Sharp HealthCare: Antimicrobial Stewardship Program Guidelines for Antimicrobial Therapy in Febrile Neutropenia

Situation: Febrile neutropenia is a common complication for patients receiving chemotherapy for treatment of cancer or patients who have a hematologic pathology affecting neutrophils. Given the relative frequency with which febrile neutropenia is encountered in the hospital setting, development of system guidelines for antimicrobial therapy in this setting will help standardize management and improve outcomes in these populations.

Background: Patients who develop neutropenia (whether due to chemotherapy for treatment of cancer or a hematologic pathology) are at increased risk for infection, and due to the lack of an adequate immune response may only present with fever. The 2024 National Comprehensive Cancer Network and 2019 American Society of Clinical Oncology/Infectious Diseases Society of America guidelines offer guidance for management of these patients in both the inpatient and outpatient settings.

Febrile neutropenia is defined as:

Single oral temperature of ≥38.3C (101F) or ≥38C (100.4F) sustained over 1hr in patient with ANC <500 (or expected to decrease to <500 in 48 hours)

Assessment: Guidelines for antimicrobial therapy in febrile neutropenia will be beneficial to encourage optimal use of broad-spectrum antimicrobials while also ensuring patients are given appropriate treatment.

Recommendation:

1. Initial Empiric Therapy
    a. Broad-spectrum anti-pseudomonal beta-lactam:
        i. Cefepime 2 g IV Q8H extended infusion
        ii. Piperacillin/tazobactam 4.5 g IV Q8H extended infusion
        iii. Meropenem 500 mg IV Q6H [reserve for patients with a history of resistant gram-negative infection/colonization within 12 months]
    b. Empiric addition of vancomycin is NOT routinely recommended due to lack of data supporting reduction in fever duration or mortality.
        i. Consider empiric vancomycin therapy in the presence of:
            1. Hemodynamic instability [hypotension (SBP < 90 mmHg or MAP < 70 mmHg) combined with tachycardia (HR ≥ 100 bpm)]
            2. Suspected pneumonia (pending MRSA nares result)
            3. Suspected skin and soft tissue infection
            4. Suspected catheter-related bloodstream infection
            5. Blood cultures with Gram-positive organisms on Gram stain
            6. Cardiovascular assist device entry site infection (if clinically apparent)

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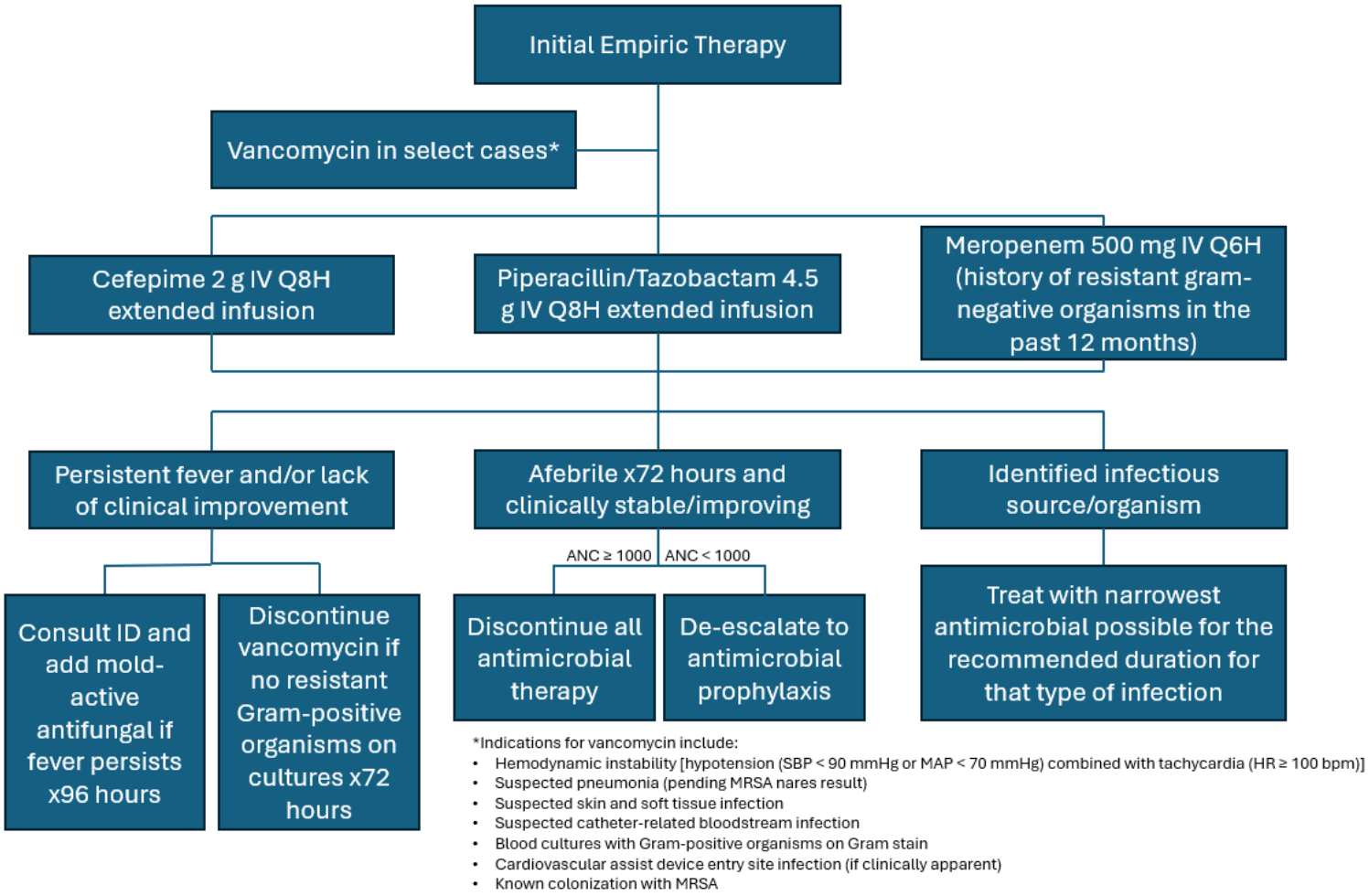
7. Known colonization with MRSA

2. Monitoring/Follow-Up
    a. Median time to fever defervescence is 5 days (typically 2-7 days) in patients receiving appropriate antimicrobial therapy. An improving fever curve is indicative of clinical response.
    b. For patients with persistent fever/fever curve not improving* for > 96 hours and/or lack of clinical improvement and no identified infectious source/organism, consider broadening coverage based on clinical and microbiologic data to include other organisms not covered by empiric regimen.
        i. Consider ID consultation and adding a mold-active antifungal (i.e. posaconazole, micafungin) to cover for possible fungal infection if fever persists for 96 hours or more.
    c. Aside from antifungal consideration, antimicrobial therapy should NOT be escalated in the absence of new specific clinical findings and/or microbiologic results.
    d. If vancomycin was added as part of empiric therapy and no resistant Gram-positive organisms are isolated on cultures in 72 hours, discontinue vancomycin.
    e. Continue empiric antimicrobial therapy until patient is afebrile for 72 hours with ANC > 1000 cells/mcL and increasing.
    f. For patients who are clinically stable/improving and are afebrile for 72 hours with no identified infectious source, discontinue broad-spectrum antimicrobial therapy.
        i. If absolute neutrophil count (ANC) is ≥1000 cells/mcL, discontinue all antimicrobial therapy.
        ii. If ANC <1000 cells/mcL, de-escalate to appropriate antimicrobial prophylaxis based on SHC Oncology Antimicrobial Prophylaxis Guidelines.
    g. For patients with an identified infectious source, treat with the narrowest antimicrobial possible that covers the infectious organism (taking into account sensitivities) for the typical duration recommended for the type of infection present.
3. See the flowchart on the next page for a visual summary of the above.

*Improving fever curve is defined as gradually lower and less frequent fever spikes. Patients who demonstrate a gradual improvement in fever curve do not require extensive work-up or change in antimicrobials despite continuous fevers.



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3. Aguilar-Guisado M, Espigado I, Martín-Peña A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. *Lancet Haematol*. 2017;4(12):e573-83.
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