Fever and Neutropenia

Children with malignancy who are undergoing chemotherapy frequently develop neutropenia during therapy. When that child (or any child with neutropenia) develops fever in the face of neutropenia, there is concern that the child may have a life-threatening infection. Protocolized care in this population has been shown to streamline care and improve outcomes. This speaker will discuss multidisciplinary protocol development and outcomes from institutions where clinical care protocols are in place.

OBJECTIVES
- Describe risk faced by a child with fever and neutropenia
- Recognize a child with fever and neutropenia including the warning signs of severe disease
- Discuss development and implementation of a protocol to manage this population of patients
- Outline outcome measures that can be monitored to ascertain if care is improving as a result of the guideline

3/24/2015
2:15 PM-2:45 PM
Grand Ballroom
TU-6

DISCLOSURES:
(+) No significant financial relationships to disclose
Management of pediatric fever and neutropenia

Joan E. Shook M.D., M.B.A. FACEP FAAP
Professor of Pediatrics
Baylor College of Medicine
Chief Safety Officer
Chief Clinical Information Officer
Texas Children’s Hospital

I have no conflicts of interest to disclose
Plan for the session

By the end of the session the participant should

1. Have an updated understanding of fever and neutropenia in children

2. Understand the utility an evidence based (EB) guideline in the management of a child with fever and neutropenia

3. Feel comfortable assessing his/her practice in light of a EB guideline
Neutropenia in children

• Children with depressed immune function, including neutropenia, are at increased risk for serious bacterial, viral and fungal infections.

• Children at risk for developing neutropenia include patients using chemotherapeutic agents or other medications that alter immune function.

Phillips et al J Clin Oncol 2012
Neutropenia in children

• Fever and neutropenia (FN) are common complications in children who receive chemotherapy for cancer
  - Risk is enhanced by the presence of in-dwelling catheters

• Children with HIV, Crohn’s, rheumatoid arthritis, lupus, and underlying immunodeficiency states either congenital or acquired may also have neutropenia

Phillips et al J Clin Oncol 2012
Definitions: Fever and Neutropenia (FN)

• Fever
  - Temperature > 38°C for more than an hour or
  - Single temperature > 38.3°C

• Neutropenia defined by absolute neutrophil count (ANC)
  - Classic: ANC < 1500/mm³
  - Moderate neutropenia: ANC between 500-1000/mm³
  - Severe neutropenia: ANC < 500/mm³

• Risk of infection increases as ANC decreases
Unsuspected neutropenia in children

• Review of 1888 children 0-21y who presented with ANC<1000 with no known risk factors for SBI (central venous line or immunodeficiency)
  - Evaluated for SBI using blood, urine and CSF
  - 15/453 (3.3%) infants < 3mos had SBI
    • 7 bacteremia
    • 4 meningitis
    • 8 UTI
  - 18/1435 (0.01%) >3mos had SBI
    • 1 bacteremia
    • 14 UTI

Melendez E and M Harper AEM  2010
Unsuspected neutropenia in children

• Review of 1888 children 0-21y who presented with ANC<1000 with no known risk factors for SBI (central venous line or immunodeficiency)

• Conclusion: children with incidental neutropenia are not at increased risk of SBI

Melendez E and M Harper AEM 2010
Pediatric cancer patients in the ED

- Review of cohort of pediatric (<19y) patients with cancer presenting between 2006-2010
  - Data source: Nationwide Emergency Department Sample database

- 294,289 visits identified
  - Fever and fever neutropenia accounted for 20% of visits
  - 44% of patients were admitted overall
    - 88% FN patients were admitted

Mueller, E et al Ped Blood Cancer 2015
Pediatric cancer patients in the ED

- 294,289 PED visits

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis</th>
<th>% visits</th>
<th>Adm%</th>
<th>Transfer%</th>
<th>Home%</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Fever</td>
<td>11.3</td>
<td>17</td>
<td>4</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>FN</td>
<td>7.9</td>
<td>82</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Bloodstream infection</td>
<td>4.3</td>
<td>75</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>URI</td>
<td>2.8</td>
<td>21</td>
<td>1</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>Pneumonia</td>
<td>2.5</td>
<td>67</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>Neutropenia</td>
<td>2.2</td>
<td>80</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>Headache</td>
<td>2.2</td>
<td>11</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>Seizure</td>
<td>1.5</td>
<td>41</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>9</td>
<td>UTI</td>
<td>1.3</td>
<td>35</td>
<td>2</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>Dehydration</td>
<td>1.3</td>
<td>56</td>
<td>3</td>
<td>39</td>
</tr>
</tbody>
</table>

Mueller, E et al *Ped Blood Cancer* 2015
Pediatric cancer patients in the ED

• Variations in practice noted
  - Patients presenting to metropolitan teaching hospital had higher odds of admission and patients presenting to non-metropolitan hospital had lower odds of admission than patients presenting to metropolitan non-teaching hospital
  - Socioeconomic factors had significant impact on admission
    • Lower odds of admission with “self pay” patients
    • Higher odds of admission with zip codes with high SES

Mueller, E et al *Ped Blood Cancer* 2015
Etiology and clinical course of FN

• Review of 337 episodes of FN in children with cancer at St. Jude’s Children’s Research Hospital
  - **Infection proven** (isolation of an organism from a sterile body site in a clinical setting consistent with an infection) in 86 (25%)
    • 54 (63%) had bacterial infections
    • 29 (34%) had viral infections
  - **Infection probable** (clinical or radiographic findings of infection where patient shows prompt response to antimicrobials) in 75 (22%)
  - **Fever of unknown origin** in 177 (53%)

• Infection related mortality: 0.6%

Hakim, H et al J Ped Hemat Oncol 2009
Etiology and clinical course of FN

• Bacteremia accounted for most of proven episodes (n=41)
  - Most common organisms: *Strep viridans* (13), *Pseudomonas* (6), *E. coli* (6)
  - Median time to positive BC 12 hours: 93% positive within 24 hours

• Viral etiologies more frequent than found in prior studies
  - Better availability of viral diagnostics

• Fever of unknown origin in 177 (53%) characterized by
  - Shorter median duration of fever
  - Longer duration since last chemotherapy
  - Less likely to have AML

Hakim, H et al J Ped Hemat Oncol 2009
Guideline for Management of FN in Children with Cancer

• International Pediatric Fever and Neutropenia Guideline panel was convened to develop an evidence based (EB) algorithm for pediatric oncology patients

  - Treatment algorithms for adults with cancer exist
  - Consensus statements exist on risk stratification for adults on when to assess for risk of adverse events
  - These algorithms cannot be applied to children
EB Guideline: clinical features

• History and physical examination
  - Patient specific markers
    • Age,
    • Malignancy type
    • Disease status
  - Treatment specific factors
    • Type and timing of chemotherapy
  - Episode specific factors
    • Height of the fever
    • Blood counts, CRP
    • Mucositis, hypotension
EB Guideline: risk stratification

• Six low risk stratification schemas have been validated in different populations

• No single low risk prediction rule exists

• Choice of strategy is institution dependent
  - Need to take into consideration the ability of the institution to implement complex rules, lab turnaround for required tests etc.

• Children with severe myelosuppression and those undergoing stem cell transplantation are always high risk
EB Guideline: lab & imaging studies

• Obtain blood cultures (BC) at the onset of FN from all lumens of central venous catheters

• Consider obtaining peripheral BC at the same time

• Consider urinalysis and urine culture in patients for whom a clean catch specimen can be obtained readily

• Obtain CXR only in symptomatic patients
A word about blood cultures

• Several studies have evaluated the utility of peripheral blood cultures
  - 13% of bacteremias are detected on the peripheral culture only
    • Not known whether this is an artifact of culture volumes
  - Peripheral blood cultures can be useful in identifying a CLABSI

• Not all centers encourage peripheral blood cultures

Henry, M and L Sung *Pedi Clin* NA 2015
How about newer diagnostics?

• Comparisons have been done of polymerase chain reaction (PCR) targeting bacterial and fungal DNA and RNA with conventional blood cultures as well as supplementing conventional blood cultures with PCR-based and conventional viral diagnostics.

• Proportion of fever and neutropenia episodes with microbiologically defined infection increases dramatically when advanced diagnostics are used.

  - Techniques lack standardization.

  - Need to understand the association of clinical findings to molecular detection results before recommending the use of these studies routinely.
EB Guideline: antibiotic choice

• Monotherapy with antipseudomonal beta-lactam or carbapenem as empiric therapy in high risk FN

• Add a second gram-negative agent or glycopeptide for patients who are clinically unstable or resistant organisms are suspected

• Considerable site- and region-specific differences in the incidence resistant organisms exist
  - Influence the initial choice of empiric antibiotics
Inpatient vs Outpatient therapy

• Study of 37 children with FN who had no signs of septic shock (hypotension, tachycardia, delayed capillary refill or rigors) and no significant comorbidities requiring monitoring or treatment (focus of infection, pain, mucositis, vomiting, diarrhea or dehydration)

  - All given cefipime 50mg/kg IV in ED

  - ANC < 500

  - Half were discharged on IV cefipime while the other half were admitted

Orme, L et al *Ped Blood Cancer* 2014
Role of outpatient management

• Outpatient management can be considered for low risk patients
  - Has been shown to be feasible
  - Intravenous and oral regimens have been studied

• Several advantages to outpatient management
  - Enhanced quality of life
  - Reduction in costs
  - Reduced risk of nosocomial infection

Henry and Sung 2015
Outpatient management low risk patients

In order to implement this approach:

1. Must be able to identify low risk population
2. Must have program in place to monitor the patient and expedite admission to the hospital if deterioration occurs
3. Social circumstances and travel considerations determine the feasibility of this approach in some patients
4. Optimal frequency of follow up has not been determined
5. Oral and intravenous antibiotic regimens have been used with equal efficacy
6. Consultation with oncology is essential

Henry and Sung 2015
Risk stratification

• No adverse outcomes due to outpatient management

• Parent questionnaires showed higher QOL for outpatient care group
  - More able to keep up with household tasks
  - More able to spend time with other family members
EB Guideline: on-going therapy

• Patients who respond to initial empiric antibiotic therapy
  - Discontinue double coverage in 24-72 hours if there is no microbiologic indication to continue it

• Patients with persistent fever or who become clinically unstable, escalate the therapy

• Initiate empiric antifungal treatment if febrile > 96 hours after initiation of antimicrobial therapy
ED Approach

• Standardization of processes improves care and allows you to evaluate outcomes

• Multidisciplinary evidence based algorithms provide shared baseline

• Electronic medical record facilitates the utilization of evidence based algorithms
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/μL), moderate (ANC ≥ 200-500/μL) or severe (ANC < 200/μL).[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, sarcoma) 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 for 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/septicaemia increases when the ANC ≤ 200. [1,2]

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

Guideline Eligibility Criteria:  
Child with fever and neutropenia receiving therapy for cancer  
Child with fever after BMT, see p. 4 & BMT algorithm  

Guideline 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 (45, Appendix B)  

<table>
<thead>
<tr>
<th>Age Specific Vital Signs</th>
<th>Age (d - m)</th>
<th>Heart Rate</th>
<th>Resp Rate</th>
<th>Systolic BP</th>
</tr>
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<tbody>
<tr>
<td>0 d - 1 m</td>
<td>&gt; 205</td>
<td>&gt; 60</td>
<td>&lt; 60</td>
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Table 2. Signs and Symptoms of Shock (45, Appendix B)  

<table>
<thead>
<tr>
<th>Exam Abnormalities</th>
<th>Pulses (central vs. peripheral)</th>
<th>Cold Shock</th>
<th>Warm Shock</th>
<th>Non-Specific</th>
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<tr>
<td>Capillary Refill</td>
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<tr>
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<td>= 3 sec</td>
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<td>Flash (&lt; 1 sec)</td>
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<td>Plaunched, rusty, erythema (other than face)</td>
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<tr>
<td></td>
<td></td>
<td>Retechnez below the nippie, any purpura</td>
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<td>Increased, irritability, confusion, inappropriate, crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtundation</td>
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History: Assess  
- 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, hx 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 Studies: Assess  
- Complete CBC, Chem 7, urinalysis (bagged or clean catch
FEVER AND NEUTROPENIA IN CHILDREN RECEIVING CANCER TREATMENT CLINICAL 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]

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<tr>
<td>≥ 1 m - 3 m</td>
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- Mental status and changes in sensorium

Laboratory Studies: Assess
- Complete CBC, Chem 7, urinalysis (bagged or clean catch only), blood culture (CVC, all lines)
### Critical Points of Evidence

<table>
<thead>
<tr>
<th>Evidence Supports</th>
<th>Evidence Inconclusive</th>
<th>Evidence Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fever and neutropenia risk factor assessment: recent chemotherapy, prolonged hospitalization, prolonged granulocytopenia, broad spectrum abx use, relapse, indwelling catheters, damaged mucosa, recent steroids, hyperalimentation, increased CRP, decreased platelets. (1-16, 46-60, Appendix A)</td>
<td>- Surveillance BC in the presence of neutropenia (32)</td>
<td>- Empiric use of carbapenems as first line agents (23, 24 systematic reviews)</td>
</tr>
<tr>
<td>- Definition of low risk patients: No comorbidity, no signs of bacterial infection, AMC &gt; 100, CRP ≤ 0.90 mg/mL (17-19)</td>
<td>- Repeated blood cultures after starting abx (1-2)</td>
<td>- HSV as a common infection in children with cancer with febrile neutropenia (31)</td>
</tr>
<tr>
<td>- Ceftazidime, piperacillin/tazobactam, imipenem/cilastatin and meropenem as suitable agents for monotherapy (9, 26-24)</td>
<td>- IL6, IL8, Procalcitonin as part of initial work up (2, 7-8)</td>
<td>- CXR in absence of respiratory symptoms (41-44)</td>
</tr>
<tr>
<td>- GCSF leads to earlier recovery but does not influence mortality (25-29)</td>
<td>- abx impregnated catheters (53)</td>
<td>- Lumbar puncture (1-2)</td>
</tr>
<tr>
<td>- Removal of central venous catheter in presence of specific pathogens such as: P. aeruginosa, Bacillus species, vancomycin-resistant enterococci, Stenotrophomonas maltophilia, C. jeikeium, Acinetobacter species, polymicrobial organisms, atypical mycobacteria, multidrug resistant organism or fungemia due to Candida (2, 23-30)</td>
<td>- GCSF routine use (24-26)</td>
<td></td>
</tr>
<tr>
<td>- HSV prolongs mucositis (51)</td>
<td>- Benefit versus toxicity of granulocytes (1-2)</td>
<td></td>
</tr>
<tr>
<td>- Combination therapy of beta-lactam with aminoglycoside increases risk of nephrotoxicity (51, Appendix A)</td>
<td>- Rotating abx through central catheter lumens (1-2)</td>
<td></td>
</tr>
<tr>
<td>- Beta lactam monotherapy has same clinically efficacy as beta lactam-aminoglycoside combination therapy (61, Appendix A)</td>
<td>- Peripheral blood cultures in patients with a CVC (53, 54-56)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Minimum blood volume for cultures (2 mL) (57)</td>
<td></td>
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<tr>
<td></td>
<td>- Piperacillin/tazobactam as safe alternative in pts &lt; 25 months (21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Early discharpe and daily outpatient therapy at 72 hours of therapy for neutropenic cancer patients who are afebrile for minimum 24 hours, negative initial blood culture or two negative repeat cultures, absence of localized infection, performance scale score of ≥ 80, ANC ≥ 100, not in or after first induction therapy for AML, reside within 1 hour of hospital (58)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Oral treatment as an acceptable alternative to IV antibiotic (abx) treatment in low risk febrile neutropenic cancer patients (excluding patients with acute leukemia) in continuation therapy who are hemodynamically stable, without organ failure not having pneumonia, infection of a central line or a severe soft tissue infection (59,60; same study sample)</td>
<td></td>
</tr>
</tbody>
</table>
Antibiotic Therapy for Oncology Patients (See Appendix A)

On Arrival in EC or TCCC/HS Clinic

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>50 mg/kg/dose IV x 1 dose; MAX: 2 grams/dose</td>
</tr>
<tr>
<td>CefTAZidime</td>
<td>50 mg/kg/dose IV every 8 h; MAX: 2 grams/dose</td>
</tr>
</tbody>
</table>

ANC < 500 – Admit on Low Risk Criteria

ANC < 500 – Admit on High Risk Criteria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Children &lt; 70 kg: 15 mg/kg/dose IV every 8 h</td>
</tr>
<tr>
<td></td>
<td>Children &gt; 70 kg: 1000 mg/kg/dose IV every 12 h; MAX: 1 gram/dose</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>Infants 2-8 months: 80 mg/kg/dose piperacillin component IV every 8 h</td>
</tr>
<tr>
<td></td>
<td>Infants &gt; 9 months and Children &lt; 40 kg: 100 mg/kg/dose piperacillin component IV every 8 h; MAX: 18 grams/DAY piperacillin</td>
</tr>
<tr>
<td></td>
<td>Children &gt; 40 kg and Adults: 3 grams IV every 6 h or 4 grams every 6-8 h; MAX: 18 grams/DAY piperacillin component</td>
</tr>
</tbody>
</table>

Considerations for Discharge

1. Afebrile ≥ 24 h
2. Negative BC for 48 h
3. No signs of focal infection (examples include: mucositis, abdominal pain, cellulitis, pneumonia)
4. ANC > 100/mm³ ***
5. Performance scale score at baseline
6. 24 h caregiver available at home, able to take temperature, live within 1 h of accessible medical care, phone and transportation access

*** or as suggested by patient’s cancer therapy protocol

Outcome Measures

- Readmission through EC or TCCC/HS triage for fever and neutropenia
- Patients transferred to PICU within 72 h of admission
- Antibiotics administration initiated within one hour of patient arrival to ER or TCCC triage
- Patients admitted for monotherapy whose ABX were changed
- Admission due to positive blood culture after discharge from EC or TCCC triage
TCH Evidence-Based Outcomes Center
Clinical Algorithm for Fever and Neutropenia in Children Receiving Cancer Treatment
EC Algorithm

Begin

- BMT patient: Refer to BMT algorithm
  - Access CVC/Portacath; if none, start peripheral IV
  - Obtain: CBC, Chem7, blood culture from all lumens, UA
  - Administer appropriate antibiotics within 1 h of arrival (see below)
  - Page Hem/Onc fellow after pt assessment

No

- Sx of sepsis

Yes

OFF algorithm – proceed with Shook Protocol

- Ceftriaxone

No

- ANC < 500 mm³

Yes

- Assess risk
  - Observe 1 h post-abs, discharge if clinically well
  - Return to clinic or EC next day if remains febrile or new symptoms arise

Assess risk

Low risk

Admit on monotherapy: Cefazidime

High risk

Admit on double antibiotic:
- Vancomycin
- Piperacillin/Tazobactam

<<Risk Assessment Criteria
Patient is considered high risk if ANY of the following criteria is present:
- ANC < 100/mm³
- Focal infection (e.g., mucositis, abdominal pain, cellulitis, pneumonia, perianal tenderness)
- < 7 days since receiving intensive chemotherapy +/- dexamethasone as cancer treatment
- Infant ALL, ALL/Lymphoma during any phase other than maintenance, AML, relapse

<<Specific Vital Signs

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>HR (bpm)</th>
<th>RR (breaths/min)</th>
<th>BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 m</td>
<td>&gt; 205</td>
<td>&gt; 80</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>1 m - 1 m</td>
<td>&gt; 205</td>
<td>&gt; 80</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>2 m - 1 y</td>
<td>&gt; 190</td>
<td>&gt; 80</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>1 y - 2 y</td>
<td>&gt; 180</td>
<td>&gt; 80</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>2 y - 4 y</td>
<td>&gt; 140</td>
<td>&gt; 80</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>4 y - 6 y</td>
<td>&gt; 140</td>
<td>&gt; 80</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>6 y - 8 y</td>
<td>&gt; 140</td>
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<td>&lt; 70</td>
</tr>
<tr>
<td>8 y - 10 y</td>
<td>&gt; 140</td>
<td>&gt; 80</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>&gt; 10 y</td>
<td>&gt; 100</td>
<td>&gt; 18</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

<<Legend

- HR: Heart Rate
- RR: Respiratory Rate
- BP: Blood Pressure
- ANC: Absolute Neutrophil Count
- NEC: Necrotizing Enterocolitis
- EUS: Endoscopy
- IV: Intravenous
TCH Evidence-Based Outcomes Center
Clinical Algorithm for Fever and Neutropenia in Children Receiving Cancer Treatment
EC Algorithm

Begin

- BMT patient: Refer to BMT algorithm
- Assess CVC/Portacath; if none, start peripheral IV
- Obtain: CBC, Chem7, blood culture from all lumens, UA
- Administer appropriate antibiotics within 1 h of arrival (see below)
- Page Heme/Onc fellow after pt assessment

<table>
<thead>
<tr>
<th>Age-specific Vital Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>0 - 1 m</td>
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<tr>
<td>≥ 1 m - 2 y</td>
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<tr>
<td>≥ 2 y - 4 y</td>
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<tr>
<td>≥ 5 y - 8 y</td>
</tr>
<tr>
<td>≥ 8 - 10 y</td>
</tr>
<tr>
<td>≥ 10 y</td>
</tr>
</tbody>
</table>

Sx of sepsis:

- Yes → Shock Protocol
- No → Ceftriaxone

ANC < 500 mm³

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

Risk Assessment Criteria
Patient is considered High Risk if ANY of the following criteria is present:
- ANC < 100/mm³
- Focal infection (e.g., mucositis, abdominal pain, cellulitis, pneumonia, perianal tenderness)
- < 7 days since receiving intensive chemotherapy +/- dexamethasone as cancer treatment
- Infant ALL, ALL/Lymphoma during any phase other than maintenance, AML, relapse

Assess risk:

- Low risk
  - Admit on monotherapy: Ceftazidime
- High risk
  - Admit on double antibiotic: Vancomycin, Piperacillin/Tazobactam
**Required**

- **Onc w/Fever, Neutropenia**
  - **Culture if Urinalysis abnormal**
  - **and Diff**
    - **DAILY**
  - **Draw Blood Culture daily from all CVC lumens (peripheral if no CVC) for T > 101° F**
    - **UNTIL SPECIFIED**
  - **Q72H**

- **Reflex Microscopic - use non-catherized specimen if not obtained in EC/Cancer Center Clinic**

**Onc w/Fever, Neutropenia** — **Required**

- Central line present) \( \leq 3 \text{ kg.} \)
- No central line present) \( \leq 3 \text{ kg.} \)
- Central line present) > 3-5 kg.
- No central line present) > 3-5 kg.
- Central line present) > 5-7 kg.
- No central line present) > 5-7 kg.
- Central line present) > 7-12 kg.
- No central line present) > 7-12 kg.
- Central line present) > 12-20 kg.
- No central line present) > 12-20 kg.
- Central line present) > 20-30 kg.
- No central line present) > 20-30 kg.
- Central line present) > 30-45 kg.
- No central line present) > 30-45 kg.
- Central line present) > 45 kg.
- No central line present) > 45 kg.

- Obtained out-of-hospital

**Onc w/Fever, Neutropenia**

- **could be ordered as portable**
- **Lateral**
Procedural Pain Medication Per Protocol
- Routine, ONE TIME First occurrence Today at 1130
  - Nursing - Please enter orderset (66) RX Procedural Medication Pain Per Protocol

Acetaminophen Per Protocol
- Routine, ONE TIME First occurrence Today at 1130
  - Nursing - Please enter orderset (67) RX Acetaminophen Per Protocol

Flush Per Protocol

IV Fluids
- sodium CHLORide 0.9% (NS) Bolus Injection
  - Intravenous, ONCE
- dextrose 5% - sodium CHLORide 0.45% (D5-1/2NS) Continuous Infusion
  - Intravenous, CONTINUOUS
- dextrose 5% - sodium CHLORide 0.46% (D5-1/2NS) - KCl 2 mEq/100 mL Continuous Infusion
  - Intravenous, CONTINUOUS

Antibiotics - Low Risk Therapy [Onc w/Fever, Neutropenia]
- cefTAZidime (FORTAZ) Injection
  - 50 mg/kg, Intravenous, EVERY 8 HOURS
- ceftriaxone Injection
  - 25 mg/kg, Intravenous

Antibiotics - High Risk [Onc w/Fever, Neutropenia]
Vancomycin dosing:
- < 70 kg: 15 mg/kg/dose IV q 8 hrs
- >/= 70 kg: 1 gram/dose IV q 12 hrs
- MAX: 1 gram/dose

There is currently a national shortage of Zosyn (piperacillin/tazobactam). Until Zosyn is available, the following drug substitution should be considered:
- High Risk: Cefepime 50 mg/kg/dose IV q 8 hrs MAX: 2 grams/dose
- High Risk with GI issues/typhilitis: Cefepime 50 mg/kg/dose IV q 8 hrs MAX: 2 grams/dose PLUS meTRONidazole 7.5 mg/kg/dose IV q 6 HOURS
- Vancomycin Injection
  - 15 mg/kg, Intravenous, EVERY 8 HOURS for 72 hours
- cefepime Injection
  - 50 mg/kg, Intravenous, EVERY 8 HOURS
- High Risk with GI issues/typhilitis: cefepime PLUS meTRONidazole

Discharge Planning
- Routine, ONE TIME First occurrence Today at 1130
  - Confirm discharge teaching completed and caregiver understands: Discharge care; Medications and how to obtain them; When follow-up is due

Ad-hoc Orders
0.9% (NS) Bolus Injection
intravenous, ONCE

m CHLORide 0.45% (D5-1/2NS) Continuous Infusion
intravenous, CONTINUOUS

m CHLORide 0.45% (D5-1/2NS) + KCl 2 mEq/100 mL Continuous Infusion
intravenous, CONTINUOUS

**Ask Therapy [Onc w/Fever, Neutropenia]**
AZ Injection
50 mg/kg, Intravenous, EVERY 8 HOURS
25 mg/kg, Intravenous

**Ask [Onc w/Fever, Neutropenia]**
Dose IV q 6 hrs
Dose IV q 12 hrs

Additional shortage of Zosyn (piperacillin/tazobactam). Until Zosyn is available, the following drug substitutions are recommended:
0 mg/kg/dose IV q 8 hrs MAX: 2 grams/dose
Pseudomonal sepsis/typhilitis: Cefepime 50 mg/kg/dose IV q 8 hrs MAX: 2 grams/dose PLUS meTRONidazole 7.5 mg/kg/dose IV q 6 hrs MAX: 500 mg/dose q 6 hrs
15 mg/kg, Intravenous, EVERY 8 HOURS for 72 hours
50 mg/kg, Intravenous, EVERY 8 HOURS
Pseudomonal sepsis/typhilitis: cefepime PLUS meTRONidazole

**[Onc w/Fever, Neutropenia]**
Teaching (Specify)
Routine, ONE TIME First occurrence Today at 1130
Confirm discharge teaching completed and caregiver understands: Discharge care; Medications and how to obtain them; When follow-up appointments are scheduled;

Request to See
to add an order in this section
Measuring quality of care

• Time to antibiotic administration is a widely used measure of quality of care for children with cancer and FN

• Retrospective study of 1628 admissions that were reviewed for the presence of an adverse event (in-hospital mortality, PICU admission, >40cc/kg within 24 hour) and length of stay
Measuring quality of care in FN

• 11.1% of admissions had an adverse event (AE)
  - 0.7% mortality
  - 4.7% PICU admission
  - 10.1% fluid resuscitation in first 24 hours of hospitalization

• TTA administration 60-120 minutes associated with AE when compared to <60 minutes

• Admission from the ED (as opposed to from clinic) associated with AE

Fletcher et al 2009
Time to Antibiotics (TTA)

• TTA<60 minutes shown to decrease need for ICU care in FN cancer patients

• 45% hospitals in Children’s Oncology Group track TTA
  - Goal is <60 minutes

• Quality improvement methods are effective in improving TTA

Salstrom, JL et al Ped Blood Cancer 2015
TTA

• Retrospective analysis of outcomes after achieving TTA<60 min
  - Reduced need for PICU
  - Reduced admissions
  - Reduced total cost of care

Salstrom et al 2015
Improving TTA

• Standardized process and order set were created for use on pediatric patients with fever and neutropenia

• 130 episodes of FN were analyzed

• After implementation of new process, time to ordering antibiotics was reduced by over half (72 minutes to 27 minutes) and time to administration also was reduced (154 minutes to 95 minutes)

Cash, T et al PEC 2014
If high risk patient (malignancy, BMT, transplant, asplenia, sickle cell disease, central line, or immunodeficiency), consider SHOCK PROTOCOL.
Fever in nonneutropenic pediatric oncology patients

• Retrospective review of 392 episodes of fever in 138 children who were nonneutropenic but had CVC

  - Mean ANC 3100/mm³
  - 24 (6%) episodes of bacteremia were documented:
    • No deaths due to bacteremia
    • 10 patients admitted directly from the ED due to chills, signs of localized infection or break in the CVC

Bartholomew, F et al J Peds 2015
Fever in nonneutropenic pediatric oncology patients

- Retrospective review of 392 episodes of fever in 138 children who were nonneutropenic but had CVC

  - Fever found to be only predictor of bacteremia (39.4 C vs 38.7 C)

  - Primary language spoken, race, income, sex, CVC type, ANC were not predictive
My daughter, Elizabeth, is a liver-small bowel transplant recipient on chemotherapy for PTLD… and on Saturday evening, (her) axillary temperature was 102.9.

When we arrived, we were placed on the “SHOCK” treatment protocol…to make a long story short, within 30 minutes of arrival, an IV was started, blood cultures were drawn, IV fluids initiated and antibiotics ordered.

This was the most amazing ER experience we have ever had…it is comforting to know that my child will be treated so rapidly and effectively…and be spared a more complicated course.

I want to thank you for the treatment that she received.