Cook children's Medical Center

Fever and neutropenia Guidelines (3/01/24)

Statement

The Clinical Pathways and Guidelines are intended to assist physicians and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. The ultimate judgment regarding care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

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I. Definitions:

A. **Fever: core body** temperature ≥38.4 once, or > 38°C (100.4°F) for > 1 hour or measured on two separate occasions over an hour apart
B. **Neutropenia:** absolute neutrophil count (ANC) mm3 or < 1000/mm^3 with a predicted decline to < 500/mm3
C. **Prolonged neutropenia:** Absolute neutrophil count ≤ 100 mm3 for ≥7 days.
D. **Bacteremia:** bacterial growth in blood culture indicating presence of a bacterial in the bloodstream.
E. Severe sepsis: presence of sepsis-induced organ dysfunction; hypotension not responsive to fluid resuscitation
F. Fever of unknown origin: fever with negative work up evaluation
G. **Typhlitis**: life threatening necrotizing enterocolitis occurring primarily in neutropenic patients.
H. **Marrow recovery –**ANC recovery ≥ 200/ mm^3 and rising
I. Antimicrobial therapy: administration of antimicrobial to treat a specific infection or condition.
J. **Antimicrobial prophylaxis:** administration of antimicrobial to prevent development of an infection
K. De- escalation: strategy to reduce the use of broad spectrum antimicrobials and switch to narrower-spectrum antibiotics.
L. **Persistent fever:** fever lasting longer than 96 hours

II. Target population

Pediatric patients age 0-18 years receiving chemotherapy for cancer and recipients of hematopoietic stem cell transplant (HSCT). The target users are health care professionals including physicians, nurse practitioners, microbiologists, nurses, pharmacists.

III. Risk stratification [1]

These guidelines divide the prophylaxis and treatment recommendations into low versus high risk patients based on diagnosis, chemotherapy regimens, duration of neutropenia and immunosuppresion and subsequent risk for infectious complications depending on level of risk.

- **Lower Risk patients**
  - APML patients AFTER Induction
  - CML patients on oral TKI
  - Low risk Wilms Tumor
  - Low risk Rhabdomyosarcoma
  - LCH
  - Low and moderate aplastic anemia
  - SCT patients day > +100 not on immune suppression or/and without line.

- **High risk patients:**
    - **Clinical aspects:**
        - ALL and lymphoma that are not in maintenance therapy
        - APML in Induction
        - AML in all the phases
        - All SCT patients < day +100
        - SCT patients > day +100 with a/c GVHD
        - SCT patients > day + 100 still on immunosuppression
        - SCT patients > day +100 with Soliris therapy within last 3 months or surgical asplenia
        - Car T cell < day +30 and/or if ANC <500
        - HLH patients
        - Severe aplastic anemia
        - Primary immunodeficiency patients
        - Relapsed /progressive leukemia
        - Down syndrome with any oncologic diagnosis, in any phase of therapy
        - Advance stage non Hodgkin lymphoma
        - Solid tumors other than those listed under low risk
        - Recurrent NHL treated with intensively myelosuppressive chemotherapy
        - *Consider high risk patients those with prolonged neutropenia lasting ≥7 days that present with fever*.

    - **Clinical features:**
        - Age < 1 year
        - Signs and symptoms of septic shock
        - Clinical or radiographic concerns of neutropenic enterocolitis
        - Changes in mental status

    - **Social factors:**
        - inability to take oral intake
        - Allergy to levofloxacin
        - Parents with history of poor compliance
        - Families live far away
        - If close follow up is not warranted.

IV. Antibiotic prophylaxis

The approach is to reduce bacterial infections and their negative consequences using antibiotic prophylaxis when appropriate to decrease infection related morbidity and mortality, bacterial bloodstream infections and febrile neutropenia in some of the patients within the high risk group (ANC < 500 for more than 7 days). However the use of fluoroquinolones is associated with increased resistance, changes in the microbiome and increased incidence of *C. diff* infections. The 8th European conference on infections in Leukemia (ECIL) guidelines don't recommend routine

antibacterial prophylaxis for pediatric patients with lymphoma, acute leukemia, relapse acute leukemia or patients with neutropenia during the pre -engraftment process in hematocellular stem cell transplant [2]

In 2020, Clinical practice guideline (CPG) for systemic antibacterial prophylaxis administration in pediatric patients with cancer and recipients of HSCT was published. [3])Levofloxacin is the preferred agent related to recent large pediatric trial showing benefits and broad spectrum activity against important organisms in pediatric high risk populations. Providers should keep in mind potential for adverse effects and should inform families and patients about these potential risks.

A. Levofloxacin prophylaxis

1. Indications: [3]
    a. Patients with leukemia expected to have significant and prolonged neutropenia (> 7 days)
        - AML
        - Relapse ALL, induction and delayed intensification
        - MDS on intense chemotherapy
        - ALL Standard risk at induction time for at least 2 week to be discontinued at discharge when ANC recovery
    b. Initiate when ANC <200- 500 and expected to decrease
    c. Discontinue when ANC > 200 and rising or if started on systemic antibiotics (other than PJP prophylaxis)
2. Levofloxacin dose (see table 1)
    a. < 5 year old: 10 mg/kg/dose every 12 hours (IV or PO)
    b. ≥5 year old: 10 mg/kg every 24 hours (IV or PO)
    c. Maximum total dose per day: 750 mg
3. Contraindications:
    a. Allergy to fluoroquinolones
    b. Chronic active arthritis
    c. Known prolonged QTC (only check if anticipated to be in levofloxacin for longer than 2 weeks)
    d. Pregnant or breastfeeding
    e. While on systemic antibiotics (Except for PJP prophylaxis)
    f. History of *strep viridans*, levofloxacin resistant
4. **Alternative: cefpodoxime at 5 mg/kg every 12 hours, max dose per day 400 mg** [4]. If not available, then ok to use suprax at 8 mg/kg every 24 hours, max dose 400 mg.
5. *C. dificile*: patients with history of *C. difficile* should not receive po vancomycin prophylaxis while on levofloxacin.

B. Secondary prevention of *Clostridium difficile* with oral vancomycin prophylaxis in patient with Fever and neutropenia: [5] [6] [7]

1. Indications: Patient with HSCT and history of *C. diff* colitis in the last 12 months and requiring broad spectrum antibiotics.

2. Dosing: Initiate with po Vancomycin prophylaxis 125 mg po or 10 mg/kg every 24 hours, Max 125 mg until 5 days after stopping systemic antibiotics.
3. See *C. Difficile* treatment recommendations below.

V. Fungal Prophylaxis.

If systemic antifungal prophylaxis is warranted, administer a mold active agent [2] [8] [9] [1]

Posaconazole and voriconazole have comparable efficacy and safety in the prevention of invasive fungal disease in AML/MDS (Almutairy R, OFID, 2020) and they both have similar spectrum of activity

A. **Indications**

1. Prophylaxis with Voriconazole or Posaconazole in patients at high risk of invasive fungal disease expected to have significant and prolonged neutropenia (more than seven days), including:
    - Relapse ALL, induction and delayed intensification
    - AML/MDS on intense chemotherapy:
    - Allogenic HSCT (pre engraftment or is receiving immunosuppression for graft-versus-host disease):
    - ALL standard risk- induction during neutropenia period
        i. Check ANC prior to discharge
        ii. Continue antifungal if hyperglycemia
        iii. Duration of the antifungal prophylaxis for at least 2 weeks (until ANC recovery). Obtain Azole level prior to discharge if still on antifungal prophylaxis.

2. If the patient has contraindication (see -section below) to the any of the azole treatment then echinocandins such as Micafungin should be used as an alternative (ALL, total XVII induction (VCR), increased risk for VOD in HSCT). Micafungin spectrum of activity includes *Candida* and *Aspergillus.* **Rezafungin is an echinocandin antifungal FDA approved (March, 2023) for treatment of candidemia and invasive candidiasis in persons ≥ 18 year old, where there are limited or no treatment options. Safety has not been established beyond 4 weekly doses, including the loading dose. Also being developed for prevention of invasive fungal disease in oncology and bone marrow transplant patients. *Will update information as available*.** [10]

3. Initiate with ANC less than 200
4. Discontinue with ANC more than 200 and rising or if a started on systemic antifungal therapy

B. **Doses** (Table2)

1. Voriconazole

- 2-12 years of age or older than 12-14 years of age and less than 50 kg:
    - IV: 9 milligrams/kilos per dose every 12 hours x2 doses (day one) followed by 8 milligram/kilos per dose every 12 hours
    - PO.: 9 milligrams/kilos per dose every 12 hours

- Maximum on 350 mg per dose
  - > 12 to 14 year old of age and weight ≥50 kg or ≥ 15-year-old
    - IV/p.o.: 4 milligrams/kilos per dose every 12 hours
    - Maximum dose to 200 mg per dose

2. **Posaconazole**: Limited data available

- **IV formulation:**
  i. -Adults**:** 300 mg iv every 12 hoursx2 , then 300 mg iv once daily
  ii. -For 2-18 year old: 6 mg/kg every 12 hours daily x1, then 6 mg/kg/daily
- **Delayed release tablets (100 mg):**
  i. -Adults: 300 mg q12hx2 then 300 mg q24h
  ii. -> 13 year old, weight >40 kg: 300 mg q12hx2 then 300 mg q24h
  iii. -In children <13 year old (doses based on unpublished data):
    1. -10-19 kg: 100 mg po Q12h x2, then 100 mg po q24h
    2. -20-29kg: 200 mg po q12h x2, then 200 mg po q24 h
    3. -≥30 kg: 300 mg po q12h x2, then 300 mg po q24h
  iv. -In children ≥ 3 years- adolescents ≤ 17 years old:
    1. -5-7 mg/kg/dose q12hx2, then q24h

3. Echinocandins:

i. Micafungin: 3-4 milligram/kg per dose IV every 24 hours. Maximum dose 50 mg

ii. Rezafungin: Loading dose 400 mg once on day 1. Maintenance dose: 200 mg once weekly beginning on day 8. **(Now included in the Cook Children's formulary)**

C. **Contraindications** to fungal prophylaxis

1. Voriconazole
   - Allergy to voriconazole or posaconazole
   - Known prolonged QTc (only check if anticipated to be on azole antifungals for more than two weeks)
   - Liver function test > 5 times ULN or known liver failure
   - Co administration with major CYP3A4 substrates (such as vinca alkaloids (VCR) and resume 24 hours after vinca alkaloid therapy completed.
2. Micafungin
   - Allergy to micafungin or and echinocandin
   - LFTs > 5 ULN

D. Therapeutic drug monitoring

1. Voriconazole: Target therapeutic level: 1.5 to 5.5 µg/ml, Target prophylaxis level: 0.5 µg/ml
2. Posaconazole: Target for fungal prophylaxis is >0.7 µg/ml.
3. Levels should be obtained after 7 days of therapy of either voriconazole or posaconazole.
4. Follow up levels once monthly

5. Reasons for checking levels more frequently:
    i. Changes in the dosage or formulation delivery, addition or withdrawal of interacting medications, perceived fungal disease progression, toxicity or concerns regarding nonadherenc

VI. Fever Neutropenia Initial work up [9] [11]

1. Blood cultures (CVL-all lumens and consider peripheral)
    - Process improvement project to increase Volume (Laura Collier, Lab quality coordinator)
        i. Increased number of detected pathogens.
        ii. Decrease in detection times.
        iii. Improved ability to differentiate pathogens from contaminants.
        iv. Improved selection for antimicrobial therapy.
        v. Reduced hospital stay/cost.
        vi. Selection against resistant microorganisms.

    - Obtain up to 8 ml in children older than 1 year of age (It should be 4-5 ml per bottle (8-10 ml per set) for patients >1 year.

    - Daily blood cultures x2 and then; the frequency will be determined according to each patient individually.
2. Consider UA and urine culture where clean catch, mid-stream specimen is readily available.
3. Viral swabs, stool tests and wound cultures should be guided by presenting symptoms.
4. CXR If respiratory symptom
    i. Other imaging studies based on clinical presentation (Ex: abdomen ultrasound if abdominal pain)

VII. Factors to consider when selecting antibiotics in Oncology [2]

A. Recent culture and sensitivity results
B. History of multidrug resistant organism (MDRO)
C. Suspected line infection
D. Antibiotic history and prophylaxis
E. Source of infection, if identified.
F. Antibiotic allergies
G. Organ dysfunction
H. Mucositis

VIII. **Antibacterial therapy in patients with febrile neutropenia. [2] [9]** See figure 1.

A. Initial empirical antibiotics (see table 3 for dosing):

1. **Monotherapy** with antipseudomonal coverage with fourth generation cephalosporin, is recommended for clinically stable patients at low risk for resistant infections
    a. **Low risk for resistant infection:**
        - Without colonization
        - No previous infections with resistant bacteria
        - Previously treated in institutions with low resistance rate
        - No antibiotic prophylaxis
2. **Carbapenem** with or without a second anti gram negative agent, with or without vancomycin is recommended for clinically unstable patients, even with a low risk for resistant gram negative bacteria
3. Empiric antibiotic is adjusted in patient with colonization with resistant gram negative bacteria, history of previous infection with resistant bacteria or coming from centers with high level of resistance.
4. **If suspected intra-abdominal or perirectal infection**:
    a. Piperacillin tazobactam (first option)
    b. Add flagyl to cefepime (option if contraindication for zosyn)
    c. Meropenem if already started due to above- see b.

B. **Penicillin allergic patients:** Many patients with history of allergy to penicillin tolerate cephalosporins. If allergy to cephalosporins, including cefepime, consider using meropenem. However, those with a history of an immediate type hypersensitivy reaction (hives and or bronchospasm) should not receive beta-lactams or carbapenems. Alternative empiric regimens for such patients include aztreonam plus vancomycin or ciprofloxacin plus clindamycin. Contact infectious disease for further recommendations.

C. Double gram-negative coverage (Tobramycin, ciprofloxacin, if no quinolones for prophylaxis [9]
1. Clinically unstable patients
2. History of colonization with resistant organisms
3. Necrotizing fasciitis
4. Positive blood culture for gram negative isolate awaiting sensitivities.

D. The addition of vancomycin is recommended for the following factors: [9] [2] [12]
1. MRSA colonization
    a. History of invasive MRSA or Streptococcus viridans infection
    b. Vascular line exit site infection or other skin/soft tissue infection suspected for central line infection. Ok to consider clindamycin for clinically stable patients. (Be aware of Cook Children's antibiogram)
    c. Mucositis
    d. Recent high-dose cytarabine
    e. Positive blood culture for gram-positive bacteria (prior to identification and susceptibility)

2. Suspected infection with bacillus species due to presence of gram positive rods in culture or gram stain
3. Skin and soft tissue infection. Ok to consider clindamycin for clinically stable patients (Be aware of Cook Children's Antibiogram)
4. Septic shock
5. Meningitis
6. Severe allergy to penicillin or cephalosporin
7. Stop date in 48-72 hours if started and negative cultures. No vancomycin levels.

E. Addition of antifungal therapy with micafungin is recommended for patient with the following risk factors: [2]

1. Exposure to broad-spectrum antibiotics for more than seven days
2. Recent abdominal surgery
3. Steroid use in the last two weeks
4. AML high risk or relapsed ALL
5. Gastrointestinal perforation
6. Necrotizing pancreatitis

IX. Central line removal [12] [13]

A. **Prompt** removal ***should be considered*** when any of the following conditions and or organisms exists:

- Severe sepsis
- Endocarditis
- Blood stream infection that continues despite > 72 hours of antimicrobial therapy to which the infecting organism is susceptible
- Infections due to *Staphylococcus Aureus*, gram negative bacilli including *P. aeruginosa, bacillus species* and or *enterococci*
- Infections due to mycobacteria
- Infections due to candida species. In the neutropenic patient, sources of candidiasis other than a CVC (eg, gastrointestinal tract) predominate. Catheter removal should be considered on an individual basis. [14]
- Tunnel site infection
- Suppurative thrombophlebitis

B. Salvage therapy can be also considered when uncomplicated CLABSI is caused by organisms other than *Staphylococcus aureus*, *Pseudomonas aeruginosa*, Bacillus spp, fungi, or mycobacteria.

C. Salvage for long term catheters (systemic therapy coupled with antimicrobial lock [heparin + high concentration of antimicrobial agent that is selected based on susceptibility results]) can be attempted in limited instances such as patients with limited vascular access sites or the ones who are solely dependent on central access for survival.

- Catheter tunnel or exit site infection are contraindications for salvage.

D. All non-tunneled catheters causing CLABSI should be removed promptly

E. Infectious Disease consultation is highly recommended.

X. Re assessment of antimicrobial therapy for febrile neutropenia:

All patients should be reassessed after 48 hours of antimicrobial therapy [9] [15].

A. Clinical response -Defervescence (see figure 2)

1. Culture negative patient (without a defined focus of infection)

a. Discontinuation of empiric antimicrobial therapy is recommended in clinically stable patients, who have been afebrile for more than 24 hours and evidence of bone marrow recovery (ANC >200) vs **regardless of ANC in low risk patient if careful follow up is ensured.**

b. Resume levofloxacin prophylaxis if applicable

c. High risk patients:

i. Consider completing antibiotics until completing 14 days rather than until ANC recovery [16]

d. If signs of sepsis/septic shock at presentation independent of risk factors with no causative pathogen or identified focus of infection:

i. Complete a course with meropenem monotherapy and discontinue tobramycin and or vancomycin.

2. Culture positive patients and culture negative with a defined focus of infection

a. Treatment for recommended duration depending on diagnosis (see table 4) for duration of antibiotic per syndrome) and patient has been afebrile for 24 hours prior to stopping antibiotic.

b. Resume levofloxacin if applicable

c. High risk patients: Duration according to documented infection and ANC recovery (>200).

3. De-escalation of empiric antibiotics

a. Empiric antimicrobial therapy should be streamlined to the most narrow option for the identified organism in clinically stable patient who had been afebrile for more than 24 hours, regardless of ANC (guided by in vitro susceptibilities)

b. **High risk patients-** wait until bone marrow recovery (ANC >200 and rising) before streamlining therapy.

B. **Persistent Fever, > 96 hours (see figure 3 and figure 4)**

1. ID consult highly recommended.
2. **Do no broaden or start vancomycin if patient clinically stable**
3. Consider antifungal therapy and fungal work up

4. Consider CT scans- see below
5. Evaluate for fungal, mycobacterial and viral infections
6. Consider galactomannan if abnormal imaging studies
7. Consider BAL if concerns about lung disease
8. Start acyclovir if evidence of HSV
9. Check levels of antibiotics if feasible
10. See algorithm for clinically stable vs unstable (Figure 3 and 4)
11. Consider next generation sequencing testing (Ex: Karius test). See below.

XI. Febrile neutropenia fungal work up [9] [2]

1. Patient with persistent fever despite broad spectrum antibiotics and prolonged neutropenia
2. Definitions:
    - **Invasive fungal disease (IFD) high-risk patients** are those with acute myeloid leukemia, high-risk acute lymphoblastic leukemia or relapsed acute leukemia; those with prolonged neutropenia; those receiving high-dose steroids; and those undergoing allogeneic HCT in the first year after HCT without evidence of T-cell reconstitution, or receiving steroids or multiple immune suppressive agents to prevent or treat graft versus-host disease.
    - **IFD low-risk patients:** Those not meeting the above criteria.
3. **ID consultation highly recommended.**
4. **CT Chest**, strong recommendation
5. **Abdomen Imaging**
    - Ok to start with abdomen ultrasound if no specific concerns about abdominal infection.
    - No need to do pelvis imaging studies
6. **Sinus CT** vs ENT consult- bedside evaluation
    - >2 year old and,
    - If symptoms compatible with sinusitis: Purulent nasal discharge, nasal congestion/obstruction, fascial congestion/fullness, fascial pain/pressure, headache, ear pain/pressure
7. **Fungal Biomarkers**
    - Galactomannan- limited usefulness particularly in patients receiving anti mold therapy. Indicated for high risk patient with prolonged fever and imaging studies concerning for invasive fungal disease
    - Galactomannan BAL or CSF as an adjunctive tool for conventional microbiological studies for the diagnosis of invasive pulmonary or CNS aspergillus infection.
    - BG- limited usefulness
        i. Sent only if high suspicion for PJP
        ii. Poor predictive value of invasive disease in pediatric patients.
        iii. False positive is common and can be caused by any of the following within three to four day time in relation to the lab draw: IVIG, albumin,

hemodialysis, received of blood products, presence of bacteremia, use of certain types or surgical gauze, IV antimicrobial use (colistin, ertapenem, cefazolin, Bactrim, cefepime, Unasyn, Zosyn), presence of mucositis or other disruption in GI integrity, enteral nutrition.

- Pulmonology consult for BAL evaluation if CT chest suggestive of invasive fungal disease (add galactomannan and Aspergillus PCR to BAL studies)
- ENT consult if CT sinus suggestive of invasive fungal infection

8. Initiate empiric antifungal therapy- Do no delay initiation while waiting for fungal workup results
    - 1St line: Micafungin
    - 2nd line: Liposomal amphotericin B (may be preferred in patient's previously on antifungal prophylaxis active against molds, such as voriconazole)
    - Could consider holding antifungal therapy if patient clinically stable and IFD low risk. See above.
    - Discontinuation of empiric anti-fungal therapy in patients with negative fungal workup
        i. Continue anti-fungal therapy until afebrile for more than 48 hours and evidence of marrow recovery
        ii. In patients that remained persistently neutropenic, empiric therapy should be continued for up to 14 days
            a. Transition to anti-fungal prophylaxis if appropriate
9. **Consider Next generation sequencing (Ex: Karius testing, see below)**
    - Could help in the evaluation for fungal infections in patient with high risk for IFD [17]

XII. Neutropenic Enterocolitis (Typhlitis)

A. ID consult recommended
B. Initiate workup for typhlitis in patients with febrile neutropenia AND clinically significant diarrhea, bloody stool, emesis, abdominal pain, or abdominal distention not explained by other diagnoses
    i. If diarrhea present:
        1. *C. difficile* screen (if > 2 years old and unexplained new-onset > 3 loose/watery stools in last 24 hours)
        2. Enteric bacterial PCR
    ii. Aerobic and anaerobic blood cultures if not already sent
    iii. Abdominal CT with PO and IV contrast; abdominal ultrasound if unable to CT
C. Criteria for diagnosis
    i. a. Fever and neutropenia
    ii. b. Bowel wall thickening seen on abdominal imaging
    iii. c. Other differential diagnoses excluded (*C. difficile*, GVHD, Salmonella enteritis, etc.)
D. Initiate empiric antimicrobial therapy:
    i. First line: Piperacillin/tazobactam
    ii. Second line: Cefepime + Metronidazole

E. Duration of therapy:
    i. 10-14 days or 7 days following marrow recovery, whichever is longer, AND until complete resolution of signs and symptoms
    ii. Longer durations may be necessary in patients with ongoing evidence of perforation or undrained abscess

XIII. Use of Next generation sequencing testing (Karius):

Metagenomics next-generation sequencing (mNGS) is a novel diagnostic approach that has been hypothesized to address some of the limitations associated with conventional microbiological methods, focus on preselected organisms, as with serology. mNGS offers unbiased sequencing and identification of microbial genetic material. Plasma mNGS, on the other hand, is sometimes described as a "liquid biopsy" for diagnosing infectious diseases, as it has been hypothesized to detect small fragments of genetic material shed from a distant or localized infection through a single blood test.

The real-world impact of plasma microbial cell-free DNA mNGS on clinical care has been evaluated through multiple retrospective studies at quaternary medical centers. Karius is microbial cell-free DNA sequencing test (KT) to identify infectious etiologies. It does not detect RNA viruses. [18]

A. To be considered in high risk patients: *Consider holding 5 ml of blood early on, in high risk patient with fever >48 hours and with an unknown source of fever.*
    i. Prolonged fever and neutropenia for > 96 hours with an unknown source of fever
    ii. Imaging findings of deep seated infections such as Pulmonary nodular infiltrates
    iii. When considering BAL, in some cases could potentially avoid an invasive procedure.
    iv. BAL cultures, biopsy and other diagnostics are negative or contraindicated

B. ID consult is recommended at this time as clinicians grow more comfortable utilizing mNGS and develop a deeper understanding of its successes and limitations. Infectious Disease consultation can help interpreting mNGS results and deciding further evaluation and management. None mNGS assay has been approved by the US Food and Drug Administration (FDA) [19]

XIV. *Clostridioides Difficile* in Oncology [6]

Immunocompromised children are at much higher risk of *Clostridioides difficile* infection (CDI) than otherwise healthy children. Children with cancer appear to be at especially high risk. Rates of CDI are also higher in pediatric hematopoietic cell transplantation compared with solid organ transplants. Development of CDI occurs at the intersection of colonization with toxigenic *C. difficile* and disruption of a healthy gut microbiota or immune system. Not all antibiotics are associated with CDI risk to the same degree. Late generation cephalosporin, carbapenems, and clindamycin are most commonly implicated in adults as well as in children. Notably, although fluoroquinolones have been implicated in adults and pediatrics, they appear protective in the

pediatric oncology and transplant populations when used for neutropenia prophylaxis during periods of intensive immunosuppression.

The disease severity stratification in immunosuppressed patients is different due to suppression of white blood cells which is traditionally utilized to diagnose severe CDI on immunocompetent populations, and the absence of data to support the clinical significance of stratification model.

One practical approach to stratification is to use requirement of critical care or the presence of hemodynamic instability, ileus, toxic megacolon, or pseudomembranous colitis to guide therapy.

For treatment recommendations see table 4 (A, B, C, D). Infectious Disease service consultation is highly recommended for management of patients with multiple recurrent episode of *C. diff* colitis.

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Table 1. Dosing levofloxacin prophylaxis

Antibacterial prophylaxis

Antimicrobial	Dosing	Patient population	When this should be used	Drug monitoring	Adverse reactions	Dosage Forms
Levofloxacin	>6months to <5 years: 10mg/kg/dose IV/PO BID ≥5 years: 10mg/kg PO daily (maximum 500 mg) IV/PO (equivalent bioavailability) -Take 2 hours before or 6 hours after calcium, aluminum, vitamins and other divalent cations -With liquid formulation, take 1 hour before or 2 hours after meals	• AML • Relapsed ALL • ALL in patient with Trisomy 21	Start when ANC falls below 200, continue until ANC is >200 or patient develops fever (then change to cefepime)	If simultaneously receiving -azoles, $5HT_3$ antagonists, Tyrosine Kinase Inhibitors or other QT prolonging agent, should have baseline then weekly EKG	Tendonitis, Clostridium difficile infection, hepatotoxicity, prolonged QT, hypoglycemia, photosensitivity, seizures, peripheral neuropathy	IV, Tablets, Oral suspension

Parents and family education

Table 2. Dosing Antifungal

Antimicrobial	Dosing	Drug Monitoring	Adverse Reactions	Dosage Forms
Voriconazole	**2-12 year or >12 year and weight < 50kg:** -IV 9 mg/kg every 12 hours (Day 1) and then 8 mg/kg every 12 hours. -PO: 9 mg/kg every 12 hours Max: 350 mg per dose (max dose can be exceeded based on drug levels). **>12-14 year and weight >50 kg or > 15 year:** -IV/PO 4 mg/kg every 12 hours. Max 200 mg/dose (max dose can be exceeded based on drug levels).	Target therapeutic level: 1.5 to 5.5 µg/ml. Target prophylaxis level: 0.5 µg/ml Levels should be obtained after 7 days of therapy Follow up levels once monthly	Hepatotoxicity Prolonged QT Photosensitivy Rash Hallucinations	IV, tablets, oral suspension
Posaconazole	**IV formulation:** -Adults: 300 mg iv every 12 hoursx2 , then 300 mg iv once daily -For 2-18 year old: 6 mg/kg every 12 hours daily x1, then 6 mg/kg/daily **Delayed release tablets (100 mg):** -Adults: 300 mg q12hx2 then 300 mg q24h -> 13 year old, weight >40 kg: 300 mg q12hx2 then 300 mg q24h -In children <13 year old (doses based on unpublished data): -10-19 kg: 100 mg po Q12h x2, then 100 mg po q24h -20-29kg: 200 mg po q12h x2, then 200 mg po q24 h -≥30 kg: 300 mg po q12h x2, then 300 mg po q24h -In children ≥ 3 years- adolescents ≤ 17 years old: -5-7 mg/kg/dose q12hx2, then q24h	Target prophylaxis: >0.7 µg/ml. Target therapeutic: ≥ 1.2 Levels should be obtained after 7 days of therapy Follow up levels once monthly	Hepatotoxicity Hypertension Prolonged QT Pruritus Thrombocytopenia Hypokalemia Hyperglycemia	IV, Delayed release tablets of 100 mg (ok to crush/cut)
Micafungin	3-4 milligram/kg per dose IV every 24 hours. Maximum dose 150 mg	N/A	Elevated LFT Renal dysfunction Infusion reactions	IV
Rezafungin	Loading dose 400 mg once on day 1. Maintenance dose: 200 mg once weekly beginning on day 8. **Not approved for pediatrics**	N/A	Infusion related reactions, photosensitivity, Elevated LFT, electrolyte disturbance	IV
Ambisome	3-5 mg/kg every 24 hours. No max dose. 5-10 mg/kg every 24 hours for mucormycosis	N/A	Nephrotoxicity, serum electrolyte imbalances	IV

Table 3. Antimicrobial Dosing

Antibiotic	Dose	Interval	Max dose
Cefepime	50 mg/kg	Every 8 hours	2000 mg
Meropenem	20-40 mg/kg	Every 8 hours	1000 mg 2000 mg (for CNS infections)
Tobramycin	6-7.5 m/kg	Every 24 hours	No max dose • Dose based on Ideal Body Weight or Adjusted Body Weight (if Actual Body Weight 30% greater than Ideal Body Weight) • Consider consultation pharmacy for therapeutic drug monitoring/dosing
Vancomycin	10-15 mg/kg	Every 6-12 hours	**See vancomycin guidelines**
Metronidazole	10 mg/kg	Every 8 hours	500 mg
Piperacillin-Tazobactam	100 mg/kg piperacillin	Every 6-8 hours	4000 mg

Table 4. Duration of Therapy per Syndrome/Diagnosis

These are general guidelines for patients with uncomplicated disease and may need to be revised for individual patients. Treatment duration can be modified depending on infection severity and patient risk factors.

Syndrome / Diagnosis	Duration
Skin and soft tissue	5-14 days
Blood stream infection	7-14 days, **consider ID consult**
Staph Aureus	14 days after first negative blood culture**, ID consult**
Yeast	> 2 weeks after first negative culture
Bacterial sinusitis	7-14 days
Bacterial pneumonia	5-14 days
Mold infections	Min 12 weeks, **ID consult**
Candida pneumonia	Min 2 weeks**, ID consult**
Hepatosplenic candidiasis	Long term. **ID consult**
Typhlitis	14 days, **ID consult**
UTI	7-14 days

High risk patients: duration according to documented infection and ANC recovery

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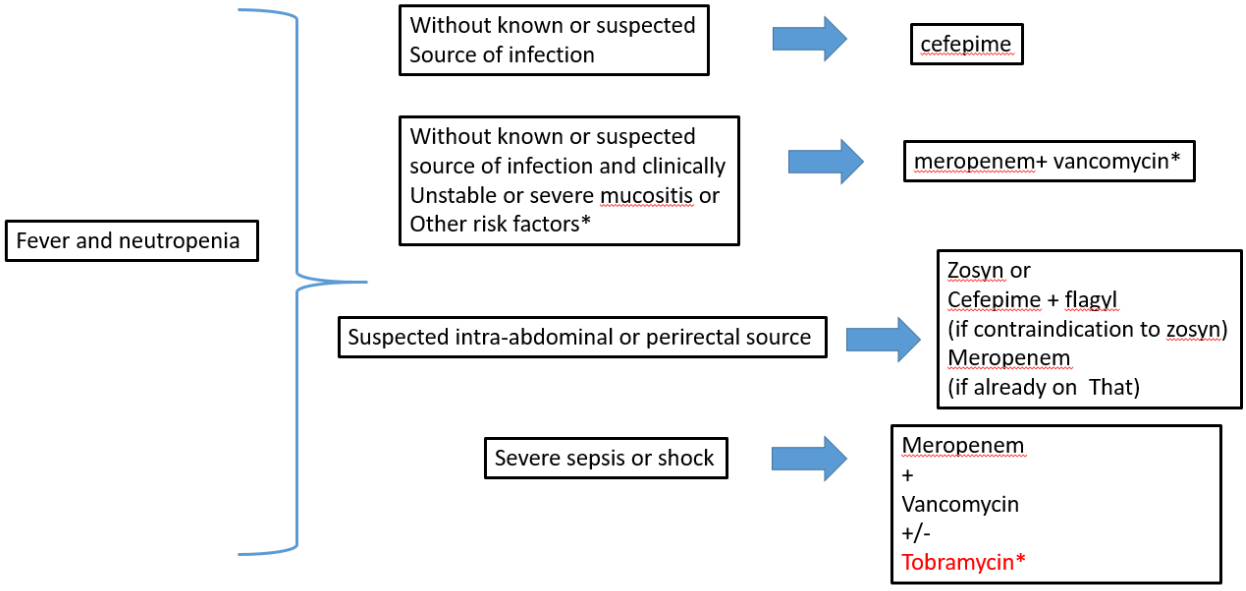
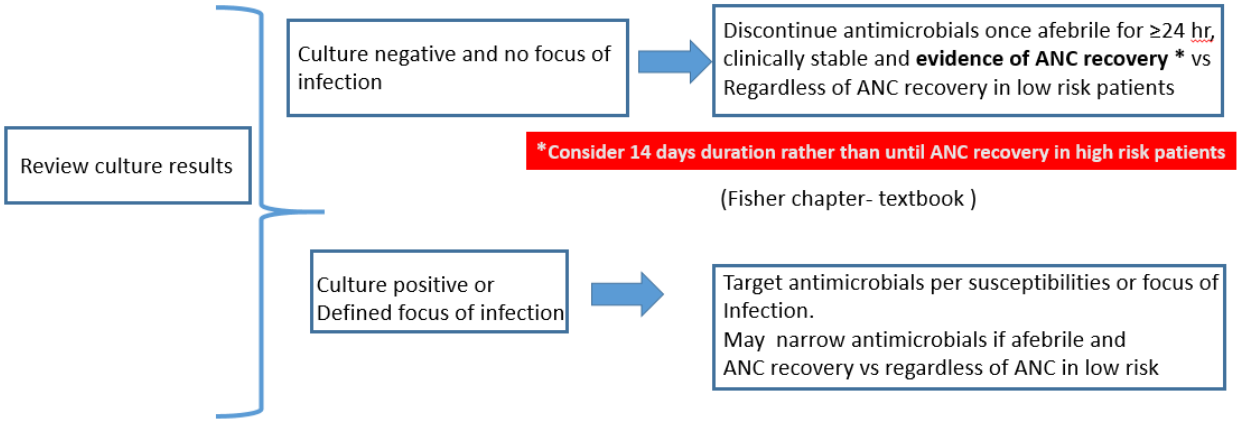
Figure 1. Empiric antimicrobial therapy for Fever and Neutropenia ANC < 500



(Groll et al., 2021) (Lehrnbecher et al., 2023).

Figure 2. Re assessment (48 h). Defervesced



*ANC recovery: ≥ 200/ mm^3 and rising

(Lehrnbecher et al., 2023, Lehrnbecher et al., 2021).

Figure 3. Persistent Fever and Clinically Stable at 48 hours

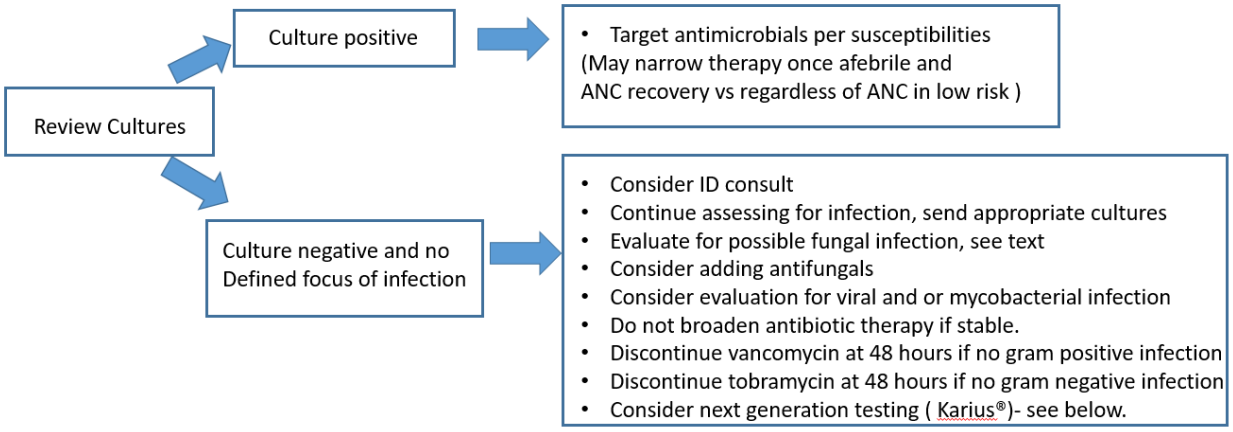
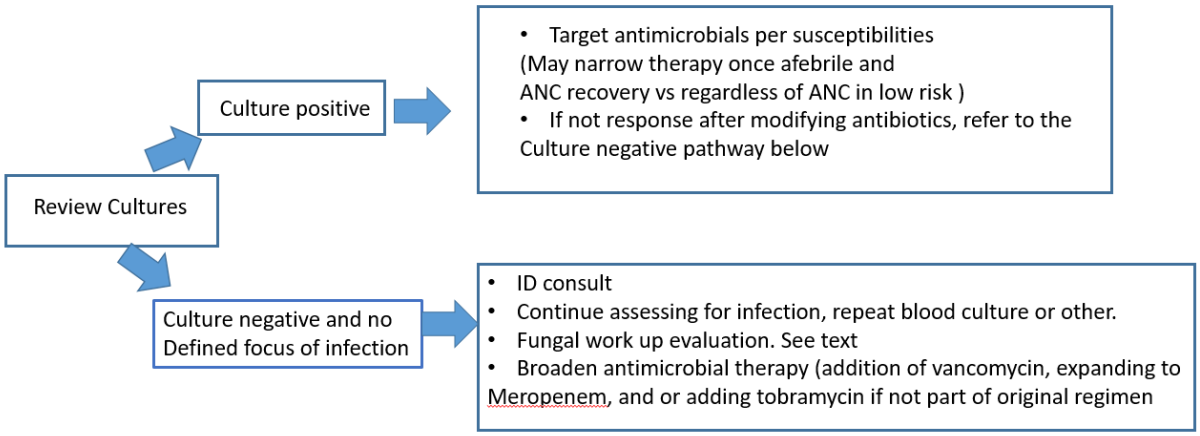


Figure 4. Persistent fever and clinically unstable at 48 hours



Lehrnbecher et al. 2023 update