BACKGROUND: Neutropenia results in a significant risk of bacterial and fungal infections, especially when neutropenia is profound (ANC <500/µL) and prolonged. Strategies are available that can reduce these risks, even possibly preventing bacterial infections from occurring during these periods of risk. When infections do occur, appropriate changes in antibiotics can improve clinical outcomes. These strategies are based on knowledge of the local microbiology at UCSF, published literature, and national practice guidelines.

1.0 OBJECTIVE:
1.1 To reduce the incidence of infections during neutropenia.
1.2 To treat infection that arises despite antibiotic prophylaxis.
1.3 To minimize the development of antibiotic-resistant organisms at UCSF.
1.4 To minimize the complications from antibiotic therapy.

2.0 PERSONNEL/SCOPE:
2.1 BMT Attending Physicians
2.2 BMT Nurse Practitioners
2.3 BMT Pharmacists
2.4 BMT Hospitalists
2.5 Transplant Infectious Diseases
2.6 Antimicrobial Stewardship Team

3.0 MATERIALS/EQUIPMENT:
None

4.0 DEFINITIONS:
4.1 * Adjust dose for renal dysfunction. Consult with malignant hematology pharmacists regarding dosing.
4.2 Antimicrobial Stewardship Pharmacy Voalte: (628)248-5602.
4.3 Transplant Infectious Disease Service Pager: (415) 443-2552.
4.4 ALL: Acute Lymphocytic Leukemia
4.5 AML: Acute Myelocytic Leukemia
4.6 ANC: Absolute Neutrophil Count
4.7 Cr Cl: Creatinine clearance
4.8 PO: Orally
4.9 IV: Intravenous
4.10 HSCT: Hematopoetic Stem Cell Transplant
4.11 GVHD: Graft Versus Host Disease
4.12 AmBisome: Liposomal amphotericin
4.13 CDI: Clostridium difficile
4.14 MRSA: Methicillin Resistant Staphylococcus aureus

5.0 POLICIES:
5.1 Neutropenia is defined as (1) ANC < 500/µL or (2) < 1000/µL and likely to fall to < 500/µL within 48 hours.

5.2 Fever in a neutropenic patient is defined as temperature > 38.0 degrees Celsius.

5.3 Fever of > 38.0 degrees Celsius requires blood cultures and antibiotics.

6.0 PROCEDURE:

6.1 **Step 1: Prophylaxis - When neutropenic (ANC < 500/µL, or, < 1000/µL and likely to fall to < 500/µL within 48 hours) if ANC expected to be low > 7 days.**

6.1.1 **Bacterial Prophylaxis:** Start levofloxacin 500 mg PO daily*. If patient unable to tolerate PO, may give 500 mg IV daily*. If unable to take levofloxacin due to allergy, intolerance, or contraindication, substitute cefpodoxime 200 mg twice daily.

6.1.2 **Fungal prophylaxis:** depends on diagnosis and regimen.

6.1.2.1 Autologous HSCT and ALL patients receiving chemotherapy:
- 6.1.2.1.1 Fluconazole 400 mg PO daily*.

6.1.2.2 Allogeneic HSCT patients and AML induction or consolidation chemotherapy:
- 6.1.2.2.1 Voriconazole 4 mg/kg PO/IV BID per protocol.

6.1.2.3 Options for patients intolerant of voriconazole include:
- 6.1.2.3.1 Posaconazole tablets 300 mg PO Q12 hours x 2 doses, then 300 mg PO daily (if able to take PO meds, no concern for CYP3A4 interactions), goal trough: 1-5.
- 6.1.2.3.2 Isavuconazolum sulfate 372 mg (Isavuconazole 200 mg), Q8 hours x 3 doses then 372 mg PO daily (if able to take PO meds, no concern for CYP3A4 interactions).
- 6.1.2.3.3 Caspofungin 70 mg IV loading dose, then 50 mg IV daily.
- 6.1.2.3.4 Liposomal amphotericin B (AmBisome) 3 mg/kg IV daily.
- 6.1.2.3.5 For patients with GVHD or other allogeneic HSCT patients on corticosteroids who are unable to take voriconazole, posaconazole, or isavuconazole, AmBisome 3 mg/kg IV daily is preferred over caspofungin.

6.1.3 **Viral prophylaxis:** Patients with ALL, Non-Hodgkin lymphoma, and any HSCT patient are to receive acyclovir 400 mg twice daily (or equivalent).

6.1.4 **New or persistent fever:** Initiate Step 2 and/or Step 3 depending on clinical assessment:
Two central line cultures should be drawn for first neutropenic fever (one culture if persistently febrile). If a 2nd episode of neutropenic fever occurs distant from the first, then again draw two central line cultures followed by single cultures if persistently febrile.
6.2 **Step 2: New fever and patient stable for medical ward. If instability is present proceed to Step 3.**

6.2.1 For the first neutropenic fever, draw two central line cultures, obtain a urinalysis and urine culture for high-risk populations, and check a chest x-ray. During influenza season, consider also testing for respiratory viruses. Additional work-up, such as abdominal imaging, should be obtained based on symptoms. Initial cultures should be drawn before antibiotics are started.

6.2.2 During influenza season (October - March) consider influenza testing and empiric therapy.

6.2.2.1 See IDMP website – treatment of influenza: [http://idmp.ucsf.edu/](http://idmp.ucsf.edu/)

6.2.3 Discontinue levofloxacin (or prophylactic antibacterial medication).

6.2.4 Start cefepime 2 g IV Q8 hours (dose adjust for renal dysfunction).

6.2.4.1 If patient has history of immediate-type hypersensitivity reaction (e.g. hives and bronchospasm) aztreonam 2 g IV Q8 hours* plus vancomycin 15-20 mg/kg IV Q12* may be used initially instead of cefepime (Note that vancomycin must be given in this case, even in instances where it would not normally be prescribed, due to the lack of gram-positive coverage by aztreonam). For ongoing treatment, providers should refer to the UCSF Inpatient Beta-lactam Allergy Guideline ([https://idmp.ucsf.edu/sites/idmp.ucsf.edu/files/beta-lactam_pathway.pdf](https://idmp.ucsf.edu/sites/idmp.ucsf.edu/files/beta-lactam_pathway.pdf)) for approach to giving beta-lactams safely as these drugs are associated with improved outcomes compared to alternative agents, such as aztreonam and vancomycin.

6.2.4.2 In patients on renal replacement therapy, there is a low but increased risk for neurotoxicity from cefepime use. Dosage should be adjusted. Alternative therapy with piperacillin/tazobactam is an option if there is concern for neurotoxicity and if a prolonged course is needed.

6.2.4.3 In patients with recent (< 90 days) clinical cultures with drug-resistant organisms, empirical therapy should typically include coverage for these organisms. Contact the Antimicrobial Stewardship Program with questions on empirical antibiotic choices.

6.2.5 **Assess for risk factors for MRSA infection: bacterial pneumonia, skin and soft tissue infection, evidence of central line infection, recent systemic MRSA infection.**

6.2.5.1 If MRSA risk present, also start vancomycin dosed for goal trough of 15-20 mcg/ml.

6.2.6 If fevers persist but patient is clinically stable and cultures are negative, do not broaden antibacterial coverage.
6.2.7 At 48 hours, discontinue vancomycin if cultures do not grow a resistant gram positive organism and there is no evidence of a resistant gram positive infection.

6.2.8 Continue IV antibiotics until:
   6.2.8.1 If cultures negative and fever resolved, discontinue IV antibiotics 72 hours after last fever (regardless of ANC) and return to prophylaxis, if indicated.
   6.2.8.2 If work-up reveals infectious organism or syndrome (i.e. pneumonia), change antibiotics to target this entity and treat until fever resolved and appropriate treatment course for infectious etiology is completed. Then discontinue antibiotics and return to prophylaxis, if indicated.

6.2.10 If fever persists despite 4-7 days of antibiotics and no fever source has been identified, proceed to Step 4 (antifungal work-up).

6.3 **Step 3: New or persistent fevers in the setting of sepsis with hemodynamic instability requiring ICU transfer or ongoing care.**

6.3.1 Discontinue levofloxacin and start meropenem 1 g IV Q8 hours (adjust for renal function). Start or continue vancomycin dosed for trough of 15-20 mcl/ml

6.3.3 If the patient remains hemodynamically unstable despite the above:
   6.3.3.2 Consider adding tobramycin 7 mg/kg IV Q24 hours.
   6.3.3.2.1 Drug levels should be drawn 6-14 hours after administration and compared to the nomogram on the antibiotic dosing card or the IDMP website ([http://idmp.ucsf.edu/aminoglycoside-dosing-and-monitoring-recommendations](http://idmp.ucsf.edu/aminoglycoside-dosing-and-monitoring-recommendations)). Contact malignant hematology or ASP pharmacists regarding appropriate dosing and monitoring.

   6.3.3.3 If on fluconazole prophylaxis and high risk for candidemia: Consider discontinuation of fluconazole and starting caspofungin 70 mg IV loading dose, then 50 mg IV Q24 hours.
   6.3.3.3.1 **Candidemia risk factors:** recent intra-abdominal procedure, current TPN, > 7 days of broad spectrum antibiotics, long-term central line, known candida colonization.

6.3.4 If remains hemodynamically unstable:
   6.3.4.1 Consultation with Transplant Infectious Disease service is recommended.

6.3.5 If improves and hemodynamically stable with negative cultures/work-up after 48 hours:
   6.3.5.1 Discontinue vancomycin.
   6.3.5.2 Discontinue tobramycin (if started).
6.3.5.3 Discontinue caspofungin after 96 hours if cultures are negative (if started).

6.3.5.4 Continue meropenem or change to piperacillin/tazobactam 4.5 g IV Q6 hours to complete 7-day antibiotic course from the point of clinical stability. Then discontinue antibiotic and return to prophylaxis, if indicated.

6.3.6 If improvement and hemodynamically stable and if work-up reveals infectious organism or site of infection, change antibiotics to target this entity and treat until:

6.3.6.1 Fever resolved and appropriate treatment course for infectious etiology is completed. Then discontinue antibiotics and return to prophylaxis, if indicated.

6.4 **Step 4: New or persistent fevers despite 4-7 days of antibiotics and current/recent neutropenia > 7 days or radiology compatible with invasive fungal infection. Also, if persistent hemodynamic instability despite broad spectrum antibiotics (Step 3).**

6.4.1 Consultation with the Transplant Infectious Diseases service is recommended.

6.4.2 Evaluate patient with chest CT +/- sinus CT (if symptomatic), serum galactomannan level, and serum beta-D-glucan level.

6.4.2.1 Consider additional fungal serologies based on exposure history.

6.4.3 If abdominal symptoms present, or above testing negative, consider abdominal CT.

6.4.4 If CT abnormalities found, biopsy or targeted microbiologic testing (e.g. BAL) is recommended to establish diagnosis.

6.4.4.1 If BAL is performed, BAL galactomannan should be ordered.

6.4.5 Discontinue fluconazole prophylaxis, start voriconazole 6 mg/kg PO Q12 hours x 2 doses, then 4 mg/kg PO Q12 hours. If already on voriconazole, check voriconazole trough (goal 2-5 mcg/mL).

6.4.5.1 Check LFTs when starting or changing dose of voriconazole.

6.4.5.2 Check voriconazole trough after 5-7 days at any new dose.

6.4.5.3 Voriconazole may also be given IV if necessary.

6.4.5.4 Depending on the clinical situation and suspicion for invasive fungal infection, various options to consider in consultation with the Transplant Infectious Disease service:

6.4.5.4.1 Concern for Aspergillus: add caspofungin 70 mg IV x 1 dose, then 50 mg IV Q24 hours to voriconazole.

6.4.5.4.1.1 Concern for Mucor: Discontinue voriconazole, start amBisome 5 mg/kg IV Q24 hours +/- caspofungin.
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6.4.6 If hemodynamically stable with positive fungal work-up or resolution of fever after 3-5 days of antifungal therapy:
   6.4.6.1 Continue antifungal agent, treatment duration based on type of infection.
   6.4.6.2 If no documented bacterial infection, discontinue broad spectrum antibiotics and return to prophylaxis, if indicated.

6.4.7 If hemodynamically stable with persistent fevers despite 3-5 days of antifungals:
   6.4.7.1 Continue antibacterials per steps above.
   6.4.7.2 Discontinue antifungal agent.
   6.4.7.3 Additional fever work-up.
   6.4.7.4 Consider Transplant Infectious Disease consultation.

6.5 CDI diagnosis: If at any point during above algorithm, a clinical syndrome consistent with CDI is diagnosed, the following are recommended:
   6.5.1 Treat per UCSF CDI guidelines (see http://idmp.ucsf.edu/).
   6.5.2 Use the narrowest systemic antibiotics for the shortest duration.

7.0 MEASURABLE OUTCOMES:
7.1 The antibiotic algorithm at UCSF is reviewed at least every 3 years by a team including BMT Physicians, Malignant Hematology Hospitalists and NPs, Malignant Hematology pharmacists, and the Antimicrobial Stewardship Program.
7.2 Antibiotic use is monitored regularly by the Antimicrobial Stewardship Program.
7.3 The incidence of infections with various organisms and the patterns of antibiotic sensitivity are tracked.
7.4 In particular, we review the incidence of bloodstream infections with:
   7.4.1 Gram positive bacteria
   7.4.2 Gram negative bacteria
   7.4.3 Candida species
7.4 We also track the incidence of:
   7.4.1 Clostridium difficile colitis (CDI)
   7.4.2 Vancomycin-resistant enterococcus (VRE)
   7.4.3 Extended-spectrum beta-lactamase (ESBL) producing enterobacteriacae
   7.4.4 Carbapenem-resistant enterobacteriacae (CRE)

8.0 REFERENCES:
8.1 Antibiotic Algorithm for Neutropenic Patients, UCSF Adult Leukemia and BMT and Adult Antimicrobial Stewardship Programs
8.3 P&P 4.1: Guidelines for the Care of the Immunocompromised Patient, UCSF Infection Control Manual
8.4 Infectious Disease Management Program at UCSF: http://idmp.ucsf.edu/
8.6 Freifeld et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases
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9.0 APPENDICES:
9.1 Flowchart for the Management of Neutropenic Fever
SOP REVISION HISTORY PAGE

<table>
<thead>
<tr>
<th>Date</th>
<th>Revision</th>
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<tbody>
<tr>
<td>10/20/2003</td>
<td>New</td>
</tr>
<tr>
<td>02/13/2007</td>
<td>Format change and change of antibiotic algorithm</td>
</tr>
<tr>
<td>03/22/2010</td>
<td>Updated revision number, header and footer, date and name change</td>
</tr>
<tr>
<td>01/27/2011</td>
<td>Revisions include:</td>
</tr>
<tr>
<td></td>
<td>1. Change imipenem to meropenem in antibiotic algorithm.</td>
</tr>
<tr>
<td></td>
<td>2. Clarified use of tobramycin.</td>
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<tr>
<td>01/27/2012</td>
<td>Revisions include:</td>
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<tr>
<td></td>
<td>1. Options for patients intolerant to voriconazole</td>
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<tr>
<td></td>
<td>2. Change vancomycin dosing to 15.20 mg/kg</td>
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<td></td>
<td>3. Consultation with ID Service</td>
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<td>4. Biopsy recommendation</td>
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<td>5. Meropenem and Tobramycin dosing</td>
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<td>6. Appendix</td>
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<tr>
<td>01/27/2014</td>
<td>Change Moxifloxacin to Levofloxacin due to increase in pseudomonas rate.</td>
</tr>
<tr>
<td></td>
<td>Change Tobramycin to daily dosing. Update Appendix. Delete step 5 as only one case per year.</td>
</tr>
<tr>
<td>10/27/2015</td>
<td>Added definition of neutropenic fever and when blood cultures to be drawn. Amended Appendix 9.1 for consistency with this SOP.</td>
</tr>
<tr>
<td>05/24/2016</td>
<td>Changed definition of neutropenia to include ANC&lt;1000/µL and expected to fall to &lt;500/µL. Defined stable and unstable. Changed recommendations for when vancomycin should be initiated. Changed recommendations for duration of IV therapy for neutropenic fever. Changed recommendations for escalation of therapy in stable patients with neutropenic fever. Added a flowsheet to assist with decision making.</td>
</tr>
<tr>
<td>02/13/2019</td>
<td>Added Cefdinir 300mg twice daily or Cefpodoxime 200 mg twice daily as bacterial prophylaxis for patient allergic to or intolerant of Levofloxacin.</td>
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<tr>
<td>3/5/2019</td>
<td>1) Change stop timing for febrile neutropenia in a stable patient without a source to 72 hours after last fever</td>
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<td>2) Change definition of fever to &gt; 38 degrees</td>
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<td>3)</td>
<td>Change escalation for unstable patients to only ICU patients and move straight to meropenem and vancomycin</td>
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<tr>
<td>4)</td>
<td>Change duration for septic patient with negative cultures from 10 to 7 days</td>
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</table>