Stony Brook University Hospital Treatment Guidelines:
Guideline for Management of Neutropenic Fever in Hospitalized Adult Patients with Cancers.

1. Background

1.1. Stony Brook University Hospital has incorporated national guidelines in its creation of hospital-wide treatment guidelines for the management of hospitalized adult cancer patients with neutropenic fever to improve appropriate use of and decrease adverse effects associated with antimicrobial agents, and emergence of multidrug-resistant organisms in these high-risk patient populations.

2. Definitions

2.1. Fever in neutropenic patients: A single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a one-hour period.

2.2. Neutropenia: An absolute neutrophil count (ANC) < 1000 cells/microL

- 2.2.1. Severe neutropenia: An ANC <500 cells/microL or an ANC that is expected to decrease to <500 cells/microL over the next 48 hours.
- 2.2.2. Profound neutropenia: An ANC <100 cells/microL

3. Initial Assessment

3.1. Patients with neutropenic fever should be evaluated carefully with a detailed history and physical examination.

3.2. Routine initial laboratory tests include

- 3.2.1. CBC with differential
- 3.2.2. Chem8 and liver function test (LFTs)
- 3.3.3. Symptoms-directed work-up with cultures and or imaging studies.
- 3.3.4. At least two sets of blood cultures, one from a peripheral venipuncture and ones from a central venous catheter (drawn from all the lumens).
- 3.3.5. If patients started on vancomycin, appropriate cultures to assess the risk of MRSA or other drug resistant gram-positive bacteria.

4. Initial Empiric Antibiotic Therapy (Figure 1)

4.1. Patients should receive antibiotics within 60 minutes of presentation.

4.2. Patients should receive a parenteral antibiotic that has antipseudomonal activity.

- 4.2.1**. Cefepime 2 gm IV every 8 H** (preferred regimen) or

4.2.2. Piperacillin/tazobactam 4.5 g IV Q8 H with extended infusion or

4.2.3. Meropenem 1 g IV Q8 H (refer to section 4.5 for indications for empiric carbapenem use).

Note: Due to decreased carbapenem susceptibility of *Pseudomonas aeruginosa* at SBUH, meropenem is not recommended at the first line empiric therapy. Please refer to the appropriate indications of carbapenem use below.

4.2.4. If there is a suspected intraabdominal or anaerobic infection, either add metronidazole 500 mg PO/IV Q8 H to cefepime or use piperacillin/tazobactam.

4.2.5. In patients who are suspected to have infections due to multidrug-resistant organisms or who are critically sick, consider an Infectious Disease consultation for assistance.

4.3. Indications for vancomycin use in patients with neutropenic fever.

4.3.1. Hemodynamic instability or other evidence of severe sepsis at presentation.

4.3.2. Pneumonia documented radiographically.

4.3.3. Positive blood cultures for gram-positive bacteria, before final identification and susceptibility testing is available.

4.3.4. Clinical suspected serious catheter-related infection (e.g. chills or rigors with infusion through catheter and cellulitis around the catheter entry/exit site).

4.3.5. Skin or soft-tissue infection at any site.

4.3.6. Colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or penicillin-resistant *Streptococcus pneumoniae*.

4.3.7. Severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empiric therapy.

Note: when vancomycin is started, send cultures or MRSA nasal PCR screen assess risk of MRSA infection.

4.4. Indications for carbapenem use in patients with neutropenic fever.

4.4.1. Seriously ill patients (e.g. septic shock, hemodynamic instability). If there is concern of multidrug-resistant *Pseudomonas aeruginosa*, carbapenem may not be appropriate.

4.4.2. Recent treatment (≥ 3 days duration) with piperacillin/tazobactam, 3rd or 4th generation cephalosporins (e.g. ceftriaxone, cefepime) within the past 30 days.

4.4.3. Known prior colonization or infection with resistant gram-negative organisms

4.4.3.1. Extended spectrum beta-lactamase (ESBL)

4.4.3.2. Other multidrug-resistant Gram-negatives

4.4.4. Worsening clinical status while on antipseudomonal penicillin or cephalosporins.

4.4.5. Persistent neutropenic fever with suspected clinical sepsis while on antipseudomonal penicillin or cephalosporin for at least 72- 96 hours.

4.4.6. Known penicillin or cephalosporin allergy.

4.5. In patients with a penicillin allergy, most can tolerate cephalosporins. Caution should be exercised in patients with a history of an immediate-type hypersensitivity reaction (e.g. hives, bronchospasm).

4.5.1. Evaluate if the patient has a true penicillin allergy. Review chart if the patients have received and tolerated beta-lactams in the past.

4.5.2. Empiric antibiotic therapy for patients with penicillin allergy.

4.5.2.1. Aztreonam 2 g IV Q8 H **PLUS** vancomycin dosed based on SBUH antimicrobial stewardship vancomycin dosing guideline.

4.5.3. Consider infectious disease or allergist consultations for assistance.

5. Reassessment of empiric antibiotic therapy (Figure 2)

5.1. The initial antibiotic regimen should be re-assessed at 72-96 hours based on the patients' clinical course and the microbiologic results.

5.2. In patients who are stable but have persistent fevers after 3-4 days of broad-spectrum antibiotics without identified infectious sources, there is no need to broaden antibiotic therapy.

5.2.1. In clinically stable patients with persistent neutropenic fever with negative initial blood cultures, repeating blood cultures after hospital day 3 without new clinical changes is low-yield and not recommended.

5.3. If patients remain febrile and are clinically deteriorating, reevaluate for diagnostic work up and antibiotic regimen.

5.3.1. If vancomycin is not started initially, consider adding vancomycin if indicated.

5.3.2. Consider resistant gram-negative bacteria and switch to carbapenem +/- aminoglycoside.

5.3.3. Consider resistant gram-positive bacteria and add an appropriate agent (e.g. daptomycin, linezolid) if indicated.

5.3.4. Evaluate for fungal, viral and other etiologies.

5.3.4.1. Consider adding antifungal therapy for persistent fever more than 4 days of empiric antibiotic therapy.

5.3.4.2 See “the Guidelines for Evaluation and Management of Cancer Patients with Neutropenic Fever Suspecting Invasive Fungal Infection”.

5.3.5. Consider infectious disease consultation.

5.4. In patients who are afebrile and clinically and hemodynamically stable since presentation, discontinuation of antibiotics after 72-96 hours should be considered.

5.4.1. If vancomycin, daptomycin or linezolid was started initially, it can be stopped after 48 hours if there is no evidence for gram-positive infection.

5.5. An IV-to-oral switch in antibiotic regimen should be considered in patients who are clinically stable and gastrointestinal absorption is adequate.

6. Duration of empiric antibiotic therapy.

6.1. In patients with clinically and microbiologically documented infections, the duration of therapy is dictated by the identified organisms and sites of infection.

6.1.1. In certain cases e.g. infection with inadequate source control, the appropriate antibiotics may need to be continued for the duration of neutropenia or longer if clinically indicated.

6.1.2. If the documented infections are appropriately treated and have resolved, patients who remain neutropenic may resume oral fluoroquinolone prophylaxis until marrow recovery (i.e. ANC > 500 cells/ microL).

6.1.2.1. In stable patients with pronged neutropenia, withholding fluoroquinolone and monitor off antibiotics can be safely done.

6.2. In patients with no documented infections, who have been afebrile and hemodynamically stable for at least 48 hours, empiric antibiotics can be safely discontinued after 72- 96 hours of empiric antibiotics or de-escalated to fluoroquinolone prophylaxis.

6.3. Patients should be closely monitored for 24- 48 hours if they are still neutropenic when antibiotic therapy is stopped. If fever recurs, they should be reevaluated and antibiotics should be re-started.

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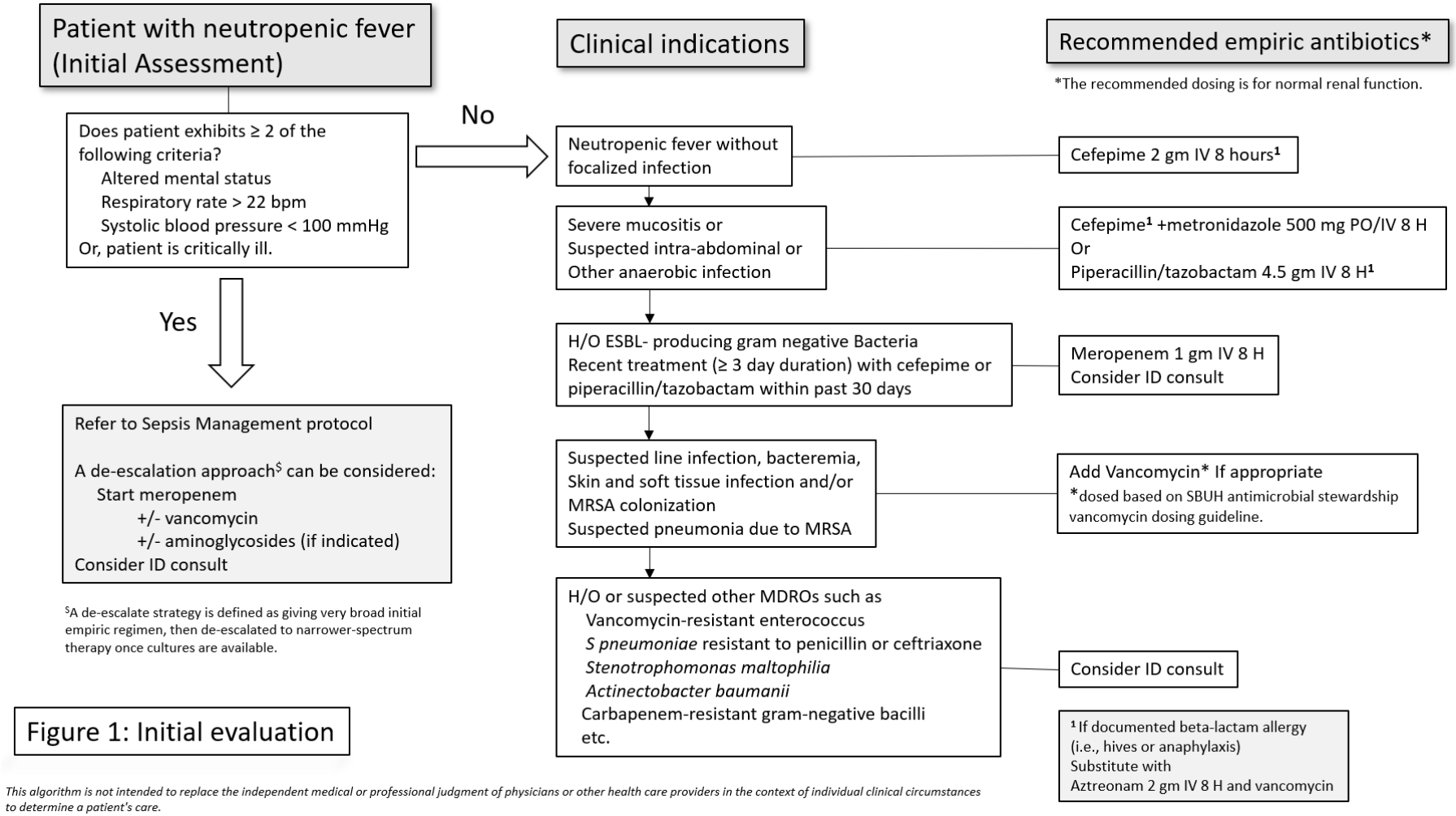

Figure 1: Initial evaluation

This algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care.

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Katherine De Jesus, PharmD; Sutthichai Sae-Tia, MD
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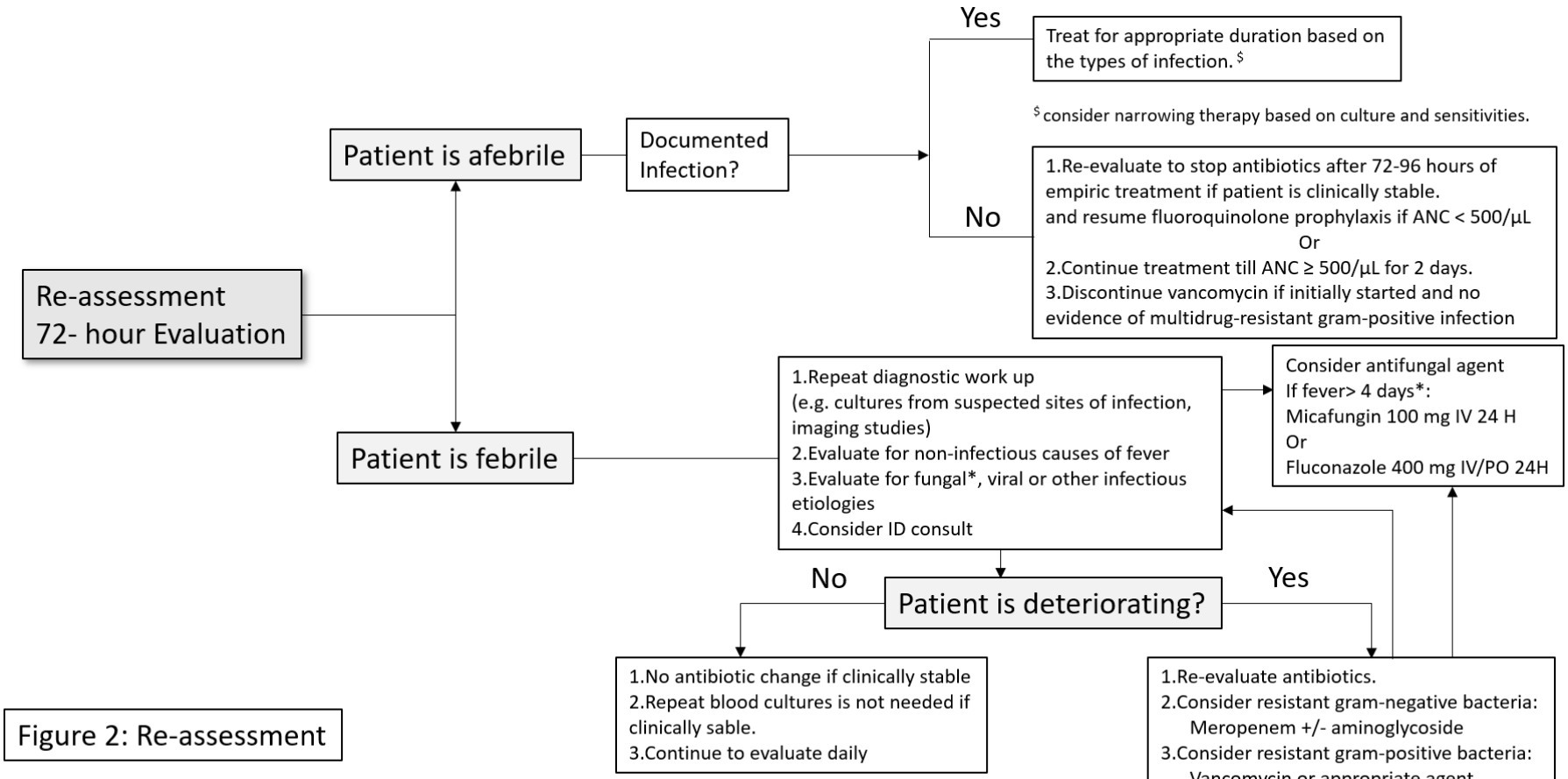

Figure 2: Re-assessment

This algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care.

*Refer to Figure3: Evaluation of invasive fungal infection.

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