DAYTON CHILDREN'S HOSPITAL

CLINICAL PRACTICE GUIDELINES

DISCLAIMER: This Clinical Practice Guideline (CPG) generally describes a recommended course of treatment for patients with the identified health needs. This CPG is not presented and should not be used as a substitute for the advice of a licensed independent practitioner, as individual patients may require different treatments from those specified, and guidelines cannot address the unique needs of each patient. Dayton Children's shall not be liable for direct, indirect, special, incidental or consequential damages related to the use of this CPG.

FEBRILE NEUTROPENIA GUIDELINE

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Definitions:

Fever – single oral temperature measurement of ≥38.3°(101°F) or a temperature of ≥38.0° (100.4°F) sustained over a one hour period. Use of axillary temperatures is discouraged because they may not accurately reflect core body temperature. Rectal temperature measurements (and rectal examinations) are avoided during neutropenia to prevent colonizing gut organisms from entering the surrounding mucosa and soft tissues.

Neutropenia – an ANC of < 500 cells/mm³ or an ANC that is expected to decrease to < 500 cells/mm³ during the next 48 hours

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Evaluation

-Obtain blood cultures at onset of FN from all lumens of central venous catheters.
-Consider peripheral-blood cultures concurrent with obtaining central venous catheter cultures.
-Consider urinalysis and urine culture in patients where clean-catch, midstream specimen is readily available.
-Obtain chest radiography only in symptomatic patients.
-One dose ceftriaxone 50-100 mg/kg within 60 minutes of presentation if ANC status not known

Neutropenia or suspected neutropenia

Non-neutropenic

With central venous catheter

Without central venous catheter

See CLABI CPG

Assess for infectious cause and treat accordingly

Risk category

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High Risk for Febrile Neutropenia[3]:

Patient and Disease related:

AML, Burkitts's lymphoma, induction ALL, progressive disease, relapsed with marrow involvement

Episode specific factors:

Hypotension, tachypnea/hypoxia < 94%, new CXR changes, altered mental status, ,severe mucositis, vomiting or abdominal pain, focal infection, other clinical reason for inpatient treatment.

Profound neutropenia: ANC < 100cells/mm³, or anticipated prolonged neutropenia.

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Low risk:

Absence of any risk factor, low risk of serious medical complication.

Patients with evidence of bone marrow recovery.

Treatment

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High-risk Febrile Neutropenia:

-Use monotherapy with antipseudomonal β-lactam:[4]

Cefepime[5](preferred): 50 mg/kg /dose over 4 hours every 8 hours, Max single dose 2000 mg

Piperacillin tazobactam: 100 mg/kg/dose over 4 hours every 8 hours, Max 16 grams per day

Meropenem* 20 - 40 mg /kg/dose over 3 hours every 8 hours, Max single dose 2000 mg

-Antibiotic choice depends on individual patient history, clinical status, local resistance patterns, and anticipated side effect profile.

-Adjust antimicrobials based on specific clinical, radiograph and/or culture data.

-For patients who are clinically unstable or when resistant infection is suspected, add gentamicin or ciprofloxacin for suspected GN sepsis or vancomycin for suspected GP sepsis.

*Due to national concern for increased resistance to antibiotics, may consider reserving carbapenems for resistant microorganisms

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Low-risk Febrile Neutropenia:

After initial ceftriaxone dose, consider step-down outpatient management.

Consider 3 days of oral antibiotic:

Ciprofloxacin: 10-20 mg/kg every 12 hours; Max dose = 1.5 g/day

Amoxicillin clavulanate: 45-90 mg amoxicillin /kg/day divided every 8-12 hours. Max single dose = 500mg

Cefpodoxime: 5 mg/kg/dose every 12 hours. Max dose = 200 mg

Administration if:

-child is able to tolerate this route of administration reliably,[6]

- there is a reliable caregiver
- availability of telephone
- availability of transportation

Recommend follow up with Hem/Onc within 24-48 hours

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Ongoing Management: ≥ 24 to 72 hours after initiation of empiric antibacterial treatment

Modification of Treatment

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Responders: (clinical improvement with resolution of fevers)
-Initial empiric antibiotics should be modified to include clinically or microbiologically documented infection.
-Discontinue double coverage for Gram-negative infection or empiric vancomycin (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue.
-Negative cultures results may allow narrowing of spectrum.

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Non-responders (fever, clinical deterioration):
-In children with persistent fever who become clinically unstable, escalate to coverage for resistant Gram-negative (gentamicin), Gram-positive (vancomycin) and anaerobic bacteria.
-Do not modify initial empiric antibacterial regimen based solely on persistent fever in children who are clinically stable[7].
Nonbacterial etiologies such as fungi and viruses should also be considered
Consider empiric antifungal therapy in these patients.

Duration/Cessation of Treatment

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All patients:
Discontinue empiric antibiotics in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours, and who have evidence of marrow recovery and appear clinically stable.
Patients with a documented focus of infection (eg: UTI, pneumonia, meningitis) should be treated with appropriate courses as dictated by type of infection and pathogen.

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Low-risk FN:
Consider discontinuation of empiric antibiotics at 72 hours in low-risk patients who have negative blood cultures and who have been afebrile for at least 24 hours, irrespective of marrow recovery status, as long as careful follow-up is ensured.
Patients with a documented focus of infection should be treated with appropriate courses as dictated by type of infection and pathogen.

FEBRILE NEUTROPENIA GUIDELINE

Empiric Antifungal Treatment:

Consider Infectious Diseases consult.

Risk Category

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High risk for Invasive Fungal Disease (IFD):
-Those with AML
-Those with relapsed acute leukemia
-Those receiving highly myelosuppressive chemotherapy for other malignancies
-Those undergoing allogeneic HSCT with persistent fever despite prolonged (≥ 96 hours) broad spectrum antibiotic therapy
-Those with expected prolonged neutropenia (> 10 days) and children receiving high dose steroids

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Low risk*:*
All others should be categorized as IFD low risk

Evaluation

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Invasive Fungal Disease high risk:
-Consider serum galactomannan twice per week for guides to duration of therapy for invasive aspergillosis.
-In IFD high-risk children with persistent FN beyond 96 hours, CT of lungs, abdomen and pelvis and targeted imaging of other clinically suspected areas of infection.
-Consider CT imaging of sinuses in children ≥ 2 years of age.
-Consider galactomannan in bronchoalveolar lavage and cerebrospinal fluid to support diagnosis of pulmonary or CNS aspergillosis.

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Invasive Fungal Disease low-risk:
Do not implement routine galactomannan screening.

Treatment

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IFD high risk:
- Initiate empiric antifungal treatment for persistent or recurrent fever of unclear etiology that is unresponsive to prolonged (≥ 96 hours) broad-spectrum antibacterial agents.
-Use micafungin[10] or liposomal amphotericin B for empiric antifungal therapy.[5]

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IFD low risk:
-Consider empiric antifungal therapy in setting of persistent FN.
-Use micafungin[10] or voriconazole for empiric antifungal therapy.[8]

FEBRILE NEUTROPENIA GUIDELINE

Research Gaps in Pediatric Febrile Neutropenia:

1. Identification of a validated high-risk stratification schema for pediatric fever and neutropenia
2. Determination of the incremental value of a peripheral-blood culture in addition to central venous catheter cultures of an adequate volume in children with FN
3. Identification of the optimal type and frequency of re-evaluation(for example, daily or every second day telephone contact or clinic visit) for pediatric outpatients with low-risk FN
4. Determination of the optimal treatment regimen for microbiologically documented sterile site infections during FN
5. Identification of the optimal frequency of blood culture sampling in persistently febrile pediatric patients with neutropenia who are either clinically stable or unstable
6. Determination of the optimal duration of antibiotic therapy for patients with high-risk FN without bone marrow recovery for prolonged periods
7. Determination of whether a strategy of routine galactomannan screening in IFD high-risk children is cost-effective and results in better clinical outcomes compared to a strategy without screening
8. Determination of the clinical utility and optimal cut-off of β-D-glucan testing in IFD high-risk children
9. Determination of the clinical utility of routine sinus imaging in children being evaluated for IFD
10. Determination of the safety and efficacy of a preemptive antifungal approach in IFD low-risk and IFD high-risk children
11. Identification of the optimal investigation and treatment for viral infections in children with FN
Abbreviations: FN, fever and neutropenia; IFD, invasive fungal disease

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