100 mg/kg/DOSE IV q8h MENINGITIC > 7-28 days of age: 75 mg/kg/DOSE IV q6h	5 doses 5 doses 6 doses
Cefepime[b]	0-28 days of age: 50 mg/kg/DOSE IV or IM q12h > 28 days of age: 50 mg/kg/DOSE IV or IM q8h	3 doses 5 doses
Ceftriaxone[c]	NON-MENINGITIC > 7 days of age: 75 mg/kg/DOSE IV or IM QDay MENINGITIC > 7 days of age: 50 mg/kg/DOSE IV q12h MENINGITIC (ED ONLY) > 7 days of age: 100 mg/kg/DOSE IV[g] X 1	2 doses 3 doses 1 dose
Gentamicin[d]	0-7 days of age: 4 mg/kg/DOSE IV or IM q24h	2 doses
Vancomycin[d]	MENINGITIC > 28 days of age: 15 mg/kg/DOSE IV q6h	6 doses

Recommended Dose for UTI (Uncomplicated Cystitis)		
Drug	**Dose**	**Duration**
Cefazolin	UTI without BACTEREMIA: 17 mg/kg/DOSE IV or IM q8h UTI with BACTEREMIA: 33 mg/kg/DOSE IV or IM q8h	Total duration IV + PO = 10 days
Cephalexin	17 mg/kg/DOSE PO TID	

Recommended Dose for Antiviral		
Drug	**Dose**	**Duration**
Acyclovir	20 mg/kg/DOSE IV q8h (0-3 months)	5 doses OR until HSV surface cultures AND PCR Blood & CSF negative (contact Infectious Disease if not resulted within 5 doses) **Exceptions:** Seizures, lethargy, or ongoing fever

[a]Dosing in this table is for patients with normal renal function. Please contact the pharmacy for assistance with dosing in renal insufficiency.

[b]Cefotaxime is no longer formulary at DCMC due to supply instability. In the instance cefotaxime should be available, cefotaxime could be substituted for cefepime, using the following doses:

0 to 7 days of age: 50 mg/kg/dose IV or IM q8h
> 7 days: 50 mg/kg/dose IV or IM q6h

[c]Ceftriaxone is contraindicated with calcium containing IV products or hyperbilirubinemia. Meningitic dosing of ceftriaxone is 80-100 mg/kg/day divided every 12-24 hours but CSF concentrations are optimal when dosed at 50mg/kg/dose IV q12h; once daily dosing should be reserved for patients to be discharged from the ED. IM dosing is inappropriate for meningitic coverage.

[d]For gentamicin or vancomycin, serum drug levels are not necessary unless treatment is anticipated or continued for more than 2 doses, SCr is increased more than 0.3 mg/dL from normal value for age, or UOP less than 1 ml/kg/hr.

[e]Duration includes any doses given in the emergency department.

[f]If cultures become positive at any time, treat specific condition, narrow agent, and lengthen antibiotic duration as appropriate.

[g]Ceftriaxone 100 mg/kg IV X 1 for any ill appearing neonate, with the first inpatient dose starting 12-24 hours after initial dose.

DCMC Specific Antibiotic Selection and Dosing for Neonatal Fever

Evidence Based Outcome Center

Suspected Source of Infection	0-7 Days	8-21 Days	22-28 Days	29-60 Days
UTI w/o bacteremia			Cefazolin (17 mg/kg/DOSE) IV or IM q8h	Cefazolin (17 mg/kg/DOSE) IV or IM q8h
UTI w/ bacteremia			Cefazolin (33 mg/kg/DOSE) IV or IM q8h	Cefazolin (33 mg/kg/DOSE) IV or IM q8h
No Focus Identified	Ampicillin (50 mg/kg/DOSE) IV or IM q8h + Gentamicin (4 mg/kg/DOSE) IV or IM q24hr	Ceftriaxone (75 mg/kg/DOSE) IV or IM qDay or Cefepime (50 mg/kg/DOSE) IV or IM q12h (when ceftriaxone contraindicated)	Ceftriaxone (75 mg/kg/DOSE) IV or IM qDay or Cefepime (50 mg/kg/DOSE) IV or IM q12h (when ceftriaxone contraindicated)	Ceftriaxone (75 mg/kg/DOSE) IV or IM qDay
Meningitis	Ampicillin (100 mg/kg/DOSE) IV q8h + Cefepime (50 mg/kg/DOSE) IV q12h +/- Acyclovir (20 mg/kg/DOSE) IV q8h (if clinical concerns of HSV)	Ampicillin (75 mg/kg/DOSE) IV q6h + Ceftriaxone (50 mg/kg/DOSE) IV q12h or Cefepime (50 mg/kg/DOSE) IV q12h (when ceftriaxone contraindicated) +/- Acyclovir (20 mg/kg/DOSE) IV q8h (if clinical concerns of HSV)	Ampicillin (75 mg/kg/DOSE) IV q6h + Ceftriaxone (50 mg/kg/DOSE) IV q12h or Cefepime (50 mg/kg/DOSE) IV q12h (when ceftriaxone contraindicated) +/- Acyclovir (20 mg/kg/DOSE) IV q8h (if clinical concerns of HSV)	Ceftriaxone (50 mg/kg/DOSE) IV q12h + Vancomycin (15 mg/kg/DOSE) IV q6h +/- Acyclovir (20 mg/kg/DOSE) IV q8h (if clinical concerns of HSV)

NOTE: This table replicates the information in the table above.

Methods

Existing External Guidelines/Clinical Pathways

Existing External Guideline/Clinical Pathway	Organization and Author	Last Update
Fever Without Localizing Signs	Texas Children's Hospital	2009
Neonatal Fever Pathway	Seattle Children's	2017
Febrile Infant Clinical Pathway	Children's Hospital of Philadelphia	2015
AAP VIP Network – REVISE II Project	American Academy of Pediatrics	2021

Any published clinical guidelines have been evaluated for this review using the **AGREE II criteria**. The comparisons of these guidelines are found at the end of this document. **AGREE II criteria** include evaluation of: Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, and Editorial Independence.

Review of Relevant Evidence: Search Strategies and Databases Reviewed

Search Strategies	Document Strategies Used
Search Terms Used:	Infant, neonate, less than 7 days of age, 28 days of age, risk of serious bacterial infections, herpes simplex virus, risk stratification, blood stream infection, enterovirus, antibiotic course, septic workup, sepsis, positive urine analysis, lumbar puncture, hospital admission, antibiotic management
Years Searched - All Questions	2007 - 2017
Language	English
Age of Subjects	0 – 6 Months of age
Search Engines	PubMed, Cochrane, Google
Government/State Agencies	National Guideline Clearinghouse

Evidence Found with Searches

Check Type of Evidence Found	Summary of Evidence – All Questions	Number of Articles Obtained
☐	Systematic Reviews	
☒	Meta-analysis articles	1
☒	Randomized Controlled Trials	2
☒	Non-randomized studies	27
☐	Review articles	
☐	Government/State agency regulations	
☐	Professional organization guidelines, white papers, ect.	
☐	Other:	

Evaluating the Quality of the Evidence

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

Recommendation	
Strong	Desirable effects clearly outweigh undesirable effects or vice versa
Weak	Desirable effects closely balanced with undesirable effects
Type of Evidence	
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

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Revision History
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