Management of Fever and Neutropenia – Pediatric – Inpatient/Ambulatory/Emergency Department – Clinical Practice Guideline

Note: Active Table of Contents – Click to follow link

Contact: CCKM@uwhealth.org
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Contact for Changes:
Name: Joshua Vanderloo, PharmD, BCPS
Phone Number: 608-890-5931
Email Address: JVanderloo@uwhealth.org

Contact for Content:
Name: Erin McCreary, PharmD, BCPS
Phone Number: (608) 263-1283
Email Address: emccreary@uwhealth.org

Guideline Author:
Erin McCreary, PharmD, BCPS

Coordinating Team Members:
Joshua Vanderloo, PharmD, BCPS; Drug Policy Program

Review Individuals/Bodies:
Monica Bogenschutz, PharmD, BCPS, BCPPS
James Conway, MD, FAAP
Sheryl Henderson, MD, PhD
Inga Hofmann, MD
Margo Hoover-Regan, MD
Nicole Lubcke, PharmD, BCOP
Joseph McBride, MD
Jessica Poehls, PharmD, BCPPS
Joshua Ross, MD
Lucas Schulz, PharmD, BCPS (AQ-ID)
Jill Strayer, PharmD, BCPS
Meghann Voegeli, PharmD, MS

Committee Approvals/Dates:
Pediatric Clinical Operations Committee: March 2017
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Executive Summary

Guideline Overview

This clinical practice guideline has been organized to guide the assessment, management and monitoring of pediatric patients with fever and neutropenia. These recommendations have been adopted from nationally published clinical practice guidelines and other pertinent primary literature.

Key Practice Recommendations

1. Information on initial presentation of children with fever and neutropenia, as well as how to triage children for outpatient (low-risk) or inpatient (high-risk) management, can be found in Section 1.
2. Initial treatment of fever and neutropenia in high-risk patients (those requiring hospitalization for treatment) can be found in Section 2.
3. Initial treatment of fever and neutropenia in low-risk patients (those appropriate for outpatient treatment) can be found in Section 3.
4. General considerations for fever and neutropenia can be found in Section 4.
5. The ongoing management of fever and neutropenia in high-risk children can be found in Section 5.
6. The treatment approach for children with persistent fever can be found in Section 6.

Companion Documents

1. Intravenous Administration of Formulary Medications – Neonatal/Pediatric – Inpatient/Ambulatory
2. Management of Neutropenic Fever – Adult – Inpatient/Ambulatory

Scope

Disease/Condition

Pediatric patients with suspected or confirmed fever and neutropenia in the emergency department or inpatient setting.

Clinical Specialty

This guideline may be used by any clinician treating a patient with fever and neutropenia, including but not limited to those that practice within: oncology, hematology, bone marrow transplant (BMT), infectious disease, and emergency medicine physicians, nurses, and pharmacists including inpatient services, ambulatory clinics, and the emergency department.

Intended Users

Physicians, Advanced Practice Providers, Pharmacists, Nurses

Objectives

The objective of this guideline is to guide risk stratification, empiric management, and definitive treatment of pediatric patients with suspected or confirmed fever and neutropenia in the emergency department or inpatient setting in order to facilitate prompt and evidence-based interventions while minimizing treatment variability and improving patient outcomes.

Target Population

Pediatric inpatients and outpatients who have received chemotherapy for the treatment of malignancy and who present with fever and neutropenia. Neutropenic fever is defined as an absolute neutrophil count < 500 cells/µL and temperature ≥ 38ºC (100.4ºF).

Interventions and Practices Considered

1. Risk stratification
2. Outpatient versus inpatient management
3. Empiric and definitive antibiotic treatment
4. Diagnostic imaging and culture data

Major Outcomes Considered

Appropriateness of initial evaluation and diagnostic work-up, timeliness of risk stratification and antimicrobial administration, composite antimicrobial use, hospital length of stay, morbidity and mortality.

Methodology

Methods Used to Collect/Select the Evidence

Electronic database searches (i.e. PUBMED) were conducted by the guideline author and workgroup members to collect evidence for review. Search terms included: fever and neutropenia, children, pediatrics. Hand searches were performed within selected evidence for other relevant resources. Expert opinion, clinical experience, and regard for patient safety/experience were also considered during discussions of the evidence.

Methods Used to Formulate the Recommendations

The workgroup members agreed to adopt recommendations developed by external organizations and/or arrived at a consensus through discussion of the literature and expert experience. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees (as appropriate).

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations

Internally developed and externally adopted recommendations were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1** in Appendix A).

Rating Scheme for the Strength of the Evidence/Recommendations

See Appendix A for the rating scheme used within this document.

Recognition of Potential Health Care Disparities:

Health care disparities exist in cancer care. For example, some diagnostic and therapeutic measures may be less available at institutions in rural areas or for underserved populations. Additional factors that may influence outcomes include distrust of the health care system, stigmas related to cancer and death, literacy and language barriers, and poor expectations regarding the outcome from cancer care. Careful considerations of these disparities should be addressed to ensure the best outcome for patients that present with fever and neutropenia.

Definitions and Abbreviations:

1. ANC: Absolute neutrophil count
   1.1 (% neutrophils + % bands)*(total WBC)
2. Fever: Any oral, axillary, or temporal artery temperature ≥ 38ºC (100.4 ºF)
3. High-risk: Patients that should be hospitalized for management of fever and neutropenia
4. Low-risk: Patients that are reasonable to consider for outpatient management of fever and neutropenia
5. Neutropenia: Absolute neutrophil count (ANC) less than 500 cells/mm^3 or an ANC expected to decline to less than 500 cells/mm^3 within the next 48 hours
6. Profound neutropenia: ANC < 100 cells/mm^3

7. Prolonged neutropenia: Anticipated duration of neutropenia greater than 7 days
8. Functional neutropenia: Any newly diagnosed leukemia or myelodysplasia

Introduction

Fever and neutropenia is a medical emergency in patients with cancer receiving chemotherapy treatment that can result in significant morbidity and mortality.[1,2] Hematologic malignancy is the most common form of cancer in children, making fever and neutropenia an even more common and critical issue for pediatric patients than in adults.[3] Children receive more intensive chemotherapy treatments, increasing the likelihood and severity of treatment-related complications.[2,3] Most patients who develop fever during neutropenia do not have an identifiable site of infection or definitive microbiological data to guide treatment.[1,4] Infection can progress rapidly in neutropenic patients due to their weakened immune response, especially in young children who have immature immune systems prior to treatment.[1,3] For these reasons, all acute care centers should aim to administer antibiotics within one hour of presentation to any patient that presents with fever and neutropenia.[2,5]

It has been documented extensively in the literature that early use of treatment pathways results in improved patient outcomes.[4,6,7] Regardless, significant variation in management of fever and neutropenia in children with cancer still exists.[8,9] Lack of a validated risk stratification tool, greater exposure to viral illnesses, the unclear role of antimicrobial therapy in certain patients, difficulty of obtaining appropriate diagnostic cultures, and decreased availability of safe, effective, and tolerable medications compared to adults all contribute to treatment difficulties and variability in the pediatric population.[3,10] The objective of this guideline is to summarize available evidence in order to guide initial and definitive treatment of fever and neutropenia in pediatric patients receiving chemotherapy at UW Health.

Recommendations

1. **Initial Presentation of Children with Fever and Neutropenia[11]**
   - 1.1 Clinical features and laboratory parameters should be used to classify pediatric patients as low- or high-risk for complications associated with fever and neutropenia.[2,12] *(UW Health moderate level of evidence, strong recommendation)*
     - 1.1.1 Standardization of clinical management via an institutionally adopted risk-stratification tool is recommended to improve outcomes.[2]
   - 1.2 Criteria in Table 1 should be used to stratify patients into risk categories. This table is a summary of the literature and guidelines from peer institutions and has not been validated.[2,11-20] *(UW Health moderate level of evidence, strong recommendation)*
     - 1.2.1 It should be noted that there is not one single rule that is more effective or reliable than others in predicting outcomes in pediatric patients. There are no validated tools to determine the patients at highest risk of developing complications from fever and neutropenia.[2,5]

Table 1. Criteria for risk stratification of children with fever and neutropenia[2,12-25]

Patients are considered high risk if they meet ONE of the following criteria in EITHER category:	Patients are considered low risk if they meet ALL of the following criteria in ALL categories:
Disease-specific criteria: • Acute lymphocytic leukemia in induction phase • Acute myeloid leukemia • Aplastic anemia • Burkitt leukemia or lymphoma • Down syndrome with leukemia • Hematopoietic stem-cell transplantation within the past 6 months • High-risk neuroblastoma • Graft-versus-host disease **Patient-specific or clinical criteria:** • Altered mental status • Hypotension • Less than 12 months of age • Receiving non-chemotherapy immunosuppressive medications • Respiratory distress or hypoxia • Suspected typhilitis	**Suitable for outpatient management:** • Access to acute care facility within one hour of fever onset • Telephone access • Vigilant family or caregiver **Disease-specific criteria:** • No comorbidities related to the heart or lungs • Predicted duration of neutropenia less than 7 days **Patient-specific or clinical criteria:** • Ability to take medication orally • Adequately hydrated • Clinically stable (well-appearing) • Not currently on antibiotic therapy except for *Pneumocystic jirovecii* prophylaxis • No GI symptoms present at fever onset • No shaking or chills

1.3 The provider should evaluate the patient with fever and neutropenia systematically to identify the anatomic focus of fever and to consider infectious and non-infectious causes of fever.[2] *(UW Health low level of evidence, strong recommendation)*

1.4 Blood samples for culture should be obtained prior to administering antibiotic therapy for all patients, regardless of suspected infection source.[2,5,26]

1.4.1 It is preferred that two sets of blood cultures are drawn in accordance with the UW Health Blood Culture Collection Policy.[2] *(UW Health moderate quality evidence, strong recommendation)*

1.4.1.1 It is reasonable to draw blood cultures from all lumens of central venous catheters (CVC). Culture bottles should be clearly labeled by lumen. *(UW Health moderate quality evidence, strong recommendation)*

1.4.1.2 Providers can consider obtaining peripheral cultures. Peripheral cultures may help diagnose CVC-related infections by serving as a measure of differential time to positivity, which can lead to CVC salvage for certain patients.[26]

1.4.2 Obtaining blood cultures should not delay antibiotic administration in unstable patients.[26] *(UW Health moderate quality evidence, strong recommendation)*

1.5 Consider urinalysis and urine culture in symptomatic patients only if the patient is able to provide a clean-catch, midstream urine specimen.[2,5] *(UW Health very low quality evidence, weak/conditional recommendation)*

1.5.1 Routine urinalysis and culture during initial fever and neutropenia evaluation is controversial in pediatric patients, as pyuria is rarely detected in pediatric patients with neutropenia and nitrite testing is less effective in pediatric patients than older patients.[2]

1.5.2 Urine collection should not delay antibiotic administration. *(UW Health moderate quality evidence, strong recommendation)*

1.5.3 A catheterized urine specimen should not be obtained in patients with suspicion of neutropenia. *(UW Health moderate quality evidence, strong recommendation)*

1.6 Chest radiography (CXR) should be obtained only for patients that exhibit respiratory signs and symptoms.[2,5] *(UW Health moderate quality evidence, strong recommendation)*

1.6.1 Asymptomatic patients that do not receive a CXR have similar outcomes to those that receive a CXR. Pneumonia is detected in fewer than 5% of asymptomatic patients.[2]

1.7 Other suspected infection sites should be cultured as clinically indicated based on the patient's signs and symptoms (e.g. lower respiratory tract, cerebral spinal fluid, stool, skin, or wounds).[2,5,10] *(UW Health low quality evidence, moderate recommendation)*

1.8 The first dose of empiric antibiotic therapy should be administered within one hour of initial evaluation.[27,28] *(UW Health high quality evidence, strong recommendation)*

1.8.1 Early broad-spectrum antibiotics should be started prior to the return of culture and assay results as this has shown to decrease mortality and morbidity.[2,5,7]

1.8.2 Antibiotic administration should not be delayed if providers are unable to obtain cultures or imaging within one hour of presentation. *(UW Health moderate quality evidence, strong recommendation)*

1.8.3 It is reasonable to write orders and prepare antibiotics for patients prior to arrival in the Emergency Department if the physician is aware the patient is en route.[7,28] *(UW Health low quality evidence, weak/conditional recommendation)*

1.9 High-risk, neutropenic patients should be admitted to the hospital.[2,7,18] *(UW Health moderate quality evidence, strong recommendation)*

1.10 It is reasonable to consider low-risk, neutropenic patients for outpatient management.[17,29,30] *(UW Health moderate quality evidence, strong recommendation)*

2. Initial Treatment of Fever and Neutropenia in High-Risk Children[11]

2.1 If high-risk children present to the Emergency Department and are clinically stable, it is reasonable to administer a dose of ceftriaxone as soon as possible, prior to the complete blood count (CBC) laboratory test results. *(UW Health low quality evidence, strong recommendation)*

2.1.1 If the patient is found to be neutropenic upon CBC results, they should receive an anti-pseudomonal β-lactam as soon as possible. *(UW Health low quality evidence, strong recommendation)*

2.1.2 If the patient is found to be non-neutropenic but has received a hematopoietic stem-cell transplantation (HSCT) within the past 6 months,

is an HSCT patient receiving non-chemotherapy immunosuppressive medications, and/or an HSCT patient with graft-versus-host disease, they should receive an anti-pseudomonal β-lactam as soon as possible. *(UW Health low quality evidence, strong recommendation)*

2.2 If high-risk children present to the Emergency Department and are clinically unstable, they should receive an anti-pseudomonal β-lactam as soon as possible, prior to the CBC laboratory test results. *(UW Health low quality evidence, strong recommendation)*

2.3 Monotherapy with an anti-pseudomonal β-lactam should be used as empiric intravenous antibiotic therapy in high-risk, neutropenic patients.[2,5,7] *(UW Health high quality evidence, strong recommendation)*

- 2.3.1 Cefepime is reasonable to be used as the first-line agent.[2,7]
  - 2.3.1.1 If anaerobic infection is suspected such as neutropenic typhlitis, metronidazole should be added.[2]
- 2.3.2 Piperacillin-tazobactam monotherapy can be considered in patients with an intra-abdominal source or those with suspected anaerobic infection.[2,31]
  - 2.3.2.1 Piperacillin-tazobactam has adequate anaerobic activity. It is not necessary to add metronidazole to piperacillin-tazobactam unless the patient has *Clostridium difficile* or an undrained abscess.
  - 2.3.2.2 It is reasonable to use piperacillin-tazobactam if cefepime is unavailable due to market shortage or other circumstance.

2.4 It is reasonable to reserve carbapenem therapy (e.g. meropenem) for patients with proven, documented multidrug-resistant organisms.[2,7,31,32] *(UW Health moderate quality evidence, weak/conditional recommendation)*

- 2.4.1 For patients with a history of extended-spectrum beta-lactamase (ESBL) producing infection, a carbapenem should be considered for empiric therapy.
- 2.4.2 Meropenem has adequate anaerobic activity. It is not necessary to add metronidazole to meropenem for any suspected infection.

2.3 Patients with a severe, non-IgE mediated reaction or an IgE-mediated β-lactam allergy to β-lactam antibiotics should avoid β-lactam antibiotics. *(UW Health moderate quality evidence, strong recommendation)*

- 2.3.1 It is reasonable to use aztreonam plus vancomycin as empiric intravenous antibiotic therapy in these patients.[2]
- 2.3.2 If anaerobic infection is suspected such as neutropenic typhlitis, metronidazole should be added.[2]

2.4 A second antibiotic with activity against Gram-negative organisms can be added if patients are clinically unstable, a multidrug-resistant infection is suspected, or there is a high rate of resistant pathogens in the area in which the patient is being treated.[2,7] *(UW Health moderate quality evidence, strong recommendation)*

- 2.4.1 An aminoglycoside (e.g. tobramycin) is the preferred agent to add to the empiric regimen in these patients.
- 2.4.2 If an aminoglycoside is used empirically, consider discontinuation within 24-48 hours if cultures are negative and the patient is clinically stable.[2,5] *(UW Health moderate quality evidence, strong recommendation)*
- 2.4.3 Randomized, controlled trials have demonstrated that aminoglycoside-containing combination therapy did not improve outcomes when compared with antipseudomonal β-lactam monotherapy for fever and neutropenia therefore aminoglycosides should not be added unless the patient meets the criteria in recommendation.[2,5,33]

2.5 Vancomycin should be used as part of the initial antibiotic regimen if the patient is clinically unstable, has acute myeloid leukemia, has a history of methicillin-resistant *Staphylococcus aureus* or β-lactam-resistant *Streptococcus* spp., or has received high-dose cytarabine.[2] *(UW Health moderate quality evidence, strong recommendation)*

2.5.1 It is reasonable to consider adding vancomycin in patients with suspicion for catheter-related infection, skin and soft-tissue infection, grade 3 or 4 mucositis, and hospital-acquired pneumonia.[2,5] *(UW Health moderate quality evidence, moderate recommendation)*

2.5.2 If vancomycin is used empirically, consider discontinuation within 24-48 hours if cultures are negative and the patient is clinically stable.[2,5] *(UW Health moderate quality evidence, strong recommendation)*

2.5.3 Clinical trials demonstrated the addition of vancomycin was associated with more adverse effects without increased treatment success and therefore it should not be added unless patient meets the criteria in recommendation.[34]

2.6 Daptomycin or linezolid may be considered for specific clinical scenarios. *(UW Health low quality evidence, strong recommendation)*

2.6.1 Considerations for daptomycin or linezolid use include a severe, non-IgE mediated reaction or an IgE-mediated allergy to vancomycin or a documented history of vancomycin-resistant *Enterococcus* spp. (VRE) or methicillin-resistant *Staphylococcus aureus* with an MIC of 2 or greater. *(UW Health moderate quality evidence, strong recommendation)*

2.6.2 Consider Pediatric Infectious Diseases consult in these patients.[2]

2.6.3 Infectious Diseases approval should not delay daptomycin or linezolid administration in patients for whom it is clinically indicated. *(UW Health low quality evidence, strong recommendation)*

2.6.4 Daptomycin should not be used empirically for patients with clinical suspicion for pneumonia due to inactivation of daptomycin by pulmonary surfactant.

2.7 Patients receiving trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* prophylaxis should continue to receive this medication while being treated for fever and neutropenia.

3. Initial Treatment of Fever and Neutropenia in Low-Risk Children[11]

3.1 Low-risk, neutropenic patients as identified by critiera in Table 1 should be considered for outpatient management if they receive careful monitoring and follow-up, as this will significantly increase health-related quality of life for children and decrease costs.[2,7,17,30,35] *(UW Health moderate quality evidence, strong recommendation)*

3.1.1 If outpatient management is chosen, the patient should have vigilant observation and prompt access to appropriate medical care at all times.

3.1.2 A provider should follow-up with the patient within 24 hours if possible. Follow-up should be complete within 48 hours of initial presentation. *(UW Health moderate quality evidence, strong recommendation)*

3.1.3 If fever persists or recurs within 48 hours, the patient should return to an acute care setting for hospitalization to receive broad-spectrum, intravenous antibiotic therapy. *(UW Health low quality evidence, strong recommendation)*

3.2 Ceftriaxone should be administered within one hour of presentation with fever and neutropenia for low-risk patients. This provides 24 hours of antibiotic coverage. *(UW Health moderate quality evidence, strong recommendation)*

3.3 Following ceftriaxone administration, low-risk patients who are able to reliably take oral medications should be prescribed 2-4 days of oral antibiotics to take in the outpatient setting.[15,30,36,37] *(UW Health moderate quality evidence, strong recommendation)*

3.3.1 Ciprofloxacin plus amoxicillin-clavulanate is a reasonable first-line option.[7,17,30] It is suggested to determine insurance coverage before ciprofloxacin is prescribed.

3.3.2 Levofloxacin is a reasonable alternative to ciprofloxacin plus amoxicillin-clavulanate in patients with a severe, non-IgE mediated reaction or an IgE-mediated allergy to β-lactam antibiotics.

3.3.2.1 Levofloxaxcin is also reasonable when one antibiotic is preferred.[17]

3.3.2.2 It is suggested to determine insurance coverage before levofloxacin is prescribed.

3.3.3 Cefixime monotherapy is a reasonable alternative.[36] It is suggested to determine insurance coverage before cefixime is prescribed.

3.3.4 It is reasonable to limit total duration of antibiotic therapy to 3-5 total days if no source of infection is identified.[37,38]

3.3.5 Systematic reviews have found that oral antibiotics are equal in terms of efficacy and safety compared with intravenous antibiotics.[30,39]

3.4 If low-risk patients are admitted to the hospital for intravenous antibiotics, early discharge within 48 hours is recommended if they are afebrile for 24 hours or longer, have negative blood cultures, and are clinically stable.[40-42] *(UW Health moderate quality evidence, strong recommendation)*

3.4.1 It is reasonable to consider discontinuation of antibiotics at discharge for these patients, even if neutropenia persists, if the patient has close outpatient follow-up.[43] *(UW Health low quality evidence, weak/conditional recommendation)*

3.4.2 If fever persists or recurs within 48 hours, the patient should return to an acute care setting for hospitalization to receive broad-spectrum, intravenous antibiotic therapy. *(UW Health low quality evidence, strong recommendation)*

4. General Considerations[11]

4.1 Empiric antibiotic administration should never be delayed to obtain culture data. All initial antibiotics should be ordered "STAT." *(UW Health moderate quality evidence, strong recommendation)*

4.2 Patients with suspicion for neutropenia should never have a rectal temperature checked or receive a rectal medication. *(UW Health moderate quality evidence, strong recommendation)*

4.3 Non-steroidal antiinflammatory drugs (NSAIDs) should be avoided in all oncology patients. *(UW Health moderate quality evidence, strong recommendation)*

4.4 The median time to defervescence after initiation of empiric antibiotics is five days for hematologic malignancies and two days for patients with solid tumors.[1]

4.4.1 Unexplained persistent fever in a clinically stable patient does not require antibiotic escalation.[1,2,5] *(UW Health low quality evidence, strong recommendation)*

4.5 In patients who remain febrile, blood cultures should be drawn no more than once daily.[44,45] *(UW Health low quality evidence, weak/conditional recommendation)*

4.5.1 If the initial blood culture is negative, blood cultures should be drawn once daily on day two and day three if fever persists. After day three of persistent fever, blood cultures should only be re-drawn if there is new culture positivity or evidence of new clinical instability in addition to fever.[45] *(UW Health low quality evidence, weak/conditional recommendation)*

4.5.2 Daily blood cultures are not recommended in afebrile patients.[44,45]

4.6 All patients, regardless of antibiotic coverage, should be evaluated daily for criteria for antibiotic use. Antibiotics should be discontinued when they are no longer indicated.[2,5,46]*(UW Health moderate quality evidence, strong recommendation)*

4.7 It is reasonable to consider narrowing or replacing initial antibiotic regimens with targeted antibiotics based on culture and susceptibility results or identification of focal infection associated with a known pathogen and susceptibility if duration of neutropenia is known or anticipated 7 days or fewer.[46] *(UW Health low quality evidence, weak/conditional recommendation)*

5. Ongoing Management of Fever and Neutropenia in High-Risk Children[11]

5.1 Discontinue second antibiotic with Gram-negative activity and/or vancomycin 24-48 hours after initiation for patients who experience a rapid clinical response to empiric therapy and no microbiologic data exists to warrant the use of either antibiotic.[1,2,7] *(UW Health moderate quality evidence, strong recommendation)*

5.2 Patients with a history of multidrug-resistant organisms that were initiated on carbapenem therapy should switch to cefepime after 24-48 hours if they are clinically stable and culture data permits de-escalation or if no microbiologic data exists to warrant the use of a carbapenem.[2,7,31,32] *(UW Health low quality evidence, strong recommendation)*

5.2.1 It is reasonable to continue carbapenem therapy in patients that remain clinically unstable even if no microbiologic data exists. *(UW Health low quality evidence, weak/conditional recommendation)*

5.3 Continue meropenem, aminoglycoside, or second antibiotic with Gram-negative activity if a multidrug-resistant Gram-negative organism grows in culture.

5.3.1 Consider Pediatric Infectious Diseases consult in these patients.[2]

5.4 Continue vancomycin if a Gram-positive organism grows in culture that is not susceptible to a β-lactam or if the patient has a culture-negative skin and soft-tissue infection with strong clinical suspicion for methicillin-resistant *Staphylococcus aureus.*

5.4.1 Consider Pediatric Infectious Diseases consult in these patients.[2]

5.5 If no source or organism is identified, antibiotics should be discontinued when patients have been afebrile for 24 hours or longer, have negative blood cultures for 48 hours, no focal signs of infection, and have an ANC ≥ 200 and is also rising.[2] *(UW Health low quality evidence, strong recommendation)*

5.5.1 If patients do not have a diagnosis of acute myeloid leukemia, hematopoietic stem cell transplant, or high-risk neuroblastoma then it may be reasonable to discharge the patient on oral antibiotics even without evidence of neutrophil recovery if they are clinically stable, afebrile for 24 hours or longer, and duration of neutropenia is anticipated 7 days or

fewer. *(UW Health low quality evidence, weak/conditional recommendation)*

5.5.2 Patients with a diagnosis of acute myeloid leukemia, hematopoietic stem cell transplant, or high-risk neuroblastoma should continue on intravenous antibiotic therapy until ANC ≥ 200 and rising. Antibiotic therapy should stop when ANC ≥ 200 and rising*. (UW Health low quality evidence, weak/conditional recommendation)*

5.6 If an organism is recovered in culture, it is reasonable to consider antibiotic de-escalation to the narrowest, acceptable antibiotic if anticipated duration of neutropenia is 7 days or fewer.[1,2,7] *(UW Health low quality evidence, weak/conditional recommendation)*

5.6.1 Continue broad-spectrum antibiotic (e.g. cefepime) if anticipated duration of neutropenia is 7 days or longer, even if the cultured organism is susceptible to a narrower spectrum antibiotic. *(UW Health low quality evidence, weak/conditional recommendation)*

5.7 If a source of infection is identified, antibiotics should continue for an evidence-based duration of treatment based on the type of infection (e.g. 7 days for hospital-acquired pneumonia) even if this duration extends beyond when an ANC ≥ 200 is achieved.[1] *(UW Health low quality evidence, strong recommendation)*

5.7.1 It is reasonable to treat with antibiotics until ANC ≥ 200 even if this duration surpasses the evidence-based duration of treatment for the identified infection.[1] *(UW Health low quality evidence, strong recommendation)*

5.8 In patients who remain or become clinically unstable after initiation of empiric antibiotics, escalate therapy to include coverage for resistant Gram-negative and Gram-positive pathogens and anaerobic bacteria.[2] *(UW Health low quality evidence, strong recommendation)*

5.8.1 Consider Pediatric Infectious Diseases consult in these patients.

5.8.2 For Gram-negative or multidrug resistant coverage, consider addition of an aminoglycoside or switch from a β-lactam to carbapenem monotherapy.[2]

5.8.3 For Gram-positive coverage, consider addition of vancomycin if not already present.

5.8.3.1 It is reasonable to switch from vancomycin to daptomycin if there is suspicion for vancomycin-resistant *Enterococcus* spp. or vancomycin-intermediate *Staphylococcus aureus.*

5.8.4 For anaerobic coverage, consider addition of metronidazole if not already present.

5.8.5 If suspected or confirmed *Clostridium difficile* infection, add oral vancomycin.

6. Approach to Persistent Fever[11]

6.1 Consider a Pediatric Infectious Diseases consult in patients who have had a persistent fever for 96 hours or longer, who have a new fever after defervescence, and/or who are initiated on antifungal therapy. *(UW Health low quality evidence, strong recommendation)*

6.2 It is not indicated to escalate antibiotic therapy in patients with persistent fever and neutropenia that are otherwise clinically stable.[2,5] *(UW Health low quality evidence, strong recommendation)*

6.2.1 Persistent fever alone is not an indication for continuing or adding vancomycin therapy.[2,5] *(UW Health low quality evidence, weak/conditional recommendation)*

6.3 Fungal, viral, and non-infectious etiologies should be considered in a patient who has been persistently febrile for 96 hours or longer.[2,47,48] *(UW Health low quality evidence, strong recommendation)*

6.3.1 Patients at high risk for invasive fungal disease include patients with acute myeloid leukemia, high-risk acute lymphoblastic leukmeia, relapsed acute leukemia, undergoing allogenic hematopoietic stem cell transplantation, or receiving high-dose corticosteroids.[2]

6.3.2 Patients that do not meet the above criteria (6.3.1) are at low risk for invasive fungal disease.[2,5]

6.4 Empiric antifungal therapy should be initiated in patients at high risk for invasive fungal disease who have persistent or recurrent fever after ≥ 96 hours of broad-spectrum antibiotics and who have not had an etiology of persistent fever identified (e.g. viral infection).[2,5] *(UW Health high quality evidence, strong recommendation)*

6.4.1 Consider Pediatric Infectious Diseases consult in these patients.

6.4.2 If a patient has not been receiving antifungal prophylaxis or has been receiving fluconazole antifungal prophylaxis, start empiric antifungal treatment with micafungin.[49] *(UW Health low quality evidence, strong recommendation)*

6.4.3 If a patient has been receiving antifungal prophylaxis with micafungin, voriconazole, or posaconazole, start empiric antifungal treatment with liposomal amphotericin B. *(UW Health low quality evidence, strong recommendation)*

6.5 It is reasonable to withhold empiric antifungal therapy in patients at low risk for invasive fungal disease who have persistent or recurrent fever after ≥ 96 hours of broad-spectrum antibiotics.[2] *(UW Health low quality evidence, weak/conditional recommendation)*

6.5.1 Consider Pediatric Infectious Diseases consult in these patients.

6.5.2 If empiric antifungal therapy is initiated, the choice of antifungal should mirror the recommendations for patients at high risk for invasive fungal disease.

6.6 Patients started on empiric antifungal therapy should receive a diagnostic work-up for invasive fungal infection.[2,5] *(UW Health low quality evidence, weak/conditional recommendation)*

6.6.1 Consider checking a serum galactomannan to evaluate for Aspergillosis.[2,47] *(UW Health low quality evidence, weak/conditional recommendation)*

6.6.1.1 The negative predictive value of serum galactomannan is high for Aspergillosis.

6.6.1.2 A serum galactomannan test cannot identify non-Aspergillus molds, which limits the usefulness of this test and limits the utility of the negative predictive value.[47]

6.6.1.3 The positive predictive value of blood galactomannan is poor. A positive result should not be used alone to make a diagnosis of an invasive fungal infection.[47]

6.6.2 Serum β-D-glucan testing is not recommended in pediatric patients due to lack of evidence for use and a poor positive predictive value to diagnose

invasive fungal infection.[2,47,50] *(UW Health low quality evidence, strong recommendation)*

6.6.3 A CT of the chest should be performed in any patient with strong clinical suspicion for invasive fungal disease.[11] *(UW Health low quality evidence, strong recommendation)*

6.6.3.1 If a pulmonary nodule or infiltrate is present, it is recommended to obtain a BAL or biopsy. *(UW Health low quality evidence, strong recommendation)*

6.6.4 A CT of the sinuses can be considered in patients ≥ 2 years of age with focal findings such as facial pain.[2,11,51] *(UW Health low quality evidence, weak/conditional recommendation)*

6.6.4.1 Consider not routinely performing CT of sinuses in patients without focal signs or symptoms.[11] *(UW Health low quality evidence, weak/conditional recommendation)*

6.6.5 Additional imaging is not necessary unless clinically indicated.

6.6.6 If the diagnostic work-up is negative, antifungal therapy should continue only until ANC ≥ 200 and rising.[2] *(UW Health low quality evidence, strong recommendation)*

UW Health Implementation

Potential Benefits

1. Appropriate initial evaluation and risk stratification
2. Timely initiation of effective treatment
3. Minimized treatment variability

Potential Harms

1. Side effects and adverse events associated with various medical/drug treatments
2. Failure to appropriately categorize patients as low- or high-risk

Guideline Metrics

Selection of antimicrobial agents and dose, timeliness of antimicrobial administration, hospital admission rates, hospital length of stay, total duration of antimicrobial therapy, and clinical outcomes including resolution of fever, morbidity, and mortality.

Implementation Plan/Clinical Tools

1. Guideline will be electronically distributed through UConnect in the dedicated location for Clinical Practice Guidelines.
2. Release of the guideline will be advertised in the Physician/APP Briefing newsletter and via email communication to all pharmacy staff.
3. Pertinent medication records will be updated to include a link to this guideline.
4. Content and hyperlinks within clinical tools, documents, or HealthLink related to the guideline recommendations (such as the following) will be reviewed for consistency and modified as appropriate.

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

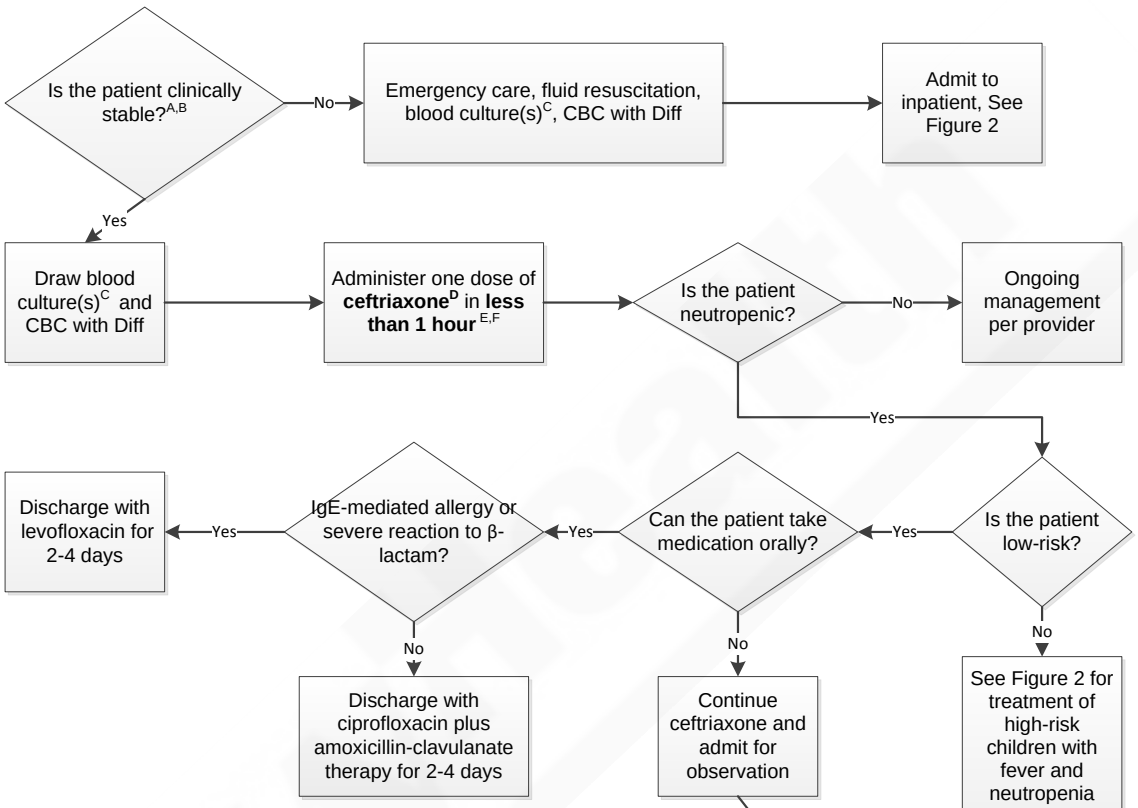
Appendix A. Summary of Key Practice Recommendations

From: [Management of Fever and Neutropenia – Pediatric – Inpatient/Ambulatory/Emergency Department – Clinical Practice Guideline]

Last Reviewed 6/2017; Last Updated 6/2017

Contact: Erin McCreary, PharmD, BCPS; emccreary@uwhealth.org

Figure 1. Empiric treatment of children with fever and possible neutropenia presenting to the Emergency Department regardless of risk status; Empiric and ongoing treatment of low-risk children with fever and neutropenia



A Fever is defined by any temperature ≥ 38°C. Discuss case with Pediatric Heme/Onc Fellow/Attending and call the PICU as soon as possible. Neutropenia defined as ANC <500.

B Patients with suspicion for neutropenia should never have a rectal temperature checked or receive a rectal medication. NSAIDS should be avoided in all oncology patients.

C Culture all lumens of central line; peripheral culture not required. Empiric antibiotic administration should never be delayed to obtain culture data. All initial antibiotics should be ordered "STAT" and administered within one hour.

D Consider aztreonam plus vancomycin if IgE-mediated allergy or severe reaction to β-lactam

E Do not wait for lab results to start antibiotics

F Check vital signs every 15 minutes

Figure 2. Empiric treatment of high-risk children with fever and neutropenia

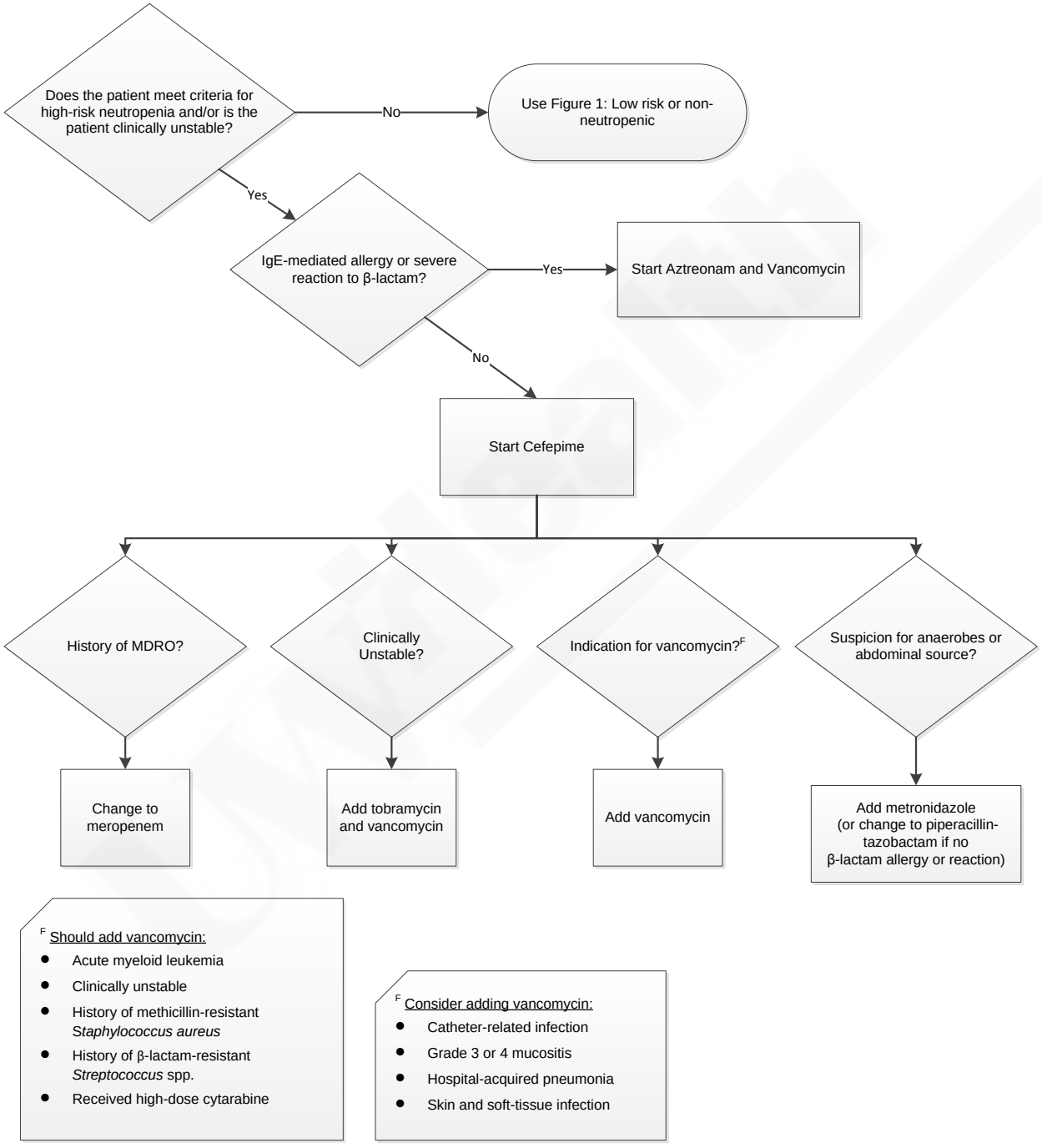


Figure 3. Ongoing treatment of children with fever and neutropenia at high risk

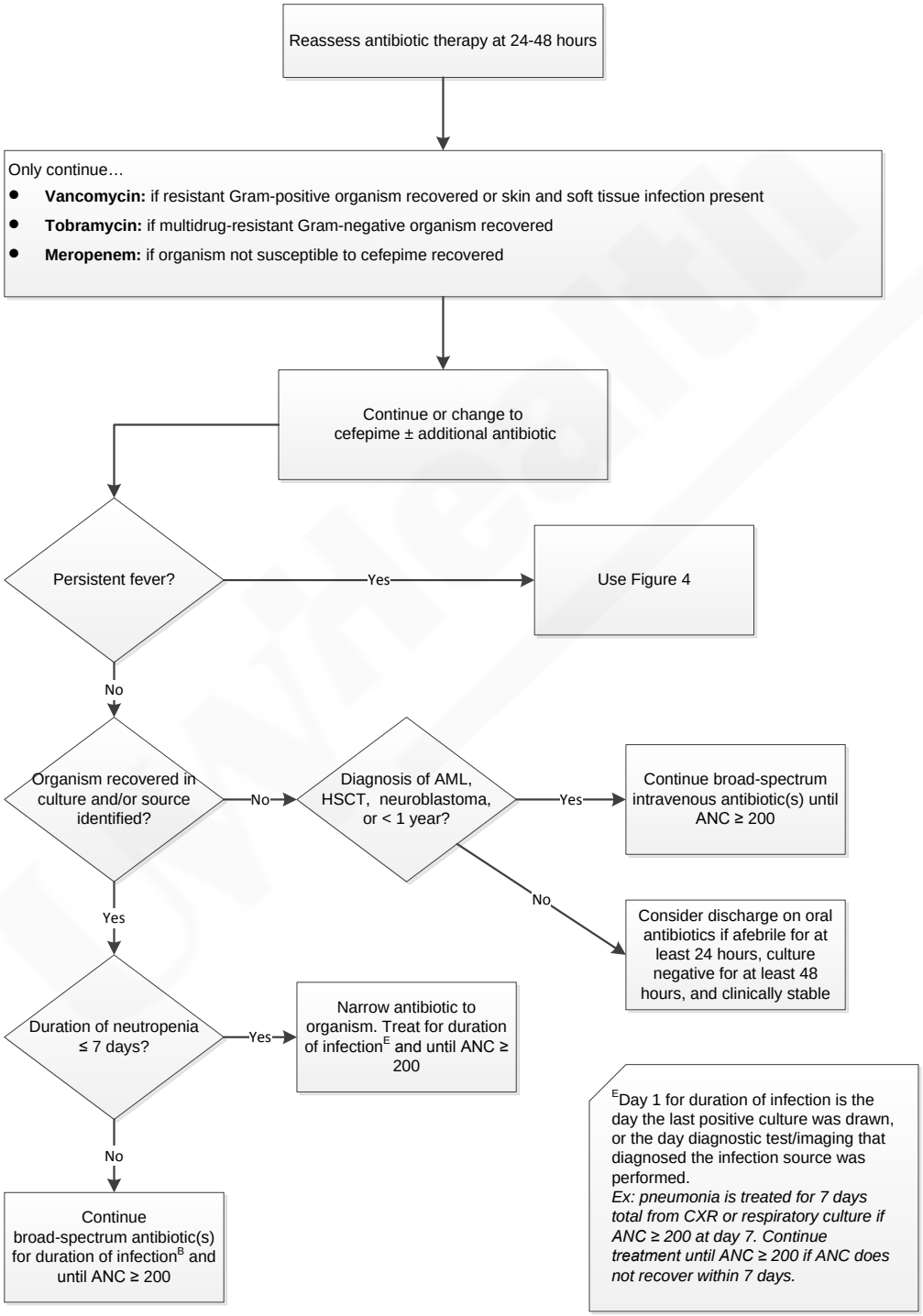
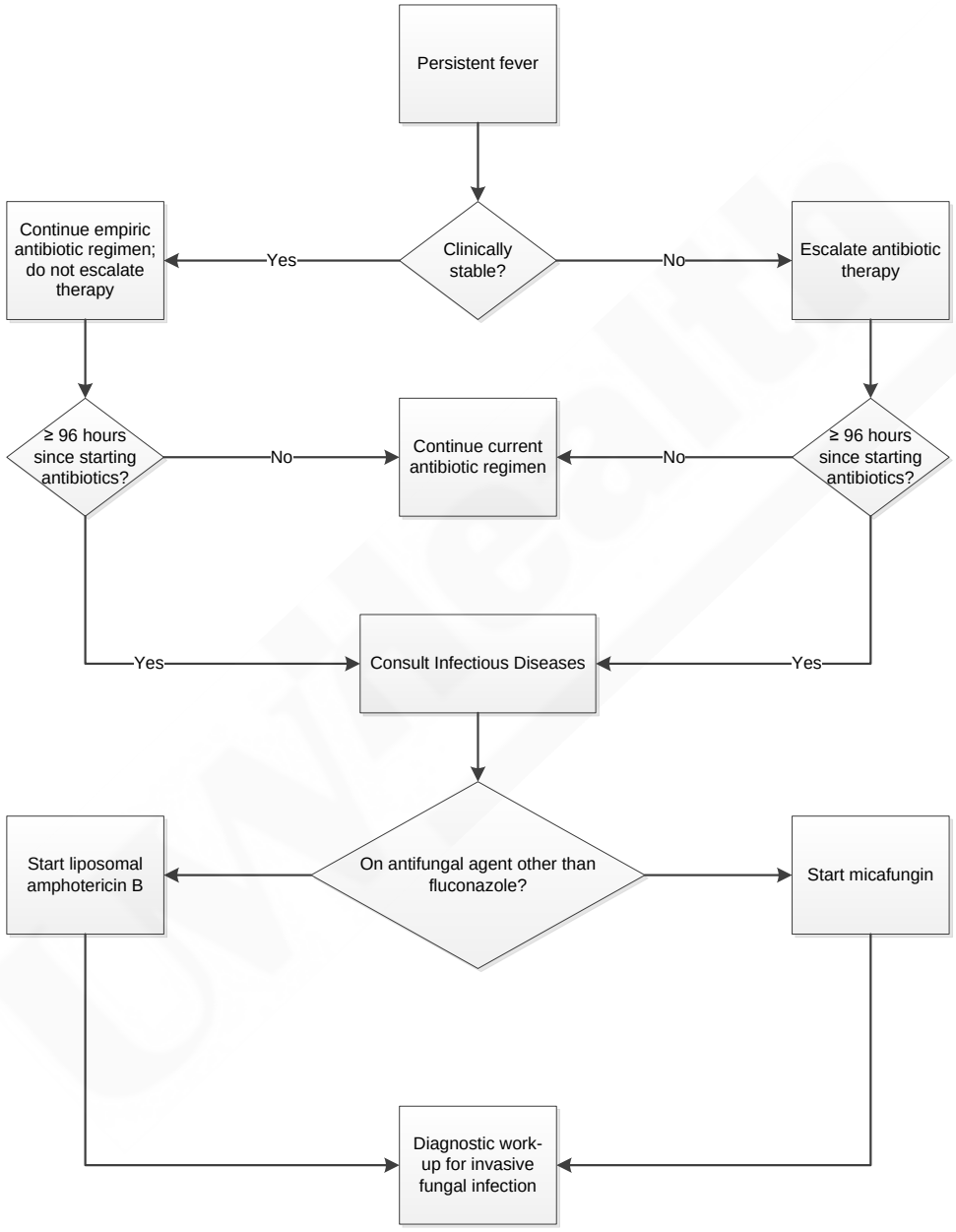
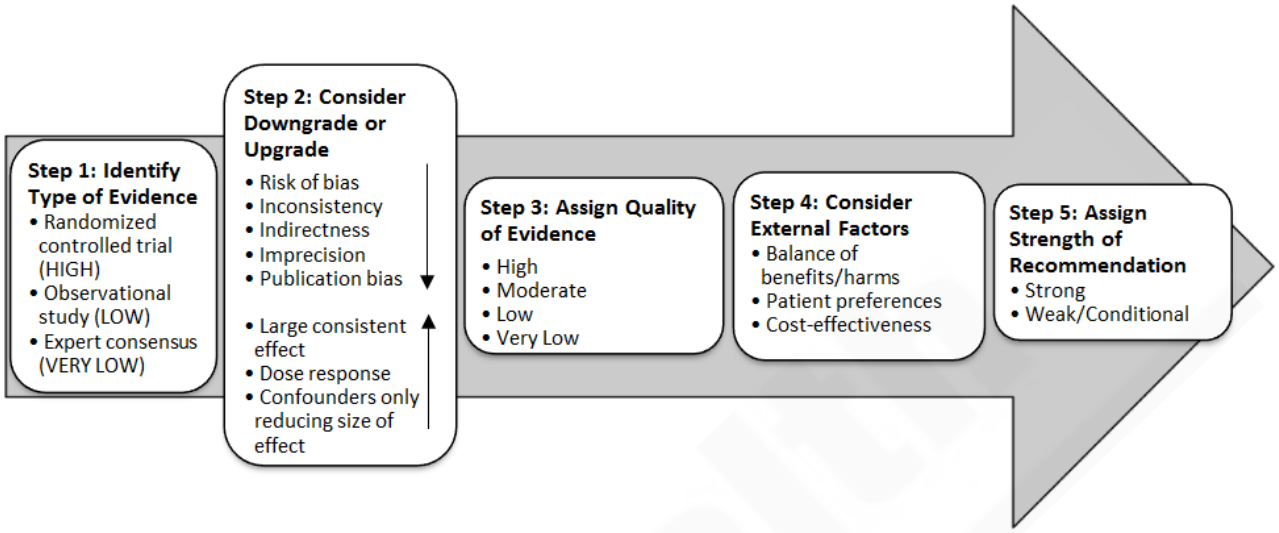


Figure 4. Evaluation and treatment of persistent fever in children at high risk



Appendix B. Evidence Grading Scheme

Figure 1. GRADE Methodology adapted by UW Health



GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Weak/conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

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