MANAGEMENT OF FEVER AND/OR SUSPECTED INFECTION IN PEDIATRIC ONCOLOGY PATIENTS

Maine Children's Cancer Program / Barbara Bush Children's Hospital

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GOAL:

1. **To outline the medical management of neutropenia occurring as a result of malignancy or conventional chemotherapy in pediatric patients.**
2. **To outline the empiric management of fever and/or ill appearance in pediatric oncology patients receiving conventional dose chemotherapy.**

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I. Definitions

A. Fever is defined as:
   1. temperature greater than or equal to 38.3 C (101 F), OR
   2. greater than or equal to 38.0 C (100.4 F) but less than 38.3 (101 F) on more than 1 occasion in an 8 hour period (with an interval of at least 1 hour between 2 time points)

B. Neutropenia is defined as ANC $\leq$ 500/mm^3 or expected to decline to < 500/mm^3 within 48 hours.

II. Initial Outpatient Management

A. Initial laboratory evaluation of oncology patients with fever should include:
   1. Central line blood culture (please see below for how to draw the blood culture – i.e. volume and type of bottle) - DRAWN THROUGH THE CENTRAL LINE
      a. If a double-lumen catheter is in place, both lumens should be cultured.
      b. Blood culture procedure – All pediatric patients should have blood cultures drawn from the central line when present. All cultures run in a pediatric blood culture bottle per institutional guidelines. Minimum 1 mL per bottle with a goal of 1-5mL.
   2. CBCD
   3. CMP

   A dose of ceftriaxone (50 mg/kg; max dose 2 g; alternative in the case of allergy: levofloxacin 10 mg/kg; max dose 750 mg) should be administered through the central line while awaiting ANC results. If patient is known to be neutropenic or appears clinically unwell, please see section C. DO NOT WAIT FOR LAB RESULTS TO GIVE ANTIBIOTICS.

   4. Other diagnostics to consider:

a. CXR
b. Urinalysis and culture should be considered and obtained if possible, but do not perform catheterization or delay initiation of antibiotic therapy.
c. Viral (Flu, RSV, other)
d. Fungal
e. Other

B. Fever in the Non-Neutropenic Patient
For febrile patients with ANC > 500/mm^3, who have central lines and look well, blood culture should be obtained from the central line as above, and ceftriaxone (50 mg/kg; max dose 2 g; alternative in the case of allergy: levofloxacin 10 mg/kg; max dose 750 mg) is the recommended empiric therapy. Patients will be observed for at least 1 hour after antibiotic administration prior to discharge home. **Patient should be discussed with MCCP provider prior to discharge.** If blood cultures are negative at 24 hours, no further parenteral antibiotic coverage is suggested, but will be at the discretion of the attending oncologist. Patient should be followed until the resolution of illness as directed by MCCP.

C. Fever and Neutropenia – Empiric Antibiotic Therapy Selection
1. Fever and neutropenia of ANC $\leq$ 500/mm^3 requires hospitalization and mandatory empiric antibiotic administration within one hour of recognition of febrile neutropenia, regardless of clinical symptoms.
2. Cefepime (50mg/kg q8h to a max of 2 grams per dose) is first line therapy for fever and neutropenia.
3. Consider addition of vancomycin with pharmacokinetic consult for patients with mucositis or suspected skin/soft tissue, respiratory, or line sources. In patients with Acute Myelogenous Leukemia (AML) and getting chemotherapy with high dose Cytarabine, vancomycin should be strongly considered as part of the initial therapy.
4. Please review if the patient has had prior positive blood cultures as that may require modifications to antibiotics. Anyone requiring more than cefepime monoptherapy will need an ID consult – this can be done on a non-emergent basis unless the patient is clinically unstable.
5. If patient has a strong clinical history of a cephalosporin allergy (e.g. hives, anaphylaxis, NOT rash or GI upset), consider meropenem (20 mg/kg q8h). This is a restricted antibiotic and will require ID approval.
6. Additional considerations in the setting of **severe sepsis** or refractory hypotension despite a total of 40 ml/kg fluid bolus:
   a. Change cefepime to meropenem (20 mg/kg per dose q8h) and add vancomycin (15 mg/kg q8h) with a pharmacokinetic consult if the patient experiences hemodynamic instability consistent with severe sepsis.
   b. The presence of chills without hemodynamic instability or focal infectious source or the persistence of fever without focal infectious source do not warrant additional antibacterial therapy. Once started, it is recommended to continue meropenem and vancomycin for a minimum of 48 hours, but after 48 hours the duration of therapy should be re-evaluated based on clinical course and cultures.

Severe sepsis is defined as one of the following organ system effects:
Note: *These guidelines are listed to aid identification of patients with evidence of severe sepsis. If, at time of clinical assessment, the patient appears to have clinical symptoms consistent with this diagnosis without establishment of all requisite criteria, additional antibiotic coverage should be considered.*

1. **Cardiovascular – *if despite boluses totaling ≥40 mL/kg (typical bolus is 20ml/kg over 1 hour):***
   - Hypotension <5th percentile
   - Pressors at any dose
   - Two of the following:
     - Capillary refill > 5 secs
     - Core to peripheral temperature gap >3^{o}C
     - Urine output <0.5 mL/kg/hr
     - Unexplained metabolic acidosis (Base deficit > 5.0 mEq/L)
     - Blood lactate > 2 x ULN
2. **Respiratory**
   - ARDS ***or***
   - Intubated ***or***
   - >50% FiO2 to keep SaO2>92%
3. **Neurologic**
   - GCS ≤11 ***or***
   - Acute decline in GCS ≥ 3 from abnormal baseline
4. **Renal:**
   - Creatinine ≥ 2 x ULN for age ***or***
   - 2-fold increase in baseline
5. **Hepatic:**
   - Bilirubin ≥4 mg/dL ***or***
   - ALT ≥2 x ULN for age

III. Inpatient Management of Fever and Neutropenia

A. Blood cultures should be repeated every 24 hours for 3 days while the patient remains febrile and neutropenic. If the patient remains clinically stable despite persistent fevers and negative cultures, additional cultures after the initial 72 hours can be considered on a case-by-case basis.

B. If a positive culture is obtained, a repeat blood culture should be obtained prior to changing antibiotic coverage. Following documentation of a positive blood culture, daily blood cultures should be obtained until documentation of 3 sequential negative blood cultures has been achieved.

C. Persistence of fever without a source
   1. Persistence of fever without a source does not warrant broadening anti-microbial coverage unless criteria are met for beginning empiric anti-fungal therapy.
   2. Anti-fungal therapy should be added to empiric anti-bacterial therapy (as per Antifungal Therapy in Neutropenia Guidelines below) in the following circumstances:
      a. Persistent fever and neutropenia for greater than 4-7 days.
      b. Recurrence of fever in a patient with neutropenia who has been receiving empiric antibiotic therapy.
   3. Discontinue prophylactic antifungal agent upon initiation of broader empiric anti-fungal therapy.

D. Consideration should be given for the discontinuation of empiric antibiotics and possibility of discharge to home in the following clinically well patients as defined by the following in addition to the clinical exam:

- For patients with a hematological malignancy in remission

- No comorbities during their admission/hospitalization (e.g. no hypotension, no concerning organ disfunction)
- No clearly defined bacterial of fungal infection (culture negative and/or no localized infection)
- Patient does not have Down's syndrome
- Clear evidence of rising counts (i.e. some combination of WBC/ANC and APC - to be discussed on rounds with the service attending)
- Adequate follow up can be ensured so that the patient can return to medical attention in a prompt manner
- Afebrile for 24 hours prior to discharge
- No comorbity that requires hospitalization

ANTIFUNGAL THERAPY IN NEUTROPENIA
ID CONSULT highly recommended

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GOAL: To standardize agents and doses used for prophylaxis and empiric management of fungal infection in pediatric oncology patients with neutropenia occurring as a result of malignancy or conventional chemotherapy.

Justification*:* Specific populations of general oncology patients are at increased risk of systemic fungal infection due to prolonged periods of neutropenia and/or concurrent immunosuppressive therapy. Fungal infections have significant clinical impact on oncology patients due to the disease itself and/or mortality associated with progression of infection and/or morbidity of antifungal therapy. Currently available antifungals include triazoles (e.g. fluconazole, itraconazole, voriconazole, posaconazole), polyenes (e.g. amphotericin B deoxycholate, and liposomal amphotericin B), and echinocandins (caspofungin, micafungin, anidulafungin). Antifungal drugs are administered prophylactically in high risk patients, empirically in patients who have persistent fever during neutropenia, and for therapy of documented infections.

I. Patient populations at risk for fungal infection

Probability of fungal infection > 10%:

- Neutropenic for ≥ 10-15 days (examples below)
  - Acute Myelogeneous Leukemia (AML), throughout therapy
  - Recurrent Acute Lymphoblastic Leukemia (ALL), in Induction therapy
  - Infant ALL, until start of Maintenance
  - Atypical Teratoid Rhabdoid Tumor
- Neutropenia associated with severe mucositis
- Significant immunosuppressive therapy
- Aplastic anemia
- Prolonged high-dose steroids
- Age > 10
- Chronic Graft vs Host Disease
- Mandated per study protocol

II. Prophylactic Antifungal Therapy

A. First Line Therapy
   1. Micafungin 2 mg/kg once daily (max dose of 50 mg daily)
      a. AML: begin once ANC < 200 and continue throughout treatment until count recovery. Resume with each cycle until completion of all chemotherapy courses (unless alternative antifungal therapy is initiated)
      b. Recurrent ALL: consider initiation once ANC < 200 and continue throughout treatment until count recovery during more intensive therapy cycles
      c. Dose modifications**:**
         - Liver function abnormality: consider discontinuing prophylactic micafungin if transaminases are > 5 times ULN or conjugated bilirubin is > 3 times ULN
      d. Alternative echinocandins can be considered based on formulary availability

B. Prophylactic Alternatives

1. Fluconazole 6 mg/kg once daily (oral administration preferred; maximum dose 400 mg/day):
    a. AML/Recurrent ALL: could be considered if echinocandins are contraindicated or in the setting of discharge if ongoing anti-fungal prophylaxis is required
    b. Discontinue fluconazole if empiric or directed systemic anti-fungal therapy initiated
    c. Renal insufficiency requires dose adjustment. Administer usual dose x 1 then:
        - For CrCl > 50 ml/min/1.73 m^2: No adjustment necessary
        - For CrCl 10-50 ml/min/1.73 m^2: Administer 50% of dose at usual interval
        - For CrCl <10 ml/min/1.73 m^2: Administer 50% of dose every 48 hours
        - Dialysis: consult pharmacy
    d. Liver function abnormality: consider discontinuing prophylactic fluconazole if transaminases are > 5 times ULN or conjugated bilirubin is > 3 times ULN
    e. Be mindful of drug interactions with triazoles in general
2. Voriconazole 4mg/kg/dose PO or IV q12 (max 200 mg/dose)
    a. May be considered in patients with a history of invasive aspergillus infection
    b. Liver function abnormality: consider discontinuing prophylactic voriconazole if transaminases are > 5 times ULN or conjugated bilirubin is > 3 times ULN.
3. Liposomal amphotericin 2 mg/kg/dose three times weekly
    a. This is an MMC-developed dose based on limited data among the wide range of prophylactic doses published.

III. Empiric Antifungal Therapy

A. Clinical Indications
    1. Persistent fever while neutropenic and on empiric systemic antibiotic therapy > 4-7 days. In general, consider starting at 5 days for patients with leukemia and at 7 days for patients with solid tumors.
    2. Recurrent fever while neutropenic and receiving broad spectrum antibiotics, AND no suspected fungal infection based on clinical and radiographic findings.

B. Required Actions
    1. Peds ID consult

C. Suggested Evaluations
    1. Blood culture
    2. CT scan of chest and imaging of abdomen/pelvis (CT preferred, but can consider US) with timing dependent on impending neutrophil recovery and/or clinical symptoms
    3. Other imaging based on clinical setting
    4. Early consultation of surgery for biopsy of suspected fungal lesion should be performed unless clinically contraindicated. Notify pathology department of impending biopsy.
    5. If pulmonary abnormality: consult Pulmonary for any consideration of BAL for galactomannan, bacterial, fungal and viral cultures and studies
    6. Blood tests for fungal infections (galactomannan, Beta D glucan, and Aspergillus PCR) have a very low positive predictive value and should only be used in select clinical settings.

D. Therapy Considerations
    1. Discontinue prophylactic antifungal therapy when beginning empiric antifungal therapy
        a. Note: Empiric antifungal combination therapy is not recommended
    2. Regardless of choice of agent, treat with antifungal therapy until resolution of fever AND neutropenia

3. Subsets of patients are at **High Risk for Mold Infection** and should **not** be treated with empiric micafungin unless significant drug/disease interactions prohibit Ambisome use. High risk populations include:
    a. Expected neutropenic period of > 14 days (this includes but is not limited to AML, recurrent ALL, ALL with Induction failure)
    b. History of prior fungal infection
    c. Prolonged fluconazole prophylaxis
    d. Known colonization with Aspergillus

E. First Line Agents
1. Liposomal amphotericin
    a. 5 mg/kg once daily
    b. If patient has had a prior infusion reaction, consider premedication with fluids, acetaminophen, and diphenhydramine.
    c. If patient experiences rigors, may treat with meperidine 1 mg/kg/dose
    d. Patients may experience potassium and magnesium wasting requiring aggressive supplementation to maintain values in the normal range
    e. Consider alternate therapy for patients with significantly elevated baseline creatinine or new evidence of renal injury

2. Micafungin – ONLY potentially for lower risk
    a. Give only for patients who do **NOT** meet criteria for "High Risk for Mold Infection" (above) and if no concern for Aspergillus
    b. Dosing:
        i. Neonates: 10 mg/kg/dose once daily
            - Dosing based on pharmacokinetic studies only
        ii. Infants and children <8 yo: 4 mg/kg/dose once daily (maximum dose: 200 mg)
        iii. Children and adolescents 8-18 yo: 3 mg/kg/dose once daily (max dose 150mg)
        iv. Adults: 150 mg once daily
    c. Additional monitoring while on empiric micafungin:
        i. ALT should be monitored at least once weekly after initiation of empiric micafungin; may reduce frequency of monitoring if liver function is stable in the first few weeks of therapy
    d. Dose modifications for liver toxicity
        i. Empiric micafungin should be discontinued if ALT is > 5x ULN

F. Therapeutic Alternatives
1. Voriconazole
    a. Due to limitations in the availability of therapeutic drug monitoring, voriconazole is not recommended for first-line empiric therapy at this time.
    b. Use IV voriconazole for initial therapy; may convert to oral dosing once therapeutic levels are achieved; loading dose is required
    c. Dosing:
        i. Children 2-12 yo: load with 9 mg/kg/dose IV q12h x 2 doses, then 8 mg/kg/dose q12h
        ii. Children > 12 yo: load with 6 mg/kg/dose IV q12h x 2 doses, then 4 mg/kg/dose q12h
    d. Trough levels should be obtained in all patients receiving empiric voriconazole
        i. Goal trough 1 – 3 mcg/mL
        ii. Obtain a trough level 30 minutes <u>before</u> the morning dose of voriconazole on the fourth or fifth day of therapy

iii. Monitoring of levels should also be performed when:
- Transitioning from IV to PO (or vice versa)
- Concerns for malabsorption of PO dosing or addition of medications with potential interaction

iv. If on prolonged therapy, consider repeating voriconazole troughs every 2 to 4 weeks once therapeutic levels are achieved.

e. Additional monitoring while on empiric voriconazole
   i. ALT and bilirubin should be monitored at least once weekly after initiation of empiric voriconazole; may reduce frequency of monitoring if liver function is stable in the first few weeks of therapy
   ii. Baseline EKG (EKG obtained at time of diagnosis, if applicable, is sufficient) and serial monitoring at 1 month, 6 months, and then q6 months is indicated
   iii. Optimize Ca, Mg, PO_4 levels to minimize cumulative impact on QTc
   iv. Skin rashes may occur
   v. Patients on prolonged therapy should be monitored for visual disturbances

f. Dose modifications for liver toxicity
   i. Empiric voriconazole should be discontinued if ALT is > 5x ULN or if conjugated bilirubin is > 3x ULN

g. Drug interactions
   i. Voriconazole is a strong inhibitor of CYP3A4 and a moderate inhibitor of CYP2C9 and CYP2C19
   ii. Consider holding voriconazole for 1-2 days before administering interacting chemotherapy (e.g. vincristine)

G. Disease Monitoring During Empiric Therapy

Patients who meet criteria for empiric antifungal therapy and/or at “High Risk for Mold Infection” require close monitoring for underlying fungal infection (serial radiographic evaluation, BAL and/or biopsy if progressive radiographic abnormality noted). Consider obtaining CT scans at time of count recovery to determine need for ongoing antifungal therapy.

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