Fever and Neutropenia in Children Receiving Cancer Treatment or with Blood Disorders
Evidence-Based Guideline

**Definition:** Fever is a common sign that suggests infection in children. However, signs and symptoms are often absent or minimized in the child with cancer because of inability to evoke an inflammatory response. In this population, fever is defined as a single temperature >38.3°C (101°F) or a temperature ≥38.0°C (100.4°F) on two occasions one hour apart. Rectal temperatures are not taken in children with cancer. Caregivers should be advised NOT to add a degree to any type of temperature reading. Neutropenia is classified as mild (ANC ≥500-1000/mm³), moderate (ANC ≥200-500/mm³) or severe (ANC <200/mm³). (1,2)

**Pathophysiology:** Chemotherapy agents and radiation therapy cause myelosuppression. In addition, certain malignancies that metastasize to the bone marrow (e.g., leukemia, lymphoma, neuroblastoma, sarcomas) cause a decrease in the number of normal blood cell precursors. When the myelosuppressive effect is severe enough, the child becomes predisposed to infection, anemia, or bleeding, depending on which blood cell line is affected. The risk of serious infection in a child receiving treatment for cancer is related to the degree and duration of neutropenia. Children with brief periods of neutropenia (ANC ≥500) and fever (<7 days) respond better than those with moderate to severe neutropenia (ANC ≤500) lasting more than 7 days. Pneumonitis, cellulitis, bacteremia and abscess can occur when the ANC falls below 500. The risk for bacteremia/sepsis increases when the ANC is <200. (1,2)

**Common Organisms:** Gram + bacteria account for 60-70% of microbial documented infections in children with cancer. (1,2)

**Inclusion Criteria**
Child with fever and neutropenia receiving therapy for cancer
Child with fever and neutropenia with a blood disorder
Child with fever after BMT, see p. 4 & BMT algorithm

**Exclusion Criteria**
Patients with shock symptoms (proceed to shock protocol)

**Diagnostic Evaluation**
Because of the high mortality rate associated with untreated infection, all febrile children with cancer who have neutropenia are considered at risk for a life-threatening infection until proven otherwise. Evaluation of a child with fever and neutropenia should be completed as quickly as possible. The child with fever and neutropenia is at risk for septic shock.

**Table 1. Vital Sign Changes of Sepsis**

<table>
<thead>
<tr>
<th>Age</th>
<th>Heart Rate</th>
<th>Resp Rate</th>
<th>Systolic BP</th>
<th>Temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0d - 1m</td>
<td>&gt; 205</td>
<td>&gt; 60</td>
<td>&lt; 60</td>
<td>&lt;36 or &gt;38</td>
</tr>
<tr>
<td>&gt; 1m - 3m</td>
<td>&gt; 205</td>
<td>&gt; 60</td>
<td>&lt; 70</td>
<td>&lt;36 or &gt;38</td>
</tr>
<tr>
<td>&gt; 3m - 1y</td>
<td>&gt; 190</td>
<td>&gt; 60</td>
<td>&lt; 70</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
<tr>
<td>&gt; 1y - 2y</td>
<td>&gt; 190</td>
<td>&gt; 40</td>
<td>&lt; 70 + (age in yr x 2)</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
<tr>
<td>&gt; 2y - 6y</td>
<td>&gt; 140</td>
<td>&gt; 40</td>
<td>&lt; 70 + (age in yr x 2)</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
<tr>
<td>&gt; 6y - 10y</td>
<td>&gt; 140</td>
<td>&gt; 30</td>
<td>&lt; 70 + (age in yr x 2)</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
<tr>
<td>&gt; 10y - 13y</td>
<td>&gt; 100</td>
<td>&gt; 30</td>
<td>&lt; 90</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
<tr>
<td>&gt; 13y</td>
<td>&gt; 100</td>
<td>&gt; 20</td>
<td>&lt; 90</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
</tbody>
</table>

**Table 2. Signs and Symptoms of Shock**

<table>
<thead>
<tr>
<th>Exam Abnormalities</th>
<th>Cold Shock</th>
<th>Warm Shock</th>
<th>Non-Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Pulses</td>
<td>Decreased or weak</td>
<td>Bounding</td>
<td></td>
</tr>
<tr>
<td>Capillary Refill (central vs. peripheral)</td>
<td>≥ 3 sec</td>
<td>Flash (&lt; 1 sec)</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Mottled, cool</td>
<td>Flushed, ruddy ery throderma (other than face)</td>
<td>Petechiae below the nipple, any purpura</td>
</tr>
<tr>
<td>Mental Status</td>
<td>Decreased, irritability, confusion, inappropriate crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtunded</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**History: Assess for**
- Date of last treatment and details of therapy (agents, dose, route)
- Onset of fever and highest temperature
- (Note: Dexamethasone may mask fever)
- Other symptoms including nausea, vomiting, diarrhea, pain (e.g., mouth, abdomen, perianal), swelling, redness, drainage
- Recent diagnosis of GI or GU tumor
- Exposure to infection (e.g., TB, history of MRSA, recent CVC infection) and seasonal illnesses (i.e., RSV, influenza)
- Recent invasive procedure
- Recent foreign travel
- Renal/Hepatic dysfunction

**Physical Examination: Assess**
- For signs/symptoms of shock (see Tables 1 and 2)
- Entire body for signs, tenderness/pain, induration, redness or discharge from any area; examine closely the skin, nose, teeth, pharynx, sinuses, joints and extremities, procedure sites, perineal and perirectal areas
- Central line - note any redness or drainage along tunnel or at exit site
- Mental status and changes in sensorium

**Laboratory Tests**
- Complete CBC, Chem 7, urinalysis (bagged or clean catch only), blood culture from central and peripheral site of appropriate volume
- Optional studies to consider: C-reactive protein (CRP), stool cultures for history of diarrhea, aspirate or biopsy of any suspicious skin lesion after attending MD consultation
- Urine culture if UA abnormal (non-catheterized)
- CXR in presence of respiratory symptoms, chest pain, tachypnea or decreased pulse oximetry (4-10)
**Critical Points of Evidence**

**Evidence Supports**
Utilize a validated risk stratification rule for patients with fever and neutropenia due to cancer treatment. (2,11-13) – Strong recommendation, moderate quality evidence

Remarks: Evaluation of the evidence does not demonstrate that one prediction rule is more effective over another. Due to the Alexander rule’s documented effectiveness for pediatric patients in North America and England, this rule was chosen as best suited for risk stratification of TCH patients presenting to the ED with fever and neutropenia due to cancer treatment.

Manage low-risk patients with fever and neutropenia due to cancer treatment outpatient with oral antibiotics ensuring frequent follow-up and monitoring. (2,12,14-16) – Strong recommendation, moderate quality evidence

Empiric antibiotics for hematology and oncology patients with fever and neutropenia should be based upon the patient’s risk for bacteremia. See below for antibiotic selection: (2,12,13,17-21) – Strong recommendation, moderate quality evidence

- **Outpatient Low Risk** – Levofloxacin
- **Inpatient Low Risk** – Ceftriaxone
- **High Risk** – Cefepime
- **High Risk with suspicion of G1 issues or typhlitis** – Add Metronidazole

Empiric antibiotics for patients with a history of bone marrow transplant should include vancomycin and cefepime. If there is a suspicion of GI issues or typhlitis, metronidazole should be added. (2,12,13,17-21) – Strong recommendation, moderate quality evidence

Administer empirical antifungal therapy to high-risk patients with no identified infectious source that have persistent fever after 4 – 7 days of broad spectrum antibiotics. (2,12,22-24) – Strong recommendation, low quality evidence

Remarks: There is no one antifungal agent that has been proven superior for use in this population. Unless the patient has concerns for renal or liver toxicity, the guideline development team would recommend the use of liposomal amphotericin B. An equally equivalent selection would be an echinocandin.

In febrile neutropenic patients, antibiotics should be discontinued (although patient may remain hospitalized for observation) if the following criteria are met: – Strong recommendation, low quality evidence (25-29)

- Blood cultures are negative for 48 hours
- Patient is afebrile for 24 hours, has no focal findings and is clinically stable

**Evidence Lacking/Inconclusive**

Draw complete blood counts (CBC) at least every three days. More frequent monitoring may be warranted in patients who are being assessed for count recovery. – Strong recommendation, very low quality evidence

Perform baseline renal functioning testing at initial presentation. – Strong recommendation, very low quality evidence

Consider liver function tests in patients with clinical concerns for liver dysfunction. – Weak recommendation, very low quality evidence

Use of prolonged steroids greater than 7 days may be associated with a higher risk of infection. (30-32) – Strong recommendation, very low quality evidence

Remarks: Knowledge of the use of prolonged steroids should heighten the clinicians’ suspicion for infection; however, management decisions may not be affected. The dose and duration of steroids along with the status of the malignancy and immunodeficiency determine the individual patient’s risk for infection.

Repeat sampling for blood cultures should be obtained from the central line, if applicable, after the initial assessment for CLABSI has been performed. (2,33-37) – Strong recommendation, low quality evidence

Remarks: Central and peripheral blood cultures are obtained initially to diagnosis CLABSI using time-to-positivity. Thereafter, repeat sampling of blood cultures can be obtained from one site. If the initial peripheral culture is positive, repeat sampling of blood cultures from the central site allow for monitoring of organism growth from the CLC and decrease the need for peripheral venipunctures in the patient.

Consider galactomannan and/or CT scans in the patients with persistent fever and neutropenia. (2,12,38-45) – Weak recommendation, low quality evidence

Consider further diagnostic evaluation such as bronchopulmonary lavage or biopsy in FN patients with pulmonary lesions that suggest invasive fungal infections. Preferred approach should be chosen based on the patient’s clinical picture. (12,46-51) – Weak recommendation, low quality evidence

**Evidence Against**

Only obtain a chest x-ray for the initial assessment of patients with fever and neutropenia if respiratory signs and/or symptoms are present. (52) – Strong recommendation, moderate quality evidence

Patients with fever and neutropenia without a clinical change in presentation should not have blood culture sampling repeated daily if adequate volume cultures were obtained on day #1. If initial blood cultures result positive, repeat blood cultures should be obtained until clearance (48 - 72 hours). (12,52-54) – Strong recommendation, low quality evidence

Remarks: If adequate volumes were not obtained on initial cultures, cultures should be repeated the next day ensuring optimal volume. Unnecessary repeat blood cultures can result in an increase rate of false positives in commensal organisms, avoidable waste of blood volume and increase attempts to access central lines. Improvements in optimal blood culture volumes and technology has resulted in the vast majority of positive blood cultures exhibiting growth within 24 hours.
Condition-Specific Elements of Clinical Management

**Risk Assessment at Presentation of FN** *(11,12)*

Patient is considered High Risk if ANY of the following clinical criteria is present:

- High-risk diagnoses
  - ALL and lymphoma patients who are not in maintenance therapy
  - Infant ALL
  - Acute Myeloid Leukemia (AML)
  - Relapsed/Progressive Leukemia
  - Bone Marrow Transplant patients
  - HLH patients
  - Severe aplastic anemia / Bone marrow failure patients
  - Primary Immunodeficiencies patients
  - Neuroblastoma enrolled in SPRING study
  - Age <1 year
  - Down Syndrome
  - 2 normal saline boluses in the ER
  - Abnormal vital signs (except temperature) at time of disposition or changes in mental status
  - Focal infection (e.g., mucositis, abdominal pain, cellulitis, pneumonia, perianal tenderness)

Patient should be admitted for Low Risk treatment management if any of the following exclusions are present:

- Inability to take PO antibiotics
- Allergy to Levofloxacin
- Parents with a history of poor compliance or follow-up
- Absence of working telephone
- Families that live farther than 1 hour/40 miles from the main campus ER of TCH
- Parental preference to be admitted
- If patient cannot be seen in the Oncology Clinic Urgent Care Bay within 3 calendar days of discharge from the ER

Patient is eligible for Low Risk outpatient management if they have no exclusion above.

**Early Assessment and Diagnostic Work-up**

- Careful, detailed history and thorough physical exam
- Initiate Life Threatening Lab System - CBC, BUN, Cr
- Draw other labs: Lytes, LFTs, urinalysis, blood culture from a central and peripheral site of appropriate volume, site specific cultures as clinically indicated
- Diagnostic Imaging - CXR if respiratory signs/symptoms present including chest pain, tachypnea, decreased pulse oximetry

**Empiric Antibiotic Selection** *(2,12-21,95)*

- **High Risk inpatient Intravenous Treatment**: Cefepime (Table 3)
- **High Risk Inpatient with GI issues and/or otitis**: Add Metronidazole (Table 3)
- **Low Risk Inpatient Intravenous Treatment**: Ceftriaxone (Table 3)

Initiate antibiotics ASAP (preferably within ONE HOUR of arrival)

All antibiotics should be rotated among the different CVC lumens, so all lumens are exposed to all antibiotics. If only one lumen has a positive blood culture, all antibiotics should then be administered through that lumen *(1,2)*

**Treatment and Ongoing Management**

- Be prepared to start IV or access CVC and draw blood
- Normal saline bolus for hypotension
- Blood product support if needed
- Daily evaluate: Central venous catheter site(s), surgical incisions, other breaks in skin, oral mucosa, peri-rectal area
- With continued fever, repeat urine, stool, and tissue cultures, obtain diagnostic imaging as clinically indicated

**Monitoring**

- Careful monitoring should continue as long as the child is neutropenic
- Complete blood count with differential at least every 3 days *(2)*
- Baseline renal function testing at initial presentation
- Monitor liver function tests if clinical concern for liver dysfunction
- Serum chemistries at least every 3 days - monitor for electrolyte depletion *(2)*
- Monitor creatinine daily if rises over baseline
- Urine samples – monitor for glycosuria, hematuria, and albuminuria, sodium and potassium, as clinically indicated
- Patients with history of renal dysfunction calculate antibiotic dosing with creatinine clearance method below

**Specific monitoring:**

- **Aminoglycosides**: Serum drug peak and trough to be obtained w/ the 3rd to 5th dose
- “Creatinine Clearance estimation method by Modified Schwartz equation:
  - GFR (mL/min/1.73 m²) = 0.413 x length (cm)/serum creatinine (mg/dL)

**Preserving/Removing the Central Line** *(2,56-58)*

The benefit of catheter removal must be weighed against the difficulty of obtaining alternate venous access for each individual patient. Prompt removal of the central line should be considered when any of the following conditions and/or organisms exists:

- Severe sepsis
- Endocarditis
- Bloodstream infection that continues despite >72 h of antimicrobial therapy to which the infecting microbes are susceptible
- Infections due to *S. aureus*, gram-negative bacilli including *P. aeruginosa*, *Bacillus* species, and/or enterococci

Prompt removal of the catheter is necessary in cases of:

- Infections due to mycobacteria and/or fungi
- Tunnel site infection (e.g., redness, inflammation along catheter line, purulent drainage)
- Suppurative thrombophlebitis

Consider removal of the central line when the integrity of the line is compromised as evidence by broken, cracked or clotted lumens.

**Management of Persistent Fever**

- If fever continues on broad spectrum antibiotics for >4 - 7 days, begin antifungal agents and perform evaluation for invasive fungal disease *(2,12,22-24)*
- Obtain an ID consult

  Consider monitoring galactomannan and/or CT scans *(2,12,38-45)*

- CT evaluations to assess fungal infection should include scans of the lungs and other areas as clinically indicated. CT scans of the sinuses can be considered in children two years of age or older, and especially in those with complaints of sinus pain *(2)*

- In patients with pulmonary lesions suggestive of fungal infection, consider further diagnostic evaluation such as bronchopulmonary lavage or biopsy. Preferred approach should be chosen based on the patient’s clinical picture *(12)*

- If there is clinical or laboratory evidence of HSV, administer antiviral treatment *(2)*

- Consider culture for HSV in patients with mucositis.
**The BMT Patient with Fever and Suspected Infection**

**Definition:** Fever is a common sign that suggests infection in children. However, signs and symptoms are often absent or minimized in the child following BMT because of inability to evoke an inflammatory response. In this population, fever is defined as a single oral temperature ≥38.0°C (100.4°F). Rectal temperatures are NOT taken in BMT patients. Caregivers should be advised to NOT add a degree to any type of temperature reading. Neutropenia is classified as mild (ANC >500-1000/mm³), moderate (ANC ≥200-500/mm³) or severe (ANC <200/mm³). (1.2)

**Pathophysiology:** After allogeneic BMT, there is a loss of both innate and acquired immunity, which persists for more than 12 months, and even longer in patients receiving immunosuppressive medications. Consequently, BMT patients are particularly at risk for not only bacterial, but fungal and viral infections post-transplant. Oftentimes, BMT patients may have systemic infection in the absence of neutropenia. In fact, the vast majority of BMT patients will not be neutropenic but may still present with bacterial sepsis, especially those with indwelling central catheters and active GVHD. While the risk for serious infection in a neutropenic child is related to the degree and duration of neutropenia, BMT patients may have serious infection with normal neutrophil counts. Judicious use of fluid resuscitation is necessary in BMT patients as they have a high incidence of capillary leak and pulmonary disease and can easily be fluid overloaded. (6941)

**Rationale:** Because of the high-risk of infection post BMT (bacterial, fungal or viral), patients who present to the EC with or without fever, should be promptly triaged and isolated from other patients. Children with underlying immune deficiencies, such as SCID, should be in reverse isolation at all times. Blood cultures and labs should be promptly obtained and appropriate antibiotics given within 60 minutes. The BMT physician on call should be notified immediately upon arrival of any BMT patient. In general, patients who are less than 100 days post BMT are at a much higher risk for serious bacterial infection and should be considered for admission after appropriate antibiotics given. Children who are hemodynamically unstable or exhibiting even mild signs of early shock (including chills) should be admitted with triple antibiotic coverage. (82)

**Common Organisms:** Gram positive bacteria account for 60-70% of microbial documented infections. (1.2)

<table>
<thead>
<tr>
<th>Gram positive</th>
<th>Gram negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus</td>
<td>Enterobacter</td>
</tr>
<tr>
<td>E. coli</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>Pseudomonas</td>
</tr>
</tbody>
</table>

**Diagnostic Evaluation:** Because of the high mortality rate associated with untreated infection, all febrile children who have received a BMT are considered at risk for a life threatening infection until proven otherwise. Additionally, BMT patients experiencing chills who may not yet have fever, also should be considered at risk for a life threatening infection until proven otherwise. Evaluation of a BMT patient with suspected infection should be completed as quickly as possible as they are at risk for septic shock. Signs and symptoms include:

- Fever and/or chills or rigors
- Tachypnea
- Pulse oximetry < 95%
- Early - w arm, flushed, dry skin
- Tachycardia
- Hypotension
- Decreased urine output
- Late - cool, clammy skin
- Increased heart rate
- Decreased breath sounds
- Poor peripheral pulses
- Mottled, cool skin
- Petechiae below the nipple, any purpura
- Decreased, irritability, confusion
- Inappropriate crying or drowsiness
- Poor interaction with parents, lethargy
- Diminished arousability, obtunded

**Table 1. Vital Sign Changes of Sepsis**

<table>
<thead>
<tr>
<th>Age</th>
<th>Heart Rate</th>
<th>Resp Rate</th>
<th>Systolic BP</th>
<th>Temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0d - 1m</td>
<td>&gt; 205</td>
<td>&gt; 60</td>
<td>&lt; 60</td>
<td>&lt;36 or &gt;38</td>
</tr>
<tr>
<td>&gt; 1m - 3m</td>
<td>&gt; 205</td>
<td>&gt; 60</td>
<td>&lt; 70</td>
<td>&lt;36 or &gt;38</td>
</tr>
<tr>
<td>&gt; 3m - 1y</td>
<td>&gt; 190</td>
<td>&gt; 60</td>
<td>&lt; 70</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
<tr>
<td>&gt; 1y - 2y</td>
<td>&gt; 190</td>
<td>&gt; 40</td>
<td>&lt; 70 + (age in yr x 2)</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
<tr>
<td>&gt; 2y - 4y</td>
<td>&gt; 140</td>
<td>&gt; 40</td>
<td>&lt; 70 + (age in yr x 2)</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
<tr>
<td>&gt; 4y - 7y</td>
<td>&gt; 140</td>
<td>&gt; 34</td>
<td>&lt; 70 + (age in yr x 2)</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
<tr>
<td>&gt; 6y - 10y</td>
<td>&gt; 140</td>
<td>&gt; 30</td>
<td>&lt; 70 + (age in yr x 2)</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
<tr>
<td>&gt; 10y - 13y</td>
<td>&gt; 100</td>
<td>&gt; 30</td>
<td>&lt; 90</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
<tr>
<td>&gt; 13y</td>
<td>&gt; 100</td>
<td>&gt; 20</td>
<td>&lt; 90</td>
<td>&lt;36 or &gt;38.5</td>
</tr>
</tbody>
</table>

**Table 2. Signs and Symptoms of Shock**

<table>
<thead>
<tr>
<th>Exam Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Pulses</td>
</tr>
<tr>
<td>Capillary Refill</td>
</tr>
<tr>
<td>≥ 3 sec</td>
</tr>
<tr>
<td>Flash (&lt; 1 sec)</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Mottled, cool</td>
</tr>
<tr>
<td>Flushed, ruddy</td>
</tr>
<tr>
<td>Petechiae below that</td>
</tr>
<tr>
<td>Mental Status</td>
</tr>
<tr>
<td>Decreased, irritability,</td>
</tr>
<tr>
<td>Decreased, irritability,</td>
</tr>
<tr>
<td>confusion, inappropriate</td>
</tr>
<tr>
<td>crying or drowsiness,</td>
</tr>
<tr>
<td>poor interaction with</td>
</tr>
<tr>
<td>parents, lethargy,</td>
</tr>
<tr>
<td>diminished arousability,</td>
</tr>
<tr>
<td>obtunded</td>
</tr>
</tbody>
</table>

**History:** Assess
- Date of BMT and time post BMT (< or > 100 days)
- Onset of fever and highest temperature
- Presence of central line
- Medications, such as immunosuppressants (tacrolimus, cyclosporine, prednisone and MMF most common)
- Other symptoms including nausea, vomiting, diarrhea, pain (e.g., mouth, abdomen, perianal), swelling, redness, drainage
- Recent invasive procedure
- Renal/Hepatic dysfunction

**Physical Examination:** Assess
- For signs/symptoms of shock (Tables 1 and 2)
- Pulse oximetry
- Entire body for signs of infection, including tenderness/pain, induration, redness or discharge from any area; examine closely the skin, nose, teeth, pharynx, sinuses, joints and extremities, procedure sites, perineal and perirectal areas
- Central line note any redness or drainage along tunnel or at exit site
- Mental status and changes in sensorium

**Diagnostic and Laboratory Studies:** Assess
- Complete CBC, Chem 10, LFTs
- Blood cultures from central (CV-C all lumens, include portacath) and peripheral site of appropriate volume
- Nasal wash for RSV, flu, viral culture and “respiratory viral panel” in patients with rhinorrhea
- Diarrheal stools for bacteria, ova/parasites, viral particles and Clostridium difficile toxin
- UA, U/C (bagged or clean catch only)
- Chest x-ray
**Considerations for Discharge**

Bedside providers should use clinical judgement and assessments to determine when to discharge patients home, taking into consideration:

- Blood cultures are negative for 48 hours
- Patient is afebrile for 24 hours (Off empiric antibiotics if blood cultures were negative)
- Patient is clinically stable
- Patient is tolerating oral intake
- Patient has no focal findings
- Patient lives within 1 hour geographically to return for immediate medical assessment if cause for concern
- If family is reliable / comfortable with managing at home

**Measures**

**Process**

- Antibiotic administration initiated within one hour of patient arrival to EC or TXCH
- Frequency of adequate volume blood cultures
- Frequency of optimal volume blood cultures
- Method of diagnosis of fungal infections

**Outcome**

- Readmission through EC or TXCH triage for fever and neutropenia
- Patients transferred to PICU within 72 hours of admission
- Patients admitted for monotherapy whose antibiotics were changed
- Admission due to positive blood culture after discharge from EC or TXCH triage
- Rate of bacteremia for low risk patients
- Admission rate for low risk patients discharged home from the EC
### Table 3. Antibiotic Therapy (2.12-21.55)
**(For Hematology/Oncology and BMT Patients)**

<table>
<thead>
<tr>
<th>Patient Class</th>
<th>Medications</th>
<th>Dose and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On Arrival in EC or TXCH Clinic</strong></td>
<td>Ceftriaxone</td>
<td>50 mg/kg/dose IV for one dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>MAX</strong>: 2 grams/dose</td>
</tr>
<tr>
<td><strong>Outpatient Low Risk Treatment</strong></td>
<td>Levofloxacin</td>
<td>Age &lt;5 years: 10 mg/kg/dose PO twice daily for 7 days</td>
</tr>
<tr>
<td>(refer to Patient Risk Assessment for eligibility)</td>
<td></td>
<td>Age ≥5 years: 10 mg/kg/dose PO once daily for 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>MAX</strong> daily dose: 750 mg</td>
</tr>
<tr>
<td><strong>Inpatient Low Risk Management</strong></td>
<td>Ceftriaxone</td>
<td>50 mg/kg/dose IV every 24 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>MAX</strong>: 2 grams/dose</td>
</tr>
<tr>
<td><strong>Inpatient High Risk Hematology/Oncology Management</strong></td>
<td>Cefepime</td>
<td>50 mg/kg/dose IV every 8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>MAX</strong>: 2 grams/dose</td>
</tr>
<tr>
<td><strong>Suspected Intra-abdominal Process</strong> Add MeTRONidazole</td>
<td>7.5 mg/kg/dose IV every 6 hours</td>
<td><strong>MAX</strong>: 500 mg/dose</td>
</tr>
<tr>
<td><strong>Inpatient Bone Marrow Transplant Management</strong></td>
<td>Vancomycin</td>
<td>Weight &lt;70 kg: 15 mg/kg/dose IV every 8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight ≥70 kg: 1000 mg/dose IV every 12 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>MAX</strong>: 1 gram/dose</td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
<td>50 mg/kg/dose IV every 8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>MAX</strong>: 2 grams/dose</td>
</tr>
<tr>
<td><strong>Suspected Intra-abdominal Process</strong> Add MeTRONidazole</td>
<td>7.5 mg/kg/dose IV every 6 hours</td>
<td><strong>MAX</strong>: 500 mg/dose</td>
</tr>
</tbody>
</table>
Clinical Algorithm for Fever and Neutropenia in Children Receiving Cancer Treatment or With Blood Disorders

EC Algorithm

Septic Shock Criteria
Immediately refer to the Septic Shock guideline and intervene rapidly if patient has toxic-appearance, ill-appearance, altered mental status, and/or compromised perfusion with abnormal vital signs

<table>
<thead>
<tr>
<th>Age</th>
<th>Heart Rate</th>
<th>Resp Rate</th>
<th>Systolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 d - 1 m</td>
<td>&gt; 205</td>
<td>&gt; 60</td>
<td>&lt; 60</td>
</tr>
<tr>
<td>&gt; 1 m - 3 m</td>
<td>&gt; 205</td>
<td>&gt; 60</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>&gt; 3 m - 1 y</td>
<td>&gt; 190</td>
<td>&gt; 60</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>&gt; 1 y - 2 y</td>
<td>&gt; 190</td>
<td>&gt; 40</td>
<td>&lt; 70 + (age in yr x 2)</td>
</tr>
<tr>
<td>&gt; 2 y - 4 y</td>
<td>&gt; 140</td>
<td>&gt; 40</td>
<td>&lt; 70 + (age in yr x 2)</td>
</tr>
<tr>
<td>&gt; 4 y - 6 y</td>
<td>&gt; 140</td>
<td>&gt; 34</td>
<td>&lt; 70 + (age in yr x 2)</td>
</tr>
<tr>
<td>&gt; 6 y - 10 y</td>
<td>&gt; 140</td>
<td>&gt; 30</td>
<td>&lt; 70 + (age in yr x 2)</td>
</tr>
<tr>
<td>&gt; 10 y - 13 y</td>
<td>&gt; 100</td>
<td>&gt; 30</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>&gt; 13 y</td>
<td>&gt; 100</td>
<td>&gt; 16</td>
<td></td>
</tr>
</tbody>
</table>

*Age-Specific Abnormal Vital Signs

- Assess risk
- Page Oncology fellow
- Observe 1 h post-abx, discharge if clinically well
- Return to clinic or ER next day if remains febrile or new symptoms arise

Diagnoses Eligible for Low Risk Management
- ALL in maintenance
- Solid Tumor

Low-Risk Inpatient Management
Admit patient to inpatient Low-Risk unit
Administer PO Levofloxacin on ceftriaxone monotherapy

Low-Risk Inpatient Management Antibiotics
- PO Levofloxacin for 7 days
  - Age < 5 years: 10 mg/kg/dose PO twice daily for 7 days
  - Age ≥ 5 years: 10 mg/kg/dose PO once daily for 7 days
  - MAX daily dose: 750 mg

- Parental preference to be admitted
- If patient cannot be seen in the Oncology Clinic Urgent Care Bay within 3 calendar days of discharge from the ER

High-Risk Criteria Exclusions
- Patient is considered High Risk if ANY of the following criteria is present:
  - High-risk diagnoses
    - ALL and lymphoma patients who are not in maintenance therapy
    - Infant ALL
    - Acute Myeloid Leukemia (AML)
    - Relapsed/Progressive Leukemia
    - Bone Marrow Transplant patients
    - HLH patients
    - Severe aplastic anemia / Bone marrow failure patients
    - Primary Immunodeficiencies patients
    - Neuroblastoma enrolled in the SPRING study
  - Age < 1 year
  - Down Syndrome
  - > 2 normal saline boluses in the ER
  - Abnormal vital signs except temperature at time of disposition
  - Changes in mental status
  - Focal infection (e.g., mucositis, abdominal pain, cellulitis, pneumonia, perianal tenderness)

Psychosocial Exclusions to Low-Risk Outpatient Management
- Inability to take PO antibiotics
- Allergy to Levofloxacin
- Parents with a history of poor compliance or follow-up
- Absence of working telephone
- Families that live farther than 1 hour/40 miles from the main campus ER of TCH

© Evidence-Based Outcomes Center
Texas Children’s Hospital
**Inpatient Algorithm**

**Admission**

- Admission

**Admitted under Low Risk Criteria**

- Yes: Eligible for discharge after 24 hours, if warranted
- No: Continue empiric antibiotics and reassess at 48 hours

**Continue empiric antibiotics and reassess at 48 hours**

- Pathogen found in culture
  - Yes: Remove CVC if needed
    - For other pathogens, consider removal of CVC with Infectious Disease Consult
    - Complete optimal antibiotic treatment for positive cultures and patient afebrile 24 hours
  - No: Meets discharge Criteria at 48 hours

**Meets discharge Criteria at 48 hours**

- Yes: Discharge with scheduled follow up
- No: Persistent fever ≥ 96 hours

**Persistent fever ≥ 96 hours**

- Yes: Discontinue empiric antibiotics
  - Blood cultures are negative x 48 hours
  - Patient is afebrile x 24 hours
  - Patient has no focal findings
  - Patient is clinically stable
  - Reassess daily for meeting discharge criteria
  - Consult Infectious Disease
    - Begin antifungal therapy
    - Consider performing a CT scan
    - Evaluate for fungal, mycobacterial and viral infections
    - Consider galactomannan testing
    - If CT suggestive of fungal infection or galactomannan positive, consider further diagnostic test such as bronchopulmonary lavage or biopsy.
    - Consider acyclovir if clinical or laboratory indication for HSV
    - Consider examining antibiotic drug levels if a history of renal dysfunction

**Discontinue empiric antibiotics if**

- Blood cultures are negative x 48 hours
- Patient is afebrile x 24 hours
- Patient has no focal findings
- Patient is clinically stable

**Reassess daily for meeting discharge criteria**

**CT Scans to Assess Fungal Infection**

- CT evaluations to assess fungal infection should include scans of the lungs and other areas as clinically indicated. CT scans of the sinuses can be considered in children two years of age or older, and especially in those with complaints of sinus pain.

**Septic Shock Criteria**

- Immediately refer to the Septic Shock guideline and intervene rapidly if patient has toxic-appearance, ill-appearance, altered mental status, and/or compromised perfusion with abnormal vital signs.

**Discharge Criteria**

- Bedside providers should use clinical judgment and assessments to determine when to discharge patients home, taking into consideration:
  - Blood cultures are negative x 48 hours
  - Patient is afebrile x 24 hours (Off empiric antibiotics if blood cultures were negative)
  - Patient is clinically stable
  - Patient is tolerating oral intake
  - Patient has no focal findings
  - Patient lives within 1 hour geographically to return for immediate medical assessment if cause for concern
  - If family is reliable/comfortable with managing at home

**Preserving/Removing the Central Line**

- Prompt removal of the central line should be considered when any of the following conditions and/or organisms exists:
  - Severe sepsis
  - Endocarditis
  - Bloodstream infection that continues despite > 72 h of antimicrobial therapy to which the infecting microbes are susceptible
  - Infections due to S. aureus, gram-negative bacilli including P. aeruginosa, Bacillus species, and/or enterococci

- Prompt removal of the catheter is necessary in cases of:
  - Infections due to mycobacteria and/or fungi
  - Tunnel site infection (e.g., redness, inflammation along catheter line, purulent drainage)
  - Suppurative thrombophlebitis
### Clinical Algorithm for Management of BMT Patient with Fever

**Begin**

- Page BMT fellow on call upon pt arrival
- Access CVC/Portacath; if none, start peripheral IV
- Obtain: CBC, Chem10, blood culture from central (all lumens) and peripheral site, UA, CXR
- Administer appropriate antibiotics within 1 h of arrival (see below)

**Septic Shock Criteria**
Immediately refer to the Septic Shock guideline and intervene rapidly if patient has toxic appearance, ill-appearance, altered mental status, and/or compromised perfusion with abnormal vital signs.

**TCH Evidence-Based Outcomes Center**

#### *Age-Specific Abnormal Vital Signs*

<table>
<thead>
<tr>
<th>Age</th>
<th>Heart Rate</th>
<th>Resp Rate</th>
<th>Systolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 d - 1 m</td>
<td>&gt; 205</td>
<td>&gt; 60</td>
<td>&lt; 60</td>
</tr>
<tr>
<td>&gt; 1 m - 3 m</td>
<td>&gt; 205</td>
<td>&gt; 60</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>&gt; 3 m - 1 y</td>
<td>&gt; 190</td>
<td>&gt; 60</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>&gt; 1 y - 2 y</td>
<td>&gt; 190</td>
<td>&gt; 40</td>
<td>&lt; 70 + (age in yr x 2)</td>
</tr>
<tr>
<td>&gt; 2 y - 4 y</td>
<td>&gt; 140</td>
<td>&gt; 40</td>
<td>&lt; 70 + (age in yr x 2)</td>
</tr>
<tr>
<td>&gt; 4 y - 6 y</td>
<td>&gt; 140</td>
<td>&gt; 34</td>
<td>&lt; 70 + (age in yr x 2)</td>
</tr>
<tr>
<td>&gt; 6 y - 10 y</td>
<td>&gt; 140</td>
<td>&gt; 30</td>
<td>&lt; 70 + (age in yr x 2)</td>
</tr>
<tr>
<td>&gt; 10 y - 13 y</td>
<td>&gt; 100</td>
<td>&gt; 30</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>&gt; 13 y</td>
<td>&gt; 100</td>
<td>&gt; 16</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

**Risk Assessment Criteria**
Patient is considered **High Risk** if ANY of the following criteria is present:
- < 100 days post-BMT
- Active GvHD
- ≥ 2 immunosuppressants
- H/o fever within 30 min. of central line flush
- Splenectomized patients
- Mucositis/Stomatitis
- Signs and symptoms of focal infection

**Fluid Management**
Judicious use of fluids due to:
- High risk of capillary leak and subsequent respiratory failure
- May have preexisting lung disease
- Early use of pressors for hypotension/sepsis
- Choose 20 ml/kg fluid bolus unless patient condition prohibits rapid fluid resuscitation. High Risk patients include history of bone marrow transplant within the last 100 days.
- If additional fluid is required, discuss with BMT team
- Assess need for stress dose steroid

**ISSUES SPECIFIC TO BMT PATIENTS**
- BMT fellow is to be called immediately upon patient arrival. If fellow does not respond within 10 minutes, please call the BMT attending.
- Fever in BMT Patient – Temp ≥ 100.4°F regardless of source
- Must check previous culture results and tailor antibiotics and/or make admission decisions accordingly (e.g., make sure to cover same bacteria present previously)
- Patient should be placed in a private room.
- SCID patients should be placed in a private room; healthcare providers must wear mask, gloves and gown in room.
- Be cautious of renal dysfunction and use renal dosing of antibiotics as necessary.
- Ask patient if they have a portacath. Many patients have both a port and an external PICC line. All lumens must be cultured.
- If admitted, must rotate antibiotics through all lumens.

**S/Sx of sepsis**

- Yes
- Admit on antibiotics:
  - Vancomycin
  - Cefepime
  - Gentamicin
  - If suspected intraabdominal process and/or typhlitis: Add Metronidazole to above regimen

- No
- Observ 1 h post-abx; if clinically well, RTC next day

**Assess risk**

- Low risk
- High risk

**Admit on antibiotics**
- Vancomycin
- Cefepime
- Gentamicin
- If suspected intraabdominal process and/or typhlitis: Add Metronidazole to above regimen

**ANC < 500/mm³**

- Yes
- Admit on antibiotics:
  - Vancomycin
  - Cefepime
  - Gentamicin
  - If suspected intraabdominal process and/or typhlitis: Add Metronidazole to above regimen

- No
- Assess risk

© Evidence-Based Outcomes Center
Texas Children's Hospital
March 2021
References


Low Risk Fever and Neutropenia Discharge Instructions - English

Low Risk Fever and Neutropenia Discharge Instructions - Spanish
Clinical Standards Preparation
This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children’s Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

Fever and Neutropenia in Children Receiving Cancer Treatment or with Blood Disorders Clinical Guideline

Content Expert Team
Adenike Adelunke-Ojo, MD, Emergency Medicine
Abhishek Bavlé, MD, Pediatric Hematology Oncology Fellow
Amanda Berger, Pharm D, Pharmacy
B. Cline, RN, Infection Control
Janet Dejean, CNS, Cancer Center
Zoann Dreyer, MD, Pediatric Hematology Oncology
Mona Shah, MD, Pediatric Hematology Oncology
Caridad Martinez, MD, BMT
Stephanie Gruner, PNP, Cancer Center
C. Phillip Steuber, MD, Pediatric Hematology Oncology
Amanda Grimes, MD, Pediatric Hematology Oncology Fellow
Katherine King, MD, Infectious Disease
Joyee Vachani, MD, Pediatric Hospital Medicine
Elizabeth Wuestner, RN, Emergency Center
Andras Hecezy, MD, Pediatric Oncology
Sheesha Porter, MSN, RN, Evidence Team
Betsy Lewis, MSN, RN, CNL, Evidence-Based Practice Specialist
Andrea Jackson, MBA, RN, Evidence-Based Practice Specialist
Amanda Berger, Pharm D, Pharmacy
Debra Palazzi, MD, Infectious Disease
Paula Revel, MD, Pathology
Moni Shah, MD, Pediatric Hematology Oncology
Sibo Zhao, MD, Pediatric Hematology Oncology Fellow
Janet Dejean, CNS, Cancer Center
Warren Boudreau, MSN, RN, Director

Additional EBOC Support
Betsy Lewis, MSN, RN, CNL, Evidence-Based Practice Specialist
Sheesha Porter, MSN, RN, Evidence-Based Practice Specialist
Anne Dyles, MSN, RN, Manager
Debra Palazzi, MD, Infectious Disease
Paula Revel, MD, Pathology
Moni Shah, MD, Pediatric Hematology Oncology
Joyee Vachani, MD, Pediatric Hospital Medicine
Elizabeth Wuestner, RN, Emergency Center
Sibo Zhao, MD, Pediatric Hematology Oncology Fellow
Amanda Berger, Pharm D, Pharmacy
Debra Palazzi, MD, Infectious Disease
Paula Revel, MD, Pathology
Moni Shah, MD, Pediatric Hematology Oncology
Sibo Zhao, MD, Pediatric Hematology Oncology Fellow
Evaluating the Quality of the Evidence

Summary: The summary of research findings provides support for treatment interventions. “Evidence Supports” provides evidence to support an intervention. “Evidence Against” provides evidence to refute an intervention. “Evidence Lacking/Inconclusive” indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn from the 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, RCTs with serious flaws or indirect evidence
Very Low
Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations
Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of Fever and Neutropenia in Children Receiving Cancer Treatment or with Blood Disorders Clinical Guideline in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process
Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children’s Hospital. Content Expert Teams are involved with every review and update.
Disclaimer
Practice recommendations are based upon the evidence available at the time the clinical standards were developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient’s family, to make the ultimate judgment regarding care.

<table>
<thead>
<tr>
<th>Action</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Originally completed</td>
<td>June 2010</td>
</tr>
<tr>
<td>Updated</td>
<td>September 2016</td>
</tr>
<tr>
<td>Revision</td>
<td>June 2017</td>
</tr>
<tr>
<td>Revision</td>
<td>September 2017</td>
</tr>
<tr>
<td>Revision</td>
<td>November 2018</td>
</tr>
<tr>
<td>Revision</td>
<td>January 2019</td>
</tr>
<tr>
<td>Revision</td>
<td>June 2020</td>
</tr>
<tr>
<td>Reaffirm</td>
<td>March 2021</td>
</tr>
</tbody>
</table>