

**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.

Clinical Criteria	
High-Risk	Low-Risk
Anticipated neutropenia > 7 days <b>and</b>	Anticipated neutropenia ≤ 7 days <b>or</b>
Absolute neutrophil count ≤ 100 cells/mm <sup>3</sup> <b>and/or</b>	None or few comorbid conditions <sup>§</sup>
Significant comorbid conditions <sup>‡</sup> including uncontrolled cancer <sup>§</sup> <b>or</b>	
Leukemic malignancies: <ul style="list-style-type: none"> <li>• Requiring more than 1 induction cycle or</li> <li>• Relapsed or refractory disease</li> </ul>	

‡ Comorbid conditions including but not limited to the following:

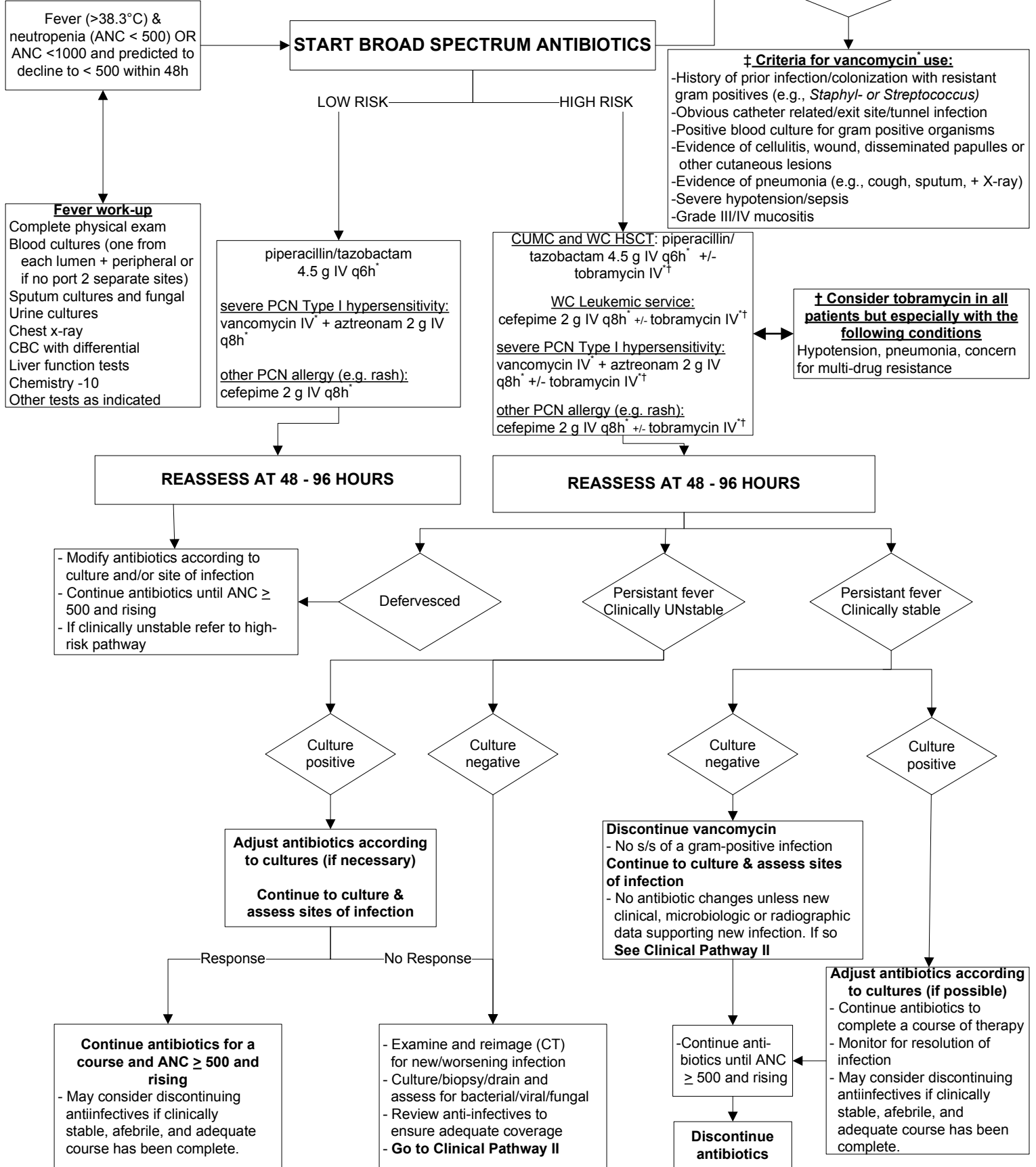
- Neurologic: concern for spinal compression or new changes in mental-status
- Pulmonary: new infiltrate, hypoxemia, or respiratory failure (PO<sub>2</sub> < 60 mmHg, adjusted for hyperventilation), underlying chronic lung disease (e.g., chronic obstructive pulmonary disease)
- Intravascular catheter 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)

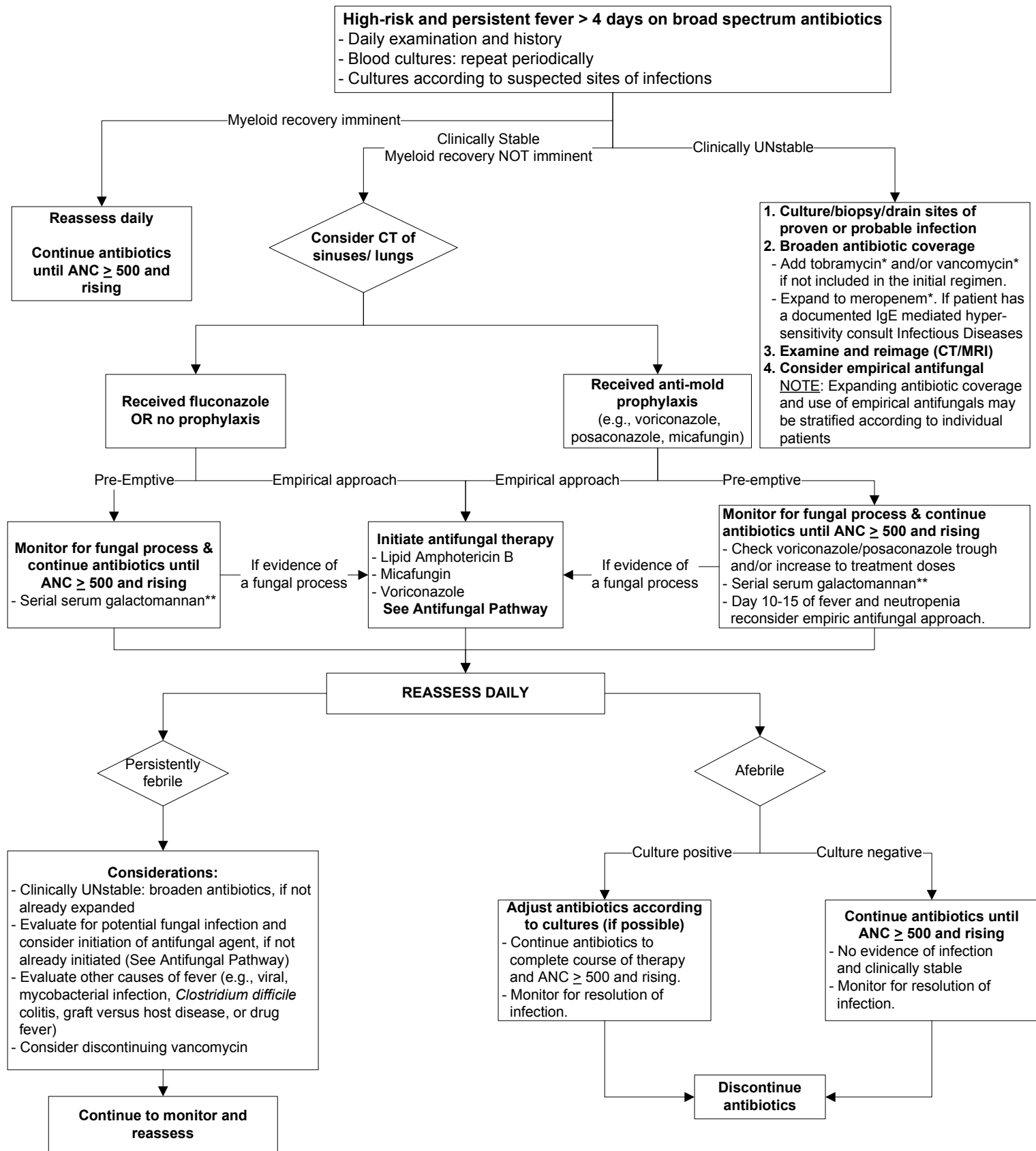
# CLINICAL PATHWAY I - Adult Fever and Neutropenia

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



\* 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/mm<sup>3</sup>), MRSA = Methicillin-resistant *Staphylococcus aureus*, PCN = penicillin, IV = intravenous

## CLINICAL PATHWAY II - Adult Fever and Neutropenia (continued)



\* 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

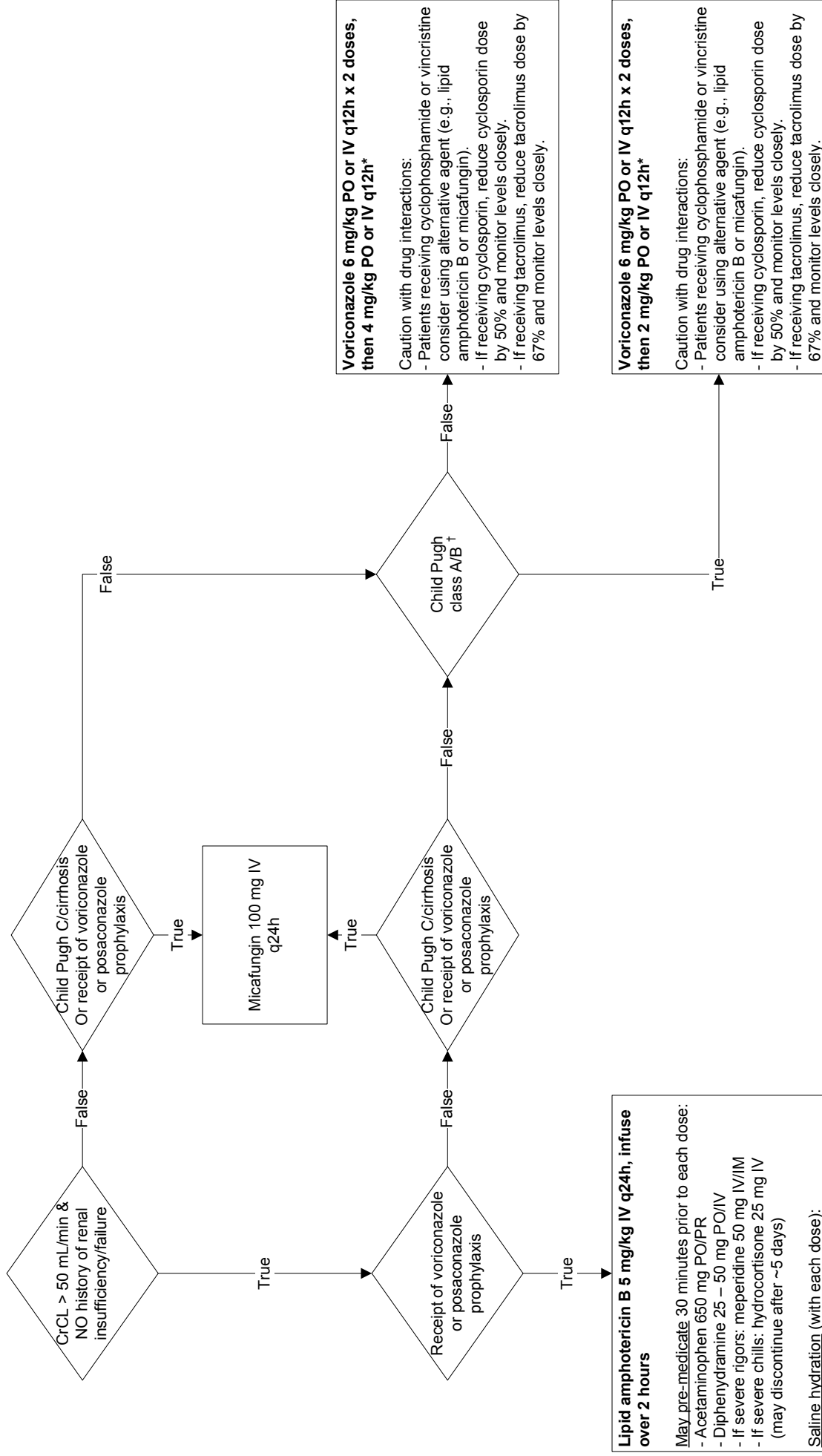
\*\*Positive galactomannan: values > 0.5.

ANC = absolute neutrophil count (all reported as cells/mm<sup>3</sup>), MRSA = Methicillin-resistant *Staphylococcus aureus*, PCN = penicillin, IV = intravenous

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# ANTIFUNGAL PATHWAY – Adult Fever and Neutropenia (continued)

## See detailed information for each Antifungal agents



\* 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).

# ANTIFUNGAL PATHWAY – 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*), and 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.*, *Fusarium sp.*, and *Candida lusitanae*.
- Toxicities include nephrotoxicity, infusion related reactions, and electrolyte abnormalities (e.g., hypomagnesemia, hypokalemia) may limit its use.
  - 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.
  - 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 Antifungal Pathway 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.

### 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 exhibits 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

Clinical and Biochemical Measurements	Points Scored for Abnormality		
	1	2	3
<i>Encephalopathy</i>	None	Grade 1 – 2 (or treated)	Grade 3 – 4
<i>Ascites</i>	Absent	Slight (or controlled)	Moderate with diuretics
<i>Bilirubin</i>	< 2 mg/dL	2 – 3 mg/dL	> 3 mg/dL
<i>Bilirubin (primary sclerosing cholangitis, primary biliary cirrhosis, cholestatic diseases)</i>	< 4 mg/dL	4 – 10 mg/dL	> 10 mg/dL
<i>INR</i>	< 1.7	1.7 – 2.3	> 2.3
<i>PT prolonged</i>	< 4 seconds	4 – 6 seconds	> 6 seconds
<i>Albumin</i>	> 3.5 g/dL	2.8 – 3.5 g/dL	< 2.8 g/dL
<b>TOTAL POINTS</b>	< 5	<b>Not considered to have hepatic impairment</b>	
	< 7	<b>Class A</b>	
	7 – 9	<b>Class B</b>	
	> 9	<b>Class C</b>	

**RESPONSIBILITY:**

Joint Subcommittee on Anti-Infective Use

**GUIDELINE DATES:**

Issued: May 2009

Reviewed: May 2010

Revised: May 2011

Medical Board Approval: June 2011

**REFERENCES:**

- 1) Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenia Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. *CID* 2011;52(4):e56-e93