CLINICAL GUIDELINE

FEVER ≥ 38°C (100.4°F) WITHOUT OBVIOUS SOURCE

(Infants 1–60 days age)

Children's MINNESOTA

Aim: Standardize evaluation and management of well-appearing febrile infants, safely reduce length of stay and any unnecessary interventions.

High risk history?

Including infant's age 1–7 days **(see note 1)**, chronic medical condition, prematurity (< 37 weeks gestation), antibiotic use within the last 72 hours, prolonged post-natal hospitalization, or other concerning clinical history.

Evaluation should occur in the ED unless patient is 29 days or older and with no high risk history and is well-appearing.

No → Infant age **8–21 days?**

No → Infant age **22–60 days**

See Page 2 and 3

Yes

Strongly consider discussion with ID and/or Neonatology

Yes

Perform Extensive Evaluation:

- CBC with differential, blood culture
- ALT and AST
- Cath urinalysis and urine culture **(see note 2)**
- Lumbar puncture (culture, gram stain, cell counts, glucose, protein, meningitis/encephalitis panel PCR, 1 ml CSF to save.)
- HSV testing if suspicion for HSV **(see note 4)**
- Consider viral testing IF viral symptoms or exposure **(see note 5)**

Admit with antimicrobials (see note 6)
Consider acyclovir if indicated (see note 4)

Bacterial culture or HSV positive?

No → **Consider discharge (see note 7)** at:

- **24 hours from time of last culture if:** Infant > 7 days old AND Interpretable LP with no concern for meningitis AND viral testing positive for non-rhinovirus pathogen **(see note 8)** AND no barriers to outpatient follow-up or return to hospital
- **36 hours from time of last culture if:** Infant > 7 days old and not meeting above criteria
- **48+ hours from time of last culture:** Infant ≤ 7 days old **(see note 1)**

Yes

Treat according to infection.

See separate UTI guideline if applicable.

See page 4-5 on Meningitis Guideline for required audiology screening in infants with confirmed viral or bacterial meningitis.

EXCLUSION GUIDELINES (see **note 9** on included infants)

Patients **excluded** from this guideline:

- Age > 60 days
- Ill-appearing (can refer to Sepsis Guideline)
- Focal bacterial infection
- Clinical bronchiolitis (see Bronchiolitis Guideline)
- Immune compromise, history of neonatal infection or neonatal surgery, or chromosomal abnormality

CLINICAL GUIDELINE

FEVER ≥ 38°C (100.4°F) WITHOUT OBVIOUS SOURCE

(Infants 1–60 days age)

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Age 22–28 days with NO high-risk history
(refer to high-risk history on page 1)
Evaluation in ED is recommended.

Perform Limited Evaluation:
- CBC with differential, blood culture
- **CRP and Procalcitonin** (if available)
- Hepatic panel
- Cath urinalysis and urine culture **(see note 2)**
- HSV testing if suspicion for HSV **(see note 4)**
- Consider viral testing IF viral symptoms or exposure **(see note 5)**

Any concerning results?
- Procalcitonin > 0.5 ng/mL
- ANC > 4000 per mm 3
- CRP > 2.0 mg/dL
- Temperature > 38.5 C

Yes

Perform Lumbar Puncture (CSF culture, gram stain, cell counts, glucose, protein, meningitis/ encephalitis panel PCR, 1 ml CSF to save)

- **If concerning CSF:** admit with antimicrobials
- **If negative CSF, could:**
  - Admit with antibiotics ***OR***
  - Hospital observation alone (not an acceptable option if UA suggests UTI) ***OR***
  - Pre-discharge IV ceftriaxone **(see note 6)** and close outpatient follow-up, if no high risk concerns
- **If no CSF obtained or CSF uninterpretable:**
  - Hospital observation **alone** preferred if no CSF obtained (not an acceptable option if UA suggests UTI) ***OR***
  - Admit with antibiotics **(see notes 3 and 6)**

No

Antibiotics if urinalysis positive, otherwise may observe inpatient +/- antibiotics

Consider LP, particularly if starting antibiotics

Strong suspicion for UTI, Bacterial culture or HSV positive?

No

Consider discharge (note 7) at:
- **24 hours from time of last culture if:** Interpretable LP with no concern for meningitis AND viral testing positive for non-rhinovirus pathogen **(see note 8)** AND no barriers to outpatient follow-up or return to hospital

Recommend an additional dose of ceftriaxone at the time of 24-hour discharge if no contraindications **(see note 6)**.
- **36 hours from time of last culture if:** no CSF obtained or patient not meeting above criteria

Yes

Treat according to infection.

See separate UTI guideline if applicable.

See page 4-5 on Meningitis Guideline for required audiology screening in infants with confirmed viral or bacterial meningitis.

CLINICAL GUIDELINE

FEVER ≥ 38°C (100.4°F) WITHOUT OBVIOUS SOURCE

(Infants 1–60 days age)

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Age 29–60 days with no high-risk history

May perform initial limited evaluation in outpatient clinic if patient is well-appearing and lab testing is available with turnaround time within 1–2 hours to make disposition decisions.

Perform Limited Evaluation:

- CBC with differential, blood culture
- **CRP and Procalcitonin** (if available)
- Cath urinalysis and urine culture **(see note 2)**
- HSV testing and ALT/AST if suspicion for HSV **(see note 4)**
- Consider viral testing IF viral symptoms or exposure **(see note 5)**

Any concerning results?

- Procalcitonin > 0.5 ng/mL
- ANC > 4000 per mm 3
- CRP > 2.0 mg/dL
- Temperature > 38.5 C

Yes

Consider LP

Particularly if multiple results are concerning, infant has had a prolonged fever, or home observation is anticipated.

If being evaluated in clinic: send to ED OR administer ceftriaxone and arrange close follow-up within 24–36 hours.

- **If concerning CSF:** admit with antimicrobials
- **If negative CSF, could (see note 10):**
  - Admit with antibiotics ***OR***
  - Hospital observation alone (not an acceptable option if UA suggests UTI) ***OR***
  - Pre-discharge IV ceftriaxone and close outpatient follow-up, if no high risk concerns
- **If LP not performed or CSF uninterpretable:**
  - Hospital observation **alone,** as long as there are no concerning results, preferred if no CSF obtained (not an acceptable option if UA suggests UTI) ***OR***
  - Admit with antibiotics **(see notes 3 and 6) *OR***
  - Consider pre-discharge IV ceftriaxone and discharge with close outpatient follow-up.

No

Is urinalysis positive? **(see note 2)**

Yes → Treat for probable UTI. See UTI guideline.

No

Able to follow-up within 24–36 hours AND caregiver comfortable with discharge?

Yes → Consider discharge home; need not administer antibiotics **(see note 7)**

No

Strong suspicion for UTI, bacterial culture or HSV positive?

No → **Consider discharge (note 7)** at:

- **24 hours from time of last culture if:** No barriers to outpatient follow-up or return to hospital

Consider an additional dose of ceftriaxone at the time of 24-hour discharge.

Yes

Treat according to infection. See separate UTI guideline if applicable. See page 4-5 on Meningitis Guideline for required audiology screening in infants with confirmed viral or bacterial meningitis.

CLINICAL GUIDELINE

FEVER ≥ 38°C (100.4°F) WITHOUT OBVIOUS SOURCE

(Infants 1–60 days age)

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Aim: Standardize evaluation and management of well-appearing febrile infants, safely reduce length of stay and any unnecessary interventions.

NOTE 1: INFANTS 1-7 DAYS OLD

- Neonates age 1–7 days old are excluded from the AAP 2021 Guideline "Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old", however based on expert input at Children's MN, they are included in this guideline with the assumption that their management will be performed in consultation with ID and/or Neonatology
- If planned or considered admission to NICU, recommend discussion of antibiotic choice with neonatologist
- Discharge of infants < 8 days old before 48 hours of negative cultures is not supported in the literature

NOTE 2: URINALYSIS AND UTI

- **Urinalysis (UA) considered positive if:** presence of **nitrites** OR **pyuria** (≥ trace leukocyte esterase or ≥ 5 WBC/hpf)
- Dilute/unspun urine specimen (SG < 1.015) may underestimate WBC count
- Several studies indicate very low risk of bacterial meningitis in well-appearing infants > 28 days of age with UTI.

NOTE 3: BACTERIAL MENINGITIS

Consider longer observation in pts with high suspicion of bacterial meningitis (i.e. CSF pleocytosis.) Mean time to positivity = 28.6 hours, 81% identified by 36 hours

- "Abnormal CSF" would be CSF with values straying from the typical ranges for age listed in the table below[1]:

	Age, days	Median	Range
WBCs per mm^3	1–28	5	0–18
	29–60	3	0–8.5
Protein mg/dL	1–28	73	15.8–131.0
	29–60	54	5.5–105.5
Glucose	1–28	46	30–61
	29–60	48	20.6–65.5

See audiology management for infants with diagnosed meningitis in Suspected Meningitis Guideline page 4-5.

NOTE 4: HSV

- Recommend HSV testing if any of the following: known HSV exposure, maternal history of genital or mucocutaneous lesions, maternal perinatal fevers (i.e. 48 hours prior to, or after, delivery), persistent hypothermia, mucus membrane ulcers, skin vesicles, seizure, leukopenia and/or thrombocytopenia, increased ALT or AST, CSF pleocytosis in the absence of positive Gram stain results
- HSV testing should include:
  - PCR on whole blood
  - PCR of the eye, mouth, nasopharynx and anus
  - PCR on CSF
  - PCR of any vesicle
- **Acyclovir dosing:** 20 mg/kg/dose IV q 8 hours

NOTE 5: ADDITIONAL VIRAL TESTING

- Consider rapid influenza and RSV in season, and SARS-CoV2
- Consider Respiratory Pathogen PCR Panel
- Consider Enterovirus PCR on plasma (more prevalent in summer and fall, but can be seen year-round)

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(Infants 1–60 days age)

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NOTE 6: ANTIBIOTIC DOSING FOR INFANTS > 2 kg*

Suspicion of Bacterial Meningitis

- **1-7 days of age: (See Note 1):** Ampicillin 100mg/kg/IV Q8H AND ceftazidime 50mg/kg IV Q12H
- **8-28 days of age:** Ampicillin 75mg/kg IV Q6H AND ceftazidime 50mg/kg IV Q8H
- **29-60 days of age:** Ceftriaxone 50mg/kg IV Q12H AND vancomycin 15mg/kg IV Q8H

No Suspicion of Bacterial Meningitis

- **1-7 days of age (See note 1):** Ampicillin 50mg/kg IV Q8H AND ceftazidime 50mg/kg IV Q12H
- **8-28 days of age:** Ampicillin 50mg/kg IV Q8H AND ceftazidime 50mg/kg IV Q8H
- **29-60 days:** Ceftriaxone 50mg/kg IV Q24H

*Ceftriaxone monotherapy prior to a discharge, or ceftriaxone plus ampicillin in an inpatient, may be considered in the appropriate clinical setting, in term neonates 22–28 days with normal bilirubin levels and not receiving IV calcium-containing fluids (including TPN).

***If infant's weight ≤ 2 kg**, consult with pharmacy and/or NICU for antibiotic dosing.

NOTE 7: SHARED DECISION MAKING – FACTORS TO CONSIDER WHEN DECIDING DISCHARGE TIMING

- Alternative source for fever and patient's risk criteria
- Caregiver experience and comfort
- Accessibility to reliable follow-up within 24–36 hours
- Proximity to hospital should new concerns arise
- Infant's fever curve and other clinical status (e.g., oral intake)
- Family awareness that cultures may turn positive after discharge, potentially necessitating return to hospital

NOTE 8: RHINOVIRUS DETECTION

- Human rhinovirus detection is common in febrile infants. Detection of this virus alone does not alter risk of invasive bacterial infection in infants 1–28 days old

NOTE 9: PATIENTS INCLUDED IN THIS GUIDELINE

Febrile infants that **remain on this pathway** include:

- Infants with diarrhea
- Infants with acute otitis media
- Infants with mild viral URI symptoms only (not bronchiolitis) and/or only viral PCR panel positivity

NOTE 10: IF A TERM INFANT 29–60 DAYS HAS AN LP WITH UNEQUIVOCALLY CLEAR CSF, OPTIONS INCLUDE:

- Discharge home after a dose of ceftriaxone AND follow-up within 24 hours OR
- Observe in the hospital without antibiotics OR
- Admit to the hospital with empiric antimicrobials

Use shared decision making with caregivers and clinical judgement considering additional factors such as barriers to follow-up.

Aim: Standardize evaluation and management of well-appearing febrile infants, safely reduce length of stay and any unnecessary interventions.

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