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) and **Neutropenia** (ANC < 500) OR ANC <1000 and predicted to decline to < 500 over next 48 hours

**Fever work-up**
- Complete physical exam
- Blood cultures (one from each port + peripheral)
- Sputum cultures
- Fungal isolator blood and sputum cultures
- Urine cultures
- Chest x-ray
- CBC with differential
- Liver function tests
- Basic metabolic panel
- Other tests as indicated

**START BROAD SPECTRUM ANTIBIOTICS**

**LOW RISK**
- piperacillin/tazobactam (Zosyn®) 4.5 g IV q6h* OR cefepime 2 g IV q8h* (NYP/WC)

**HIGH RISK**
- piperacillin/tazobactam (Zosyn®) 4.5 g IV q6h* OR cefepime 2 g IV q8h* (NYP/WC)
  - +/− tobramycin IV *

**REASSESS AFTER 72 HOURS**

Persistently febrile
- Signs and symptoms of infection NOT improving, clinically unstable

Afebrile
- Signs and symptoms of infection improved and clinically stable

**GO TO CLINICAL PATHWAY II**

**ANC ≥ 500**
- Culture positive
  - Adjust antibiotics according to cultures (if possible)
    - Continue antibiotics to complete a course of therapy
    - Monitor for resolution of infection
  - Culture negative
    - No evidence of infection and clinically stable
- Culture negative
  - Continue antibiotics until ANC ≥ 500

**ANC < 500**
- Culture positive
  - Adjust antibiotics according to cultures (if possible)
    - Continue antibiotics to complete a course of therapy
    - Monitor for resolution of infection

- Culture negative
  - Discontinue antibiotics

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* Criteria for vancomycin* use:
- History of prior infection/colonization with resistant gram positives (e.g., Staphylococcus sp. or Streptococcus sp).
- Obvious catheter related/exit site/tunnel infection
- Positive blood culture for gram positive organisms (pending sensitivity)
- Evidence of cellulitis, wound, disseminated papulles or other cutaneous lesions
- Severe hypotension/sepsis
- Grade III/IV mucositis

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

ANC = absolute neutrophil count, MRSA = Methicillin-resistant Staphylococcus aureus, PCN = penicillin, IV = intravenous

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Persistent fever > 72 hours on broad spectrum antibiotics

Clinically stable

Expected ANC recovery within ~ 5 days and no new data

ANC is NOT expected to recover within ~5 days

Continue antibiotics until ANC ≥ 500
  - Consider discontinuation of vancomycin
  - Continue to culture as necessary

Clinically unstable

Consider adding an antifungal agent
  - If new evidence of infection or progressive disease, AND current antibiotics are considered inadequate; Consider ID consult

Considerations:
1) Evaluate for potential fungal infection and consider initiation of antifungal agent (See Clinical Pathway II – Empirical Antifungal Therapy and considerations for choosing antifungal therapy)
2) May add vancomycin* IV if not included in the initial regimen

Perform imaging studies as clinically indicated

REASSESS DAILY

Persistently febrile

ANC ≥ 500

Discontinue antibiotics after 4-5 days ANC ≥ 500

Discontinue antibiotics after 4-5 days ANC ≥ 500

Continue to monitor and reassess

ANC < 500

Considerations:
- Evaluate for potential fungal infection and consider initiation of antifungal agent, if not already initiated (See Clinical Pathway II – Empirical Antifungal Therapy considerations for choosing antifungal therapy)
- Evaluate other causes of fever (e.g., viral, mycobacterial infection, Clostridium difficile colitis, graft versus host disease, or drug fever)
- Consider broadening gram (-) antibiotics
- Consider discontinuing vancomycin

Afebrile

ANC ≥ 500

Culture positive or documented site of infection (e.g., cellulitis)

Culture negative

Culture negative

Culture positive or documented site of infection (e.g., cellulitis)

Adjust antibiotics according to cultures (if possible)
  - Continue antibiotics to complete course of therapy;
  - Monitor for resolution of infection

Adjust antibiotics according to cultures (if possible)
  - Continue antibiotics to complete a course of therapy;
  - Monitor for resolution of infection

- No evidence of infection and clinically stable

Discontinue antibiotics

Continue antibiotics until ANC ≥ 500

ANC < 500

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

ANC = absolute neutrophil count, MRSA = Methicillin-resistant Staphylococcus aureus, PCN = penicillin, IV = intravenous
Risk Factor Assessment – Adult Fever and Neutropenia
(Talcott JA, J Clin Oncol 1992: 316-22)

**based on status at diagnosis of fever and neutropenia**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient/outpatient</td>
<td>Inpatient</td>
<td>Outpatient</td>
<td>Outpatient</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Presence of serious concurrent comorbidity(^1)</td>
<td>+ / -</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Presence of uncontrolled cancer(^2)</td>
<td>+ / -</td>
<td>+ / -</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Risk classification</td>
<td>HIGH RISK</td>
<td>HIGH RISK</td>
<td>HIGH RISK</td>
<td>LOW RISK</td>
</tr>
</tbody>
</table>

1 comorbidity: hypotension (systolic blood pressure < 90 mmHg), altered mental status, respiratory failure (P\(_{O_2}\) < 60 mmHg, adjusted for hyperventilation), uncontrolled bleeding with severe thrombocytopenia (platelets < 40,000/\(\mu\)L), inadequate outpatient fluid intake or pain control, suspected spinal cord compression, symptomatic hypercalcemia, and other conditions requiring hospitalization as determined by the treating physician

2 control of cancer: for patients with leukemia, uncontrolled cancer defined as the absence of documented complete remission

for patients with lymphoma or solid tumors, uncontrolled cancer defined as either 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 II – Adult Fever and Neutropenia (continued)
CONSIDERATIONS FOR CHOOSING ANTIFUNGAL THERAPY

Lipid amphotericin B (Abelcet®)
- Amphotericin B is considered the gold standard for empiric antifungal therapy in patients with persistent fever and neutropenia.
  - Provides activity against most Candida sp., the most commonly isolated Aspergillus sp. (e.g. A. fumigatus, A. flavus), the Zygomycetes (e.g. Rhizopus sp., Mucor sp.)
  - Limited activity against some Aspergillus sp. (e.g. A. terreus, A. niger) and some rare fungi like Scedosporium sp., and Fusarium sp.
- Toxocities include nephrotoxicity, infusion related reactions, and electrolyte abnormalities (e.g., hypomagnesemia, hypokalemia).
  - Please see Clinical Pathway II: Empirical Antifungal Therapy 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 alternative antifungal.
- Dosage, please see Pathway II: Empirical Antifungal Therapy 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 hematopoetic 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.
  - 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.
  - 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 Pathway II: Empirical Antifungal Therapy for further dosing recommendations.
  - 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.

Caspofungin (Cancidas®)
- 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 hematopoetic stem cell transplant recipients. Caspofungin was associated with significantly less toxicities.
- Caspofungin has a limited spectrum of activity, specifically only Candida sp. and Aspergillus sp. Unlike amphotericin B and voriconazole which are fungicidal against Aspergillus sp., caspofungin exhibits only fungistatic activity against Aspergillus sp.
- Toxicities are minimal, including fever, flushing, thrombophlebitis, nausea/vomiting, and liver enzyme abnormalities.
- Dosage adjustments are required in patients with Child-Pugh Class C (e.g., caspofungin 70 mg x 1 dose, then 35 mg q24h).
**CLINICAL PATHWAY II – Adult Fever and Neutropenia (continue)**

**EMPIRICAL ANTIFUNGAL THERAPY**

- **Lipid amphotericin B 5 mg/kg IV q24h, infuse over 2 hours**
  - **Pre-medication** (30 minutes prior to each dose):
    - Acetaminophen 650 mg PO/PR
    - Diphenhydramine 25 – 50 mg PO
    - 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.).

- **Voriconazole 400 mg PO q12h x 2 doses, then 100 mg PO q12h**
  - Caution with drug interactions:
    - If receiving cyclosporin, reduce cyclosporin dose by 50% and monitor levels closely
    - If receiving tacrolimus, reduce tacrolimus dose by 67% and monitor levels closely

- **Voriconazole 6 mg/kg IV q12h x 2 doses, then 2 mg/kg IV q12h**
  - Caution with drug interactions:
    - If receiving cyclosporin, reduce cyclosporin dose by 50% and monitor levels closely
    - If receiving tacrolimus, reduce tacrolimus dose by 67% and monitor levels closely

* 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.
Child-Pugh Grading System for Liver Disease

<table>
<thead>
<tr>
<th>Clinical and Biochemical Measurements</th>
<th>Points Scored for Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Bilirubin (primary sclerosing cholangitis, primary biliary cirrhosis, cholestatic diseases)</td>
<td>&lt; 4 mg/dL</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt; 2 mg/dL</td>
</tr>
<tr>
<td>INR</td>
<td>&lt; 1.7</td>
</tr>
<tr>
<td>PT prolonged</td>
<td>&lt; 4 seconds</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt; 3.5 g/dL</td>
</tr>
</tbody>
</table>

**TOTAL POINTS**

- < 7 Class A
- 7 – 9 Class B
- > 9 Class C