TITLE: FEVER AND NEUTROPENIA - ADULT GUIDELINES

GUIDELINES:
Based on recommendations from the Subcommittee on Anti-Infective Use and the Formulary and Therapeutics Committee, these guidelines shall be used by prescribers and pharmacy personnel to aid in the initiation and discontinuation of anti-infectives for adult patients with fever and neutropenia.

PURPOSE:
To aid in the initiation and discontinuation of anti-infectives for adult patients with neutropenic fever based upon clinical symptoms, laboratory results, and imaging.

APPLICABILITY:
Prescribers and pharmacists

PROCEDURE:
1. Refer to page 2 for identification of low- or high-risk patients with fever and neutropenia
2. Reference Clinical Pathway I for antimicrobial therapy
3. Low-risk patients with persistent fever are unlikely to develop an invasive fungal process. However, patients with risk factors for invasive candidiasis (e.g., intra-abdominal primary or metastatic tumors, receipt of total parenteral nutrition, extended use of broad-spectrum antibiotics) may benefit from initiation of fluconazole 400 – 800 mg daily adjusted for renal dysfunction or micafungin 100 mg daily for patients that have received more than fluconazole for more than 48 hours in the previous 30 days.
4. Reference Clinical Pathway II and Antifungal Pathway for persistent fever or clinically unstable high-risk patients
   a. Pre-emptive approach: may be used to monitor high-risk patients with persistent fever without clinical, radiological (CT chest and/or sinus), or microbiological/serological evidence of fungal infection
      i. Serial galactomannan: Performed 2 times weekly. A positive test (> 0.5).
      ii. Patients who received prophylaxis with an anti-mold agent (e.g., voriconazole or posaconazole) should have a trough obtained and/or dose titrated to treatment doses.
         • Treatment doses: Voriconazole 4 mg/kg q12h adjusted for liver disease and posaconazole 200 mg q6h given with food or nutritional supplement
         • Voriconazole/posaconazole trough: Obtain a blood sample within 1 hour of the next dose in a RED top tube place on ice with a manual requisition to the send out lab.
   b. Empirical approach: should be used in high-risk patients that are clinically UNstable and agent should be selected based upon likely etiology, toxicities, and cost. Please see Antifungal Agents for complete details.
Risk Factor Assessment – Adult Fever and Neutropenia

Below are two algorithms to assess a patient's risk of experiencing complication due to the fever and neutropenia. Both are intended to be used at the time of diagnosis of fever and neutropenia.

<table>
<thead>
<tr>
<th>Clinical Criteria</th>
<th>High-Risk</th>
<th>Low-Risk</th>
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<tbody>
<tr>
<td>Anticipated neutropenia &gt; 7 days and</td>
<td>Absolute neutrophil count &lt; 100 cells/mm³ and/or</td>
<td>Anticipated neutropenia ≤ 7 days or</td>
</tr>
<tr>
<td>Significant comorbid conditions† including uncontrolled cancer§ or</td>
<td>None or few comorbid conditions§</td>
<td></td>
</tr>
</tbody>
</table>

Leukemic malignancies:
- Requiring more than 1 induction cycle or
- Relapsed or refractory disease

‡ Comorbid conditions including but not limited to the following:
- Neurologic: concern for spinal compression or new changes in mental-status
- Pulmonary: new infiltrate, hypoxemia, or respiratory failure (PO₂ < 60 mmHg, adjusted for hyperventilation), underlying chronic lung disease (e.g., chronic obstructive pulmonary disease)
- Intravascular catheter infection (especially tunneled catheter infection)
- Older than 60 years of age
- Oral or gastrointestinal mucositis causing dysphasia or severe diarrhea
- Gastrointestinal symptoms (new): abdominal pain, nausea and vomiting
- Hepatic insufficiency: defined as aminotransferase levels > 5 times normal
- Renal insufficiency: defined as a creatinine clearance less than 30 mL/min
- Hematologic: uncontrolled bleeding and thrombocytopenia platelets < 40,000 cells/microliter

§ Uncontrolled cancer (lymphoma or solid tumor):
- Development of new lesions,
- 25% or more enlargement of a measurable lesion while on chemotherapy, or
- Premature termination of chemotherapy due to other evidence of failure (usually progressive cancer symptoms)
CLINICAL PATHWAY I - Adult Fever and Neutropenia

The following is only a guideline for the management of neutropenic fever in the adult patient. Clinical judgement should be used at all times.

Fever (>38.3°C) & neutropenia (ANC < 500) OR ANC < 1000 and predicted to decline to < 500 within 48h

START BROAD SPECTRUM ANTIBIOTICS

LOW RISK

HIGH RISK

CUMC and WC HSCT: piperacillin/tazobactam 4.5 g IV q6h
severe PCN Type I hypersensitivity: vancomycin IV + aztreonam 2 g IV q8h
other PCN allergy (e.g. rash): cefepime 2 g IV q8h

START BROAD SPECTRUM ANTIBIOTICS

HIGH RISK

CUMC and WC HSCT: piperacillin/tazobactam 4.5 g IV q6h ±/− tobramycin IV†
WC Leukemic service: cefepime 2 g IV q8h ±/− tobramycin IV†
severe PCN Type I hypersensitivity: vancomycin IV + aztreonam 2 g IV q8h ±/− tobramycin IV†
other PCN allergy (e.g. rash): cefepime 2 g IV q8h ±/− tobramycin IV†

REASSESS AT 48 - 96 HOURS

- Modify antibiotics according to culture and/or site of infection
- Continue antibiotics until ANC ≥ 500 and rising
- If clinically unstable refer to high-risk pathway

Defervesced

Persistant fever Clinically Unstable

Persistant fever Clinically stable

Culture positive

Culture negative

Discontinue vancomycin
- No s/s of a gram-positive infection
- Continue to culture & assess sites of infection
- No antibiotic changes unless new clinical, microbiologic or radiographic data supporting new infection. If so See Clinical Pathway II

Adjust antibiotics according to cultures (if necessary)
Continue to culture & assess sites of infection

Adjust antibiotics according to cultures (if possible)
- Continue antibiotics to complete a course of therapy
- Monitor for resolution of infection
- May consider discontinuing antifungicals if clinically stable, afebrile, and adequate course has been complete.

Response

No Response

Continue antibiotics for a course and ANC ≥ 500 and rising
- May consider discontinuing antifungals if clinically stable, afebrile, and adequate course has been complete.

- Continue antibiotics until ANC ≥ 500 and rising
- Monitoring for resolution of infection
- May consider discontinuing antifungals if clinically stable, afebrile, and adequate course has been complete.

-Examine and reimage (CT) for new/worsening infection
- Culture/biopsy/drain and assess for bacterial/viral/fungal
- Review antifungals to ensure adequate coverage
- Go to Clinical Pathway II

Go to Clinical Pathway II

* adjust dose for renal dysfunction (pip/tazo, tobramycin, cefepime, aztreonam, vancomycin) and adjust dose based on weight (tobramycin, vancomycin)

± HSCT = hematopoietic stem cell transplant, AML = acute myelogenous leukemia, ALL = acute lymphoblastic leukemia, MDS = myelodysplastic syndrome, CML crisis = chronic myelogenous leukemia with myeloid or lymphoid crisis
ANC = absolute neutrophil count (all reported as cells/mm³), MRSA = Methicillin-resistant Staphylococcus aureus, PCN = penicillin, IV = intravenous

Last modified 5-24-11
High-risk and persistent fever > 4 days on broad spectrum antibiotics
- Daily examination and history
- Blood cultures: repeat periodically
- Cultures according to suspected sites of infections

Myeloid recovery imminent
Clinically Stable
Myeloid recovery NOT imminent
Clinically UNstable

1. Culture/biopsy/drain sites of proven or probable infection
2.Broaden antibiotic coverage
- Add tobramycin* and/or vancomycin* if not included in the initial regimen.
- Expand to meropenem*. If patient has a documented IgE mediated hypersensitivity consult Infectious Diseases
3. Examine and reimage (CT/MRI)
4. Consider empirical antifungal

NOTE: Expanding antibiotic coverage and use of empirical antifungals may be stratified according to individual patients

Pre-Emptive
Empirical approach
Empirical approach
Pre-emptive

Monitor for fungal process & continue antibiotics until ANC ≥ 500 and rising
Pre-Emptive
Initiate antifungal therapy
- Lipid Amphotericin B
- Micafungin
- Voriconazole
See Antifungal Pathway

Continue antibiotics until ANC ≥ 500 and rising

Persistently febrile
Considerations:
- Clinically UNstable: broaden antibiotics, if not already expanded
- Evaluate for potential fungal infection and consider initiation of antifungal agent, if not already initiated (See Antifungal Pathway)
- Evaluate other causes of fever (e.g., viral, mycobacterial infection, *Clostridium difficile* colitis, graft versus host disease, or drug fever)
- Consider discontinuing vancomycin

Adjust antibiotics according to cultures (if possible)
- Continue antibiotics to complete course of therapy and ANC ≥ 500 and rising.
- Monitor for resolution of infection.

Continue antibiotics until ANC ≥ 500 and rising

Culture positive
Culture negative

Discontinue antibiotics

Persistently febrile
Considerations:
- Clinically UNstable: broaden antibiotics, if not already expanded
- Evaluate for potential fungal infection and consider initiation of antifungal agent, if not already initiated (See Antifungal Pathway)
- Evaluate other causes of fever (e.g., viral, mycobacterial infection, *Clostridium difficile* colitis, graft versus host disease, or drug fever)
- Consider discontinuing vancomycin

Adjust antibiotics according to cultures (if possible)
- Continue antibiotics to complete course of therapy and ANC ≥ 500 and rising.
- Monitor for resolution of infection.

Continue antibiotics until ANC ≥ 500 and rising

Culture positive
Culture negative

Discontinue antibiotics

*

ANC = absolute neutrophil count (all reported as cells/mm³), MRSA = Methicillin-resistant *Staphylococcus aureus*, PCN = penicillin, IV = intravenous

HSCT = hematopoietic stem cell transplant, AML = acute myelogenous leukemia, ALL = acute lymphoblastic leukemia, MDS = myelodysplastic syndrome, CML crisis = chronic myelogenous leukemia with myeloid or lymphoid crisis

*Positive galactomannan: values > 0.5.

Last modified 5-24-11
**ANTIFUNGAL PATHWAY** – Adult Fever and Neutropenia (continued)
See detailed information for each Antifungal agents

- **CrCL > 50 mL/min & NO history of renal insufficiency/failure**
  - False → **Child Pugh C/cirrhosis**
    - True
    - **Voriconazole 6 mg/kg PO or IV q12h x 2 doses, then 4 mg/kg PO or IV q12h***
      - Caution with drug interactions:
        - Patients receiving cyclophosphamide or vincristine consider using alternative agent (e.g., lipid amphotericin B or micafungin).
        - If receiving cyclosporin, reduce cyclosporin dose by 50% and monitor levels closely.
        - If receiving tacrolimus, reduce tacrolimus dose by 67% and monitor levels closely.
    - False
      - **Receipt of voriconazole or posaconazole prophylaxis**
        - False → **Child Pugh class A/B †**
          - False
          - **Voriconazole 6 mg/kg PO or IV q12h x 2 doses, then 2 mg/kg PO or IV q12h***
            - Caution with drug interactions:
              - Patients receiving cyclophosphamide or vincristine consider using alternative agent (e.g., lipid amphotericin B or micafungin).
              - If receiving cyclosporin, reduce cyclosporin dose by 50% and monitor levels closely.
              - If receiving tacrolimus, reduce tacrolimus dose by 67% and monitor levels closely.
          - True
            - **Animal amphotericin B 5 mg/kg IV q24h, infuse over 2 hours**
              - May pre-medicate 30 minutes prior to each dose:
                - Acetaminophen 650 mg PO/PR
                - Diphenhydramine 25 – 50 mg PO/IV
                - If severe rigors: meperidine 50 mg IV/IM
                - If severe chills: hydrocortisone 25 mg IV (may discontinue after ~5 days)
              - **Saline hydration** (with each dose):
                - Administer 500 mL normal saline over 1 – 2 hours pre- and post-dose (total of 1000 mL) if able to tolerate. May consider only pre-hydration if administration of fluids is difficult (e.g., renal disease, heart failure, etc.).

* Use intravenous voriconazole with CAUTION in patients with impaired renal function (i.e., CrCL < 50 mL/min), due to potential of accumulation of the cyclodextrin vehicle. If possible use oral therapy.
† Leukemia alone may cause elevations of AST and ALT. Consider the risks and benefits of voriconazole therapy, consider dose adjustment or alternative therapy (e.g., liposomal amphotericin B or micafungin).

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Lipid amphotericin B (Abelcet®)
- Amphotericin B is considered the gold standard for empiric antifungal therapy in patients with persistent fever and neutropenia.
  o Provides activity against most Candida sp., the most commonly isolated Aspergillus sp. (e.g. A. fumigatus, A. flavus), and the Zygomycetes (e.g. Rhizopus sp., Mucor sp.).
  o Limited activity against some Aspergillus sp. (e.g. A. terreus, A. niger) and some rare fungi like Scedosporium sp., Fusarium sp., and Candida lusitaniae.
- Toxicities include nephrotoxicity, infusion related reactions, and electrolyte abnormalities (e.g., hypomagnesemia, hypokalemia) may limit its use.
  o Please see Antifungal Pathway for detailed information regarding pre-medications.
- Severe renal insufficiency at baseline (SCR > 2 mg/dL or CrCL < 50 mL/min) or the development of renal insufficiency during lipid amphotericin B therapy (SCR increase 2x baseline) may warrant the use of an alternative antifungal.
- Dosage, please see Antifungal Pathway for further dosing recommendations.

Voriconazole (Vfend®)
- Voriconazole has been compared to lipid amphotericin B for empiric antifungal therapy in patients with fever and neutropenia. While the five component composite endpoint in this study did not meet the criteria for non-inferiority, voriconazole was associated with less breakthrough fungal infections compared to lipid amphotericin B. In addition, patients studied included hematopoietic stem cell transplant recipients and results were comparable in these patients. Voriconazole therapy was associated with significantly less toxicities.
- Voriconazole provides activity against all Aspergillus sp., including those that may be resistant to amphotericin B, most Candida sp., and rare fungi like Scedosporium sp., and Fusarium sp. Voriconazole does not provide any activity against the Zygomycetes (e.g. Rhizopus sp., Mucor sp.).
- Toxicities include visual disturbances, hepatotoxicity, hallucinations, and rash.
  o Caution must be exercised with regard to drug interactions. Voriconazole is an inhibitor of CYP450 2C9, 2C19, and 3A4.
- Voriconazole may be problematic in allogenic stem cell transplant recipients due to drug interactions with immunosuppressants and risk of hepatotoxicity.
  o The occurrence of hepatic profile abnormalities may be difficult to distinguish from hepatic involvement associated with graft versus host disease (GvHD).
- Voriconazole has excellent oral bioavailability (>95%). Oral therapy is preferred in patients with presumed normal gut absorption. This includes patients without nausea, vomiting, diarrhea, and severe mucositis, who may also be receiving other medications by mouth.
- Dosage, please see Antifungal Pathway for further dosing recommendations.
  o Intravenous voriconazole is formulated with a cyclodextrin that accumulates in patients with severe renal insufficiency. Oral therapy may be preferred in patients with CrCL< 50 mL/min.

Echinocandins (formulary agent, micafungin)
- Echinocandins (e.g., caspofungin) has been compared to lipid amphotericin B for empiric antifungal therapy in patients with fever and neutropenia and met predefined criteria for non-inferiority. This study included predominantly patients with AML and did not include many hematopoietic stem cell transplant recipients. Echinocandin class is associated with significantly less toxicities. Echinocandin class of anti-infectives has a limited spectrum of activity, specifically only Candida sp. and Aspergillus sp. Unlike amphotericin B and voriconazole which are fungicidal against Aspergillus sp., echinocandins exhibit only fungistatic activity against Aspergillus sp.
- Toxicities are minimal, including fever, flushing, thrombophlebitis, nausea/vomiting, and liver enzyme abnormalities.
- Micafungin does not require dosage adjustments for renal or mild to moderate hepatic dysfunction. The prophylactic dose is 50 mg q24h and treatment dose is 100 mg q24h. There is no data regarding dosage adjustments for patients with severe hepatic insufficiency.
## Child-Pugh Grading System for Liver Disease

<table>
<thead>
<tr>
<th>Clinical and Biochemical Measurements</th>
<th>Points Scored for Abnormality</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Encephalopathy</strong></td>
<td></td>
<td>None</td>
<td>Grade 1 – 2 (or treated)</td>
<td>Grade 3 – 4</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td></td>
<td>Absent</td>
<td>Slight (or controlled)</td>
<td>Moderate with diuretics</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td></td>
<td>&lt; 2 mg/dL</td>
<td>2 – 3 mg/dL</td>
<td>&gt; 3 mg/dL</td>
</tr>
<tr>
<td><strong>Bilirubin (primary sclerosing cholangitis, primary biliary cirrhosis, cholestatic diseases)</strong></td>
<td></td>
<td>&lt; 4 mg/dL</td>
<td>4 – 10 mg/dL</td>
<td>&gt; 10 mg/dL</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td></td>
<td>&lt; 1.7</td>
<td>1.7 – 2.3</td>
<td>&gt; 2.3</td>
</tr>
<tr>
<td><strong>PT prolonged</strong></td>
<td></td>
<td>&lt; 4 seconds</td>
<td>4 – 6 seconds</td>
<td>&gt; 6 seconds</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td></td>
<td>&gt; 3.5 g/dL</td>
<td>2.8 – 3.5 g/dL</td>
<td>&lt; 2.8 g/dL</td>
</tr>
</tbody>
</table>

**TOTAL POINTS**

<table>
<thead>
<tr>
<th>&lt; 5</th>
<th>Not considered to have hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7</td>
<td>Class A</td>
</tr>
<tr>
<td>7 – 9</td>
<td>Class B</td>
</tr>
<tr>
<td>&gt; 9</td>
<td>Class C</td>
</tr>
</tbody>
</table>
RESPONSIBILITY:
Joint Subcommittee on Anti-Infective Use

GUIDELINE DATES:
Issued: May 2009
Reviewed: May 2010
Revised: May 2011
Medical Board Approval: June 2011

REFERENCES: