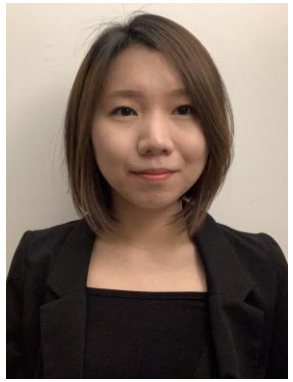
PREVENTION AND TREATMENT OF CANCER-RELATED INFECTIONS IN ADULT PATIENTS



Soo Jin Koo, PharmD
PGY-1 Pharmacy Resident
Atlantic Health System

Pamela Giordano, PharmD, BCPS, BCIDP, Preceptor
Mohamed Eldib, PharmD, BCOP, Preceptor

DISCLOSURES

The presenter and her preceptors have no financial relationships with any commercial interests pertinent to this presentation.

This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research.

Such examples are intended for educational and information purposes and should not be perceived as an endorsement of any supplier, brand or drug.

OBJECTIVES FOR PHARMACISTS AND NURSES

Identify	Recall	Recognize
Identify validated risk stratification tools to determine route, location of treatment and spectrum of agents recommended for oncology patients	Recall prophylactic antimicrobial regimen for patients at risk for febrile neutropenia (FN)	Recognize appropriate antimicrobial therapy for patients with FN

OBJECTIVES FOR PHARMACY TECHNICIANS

Define	Define neutropenic fever
Recognize	Recognize appropriate drug category for antimicrobials
Identify	Identify agents used in the management of febrile neutropenia

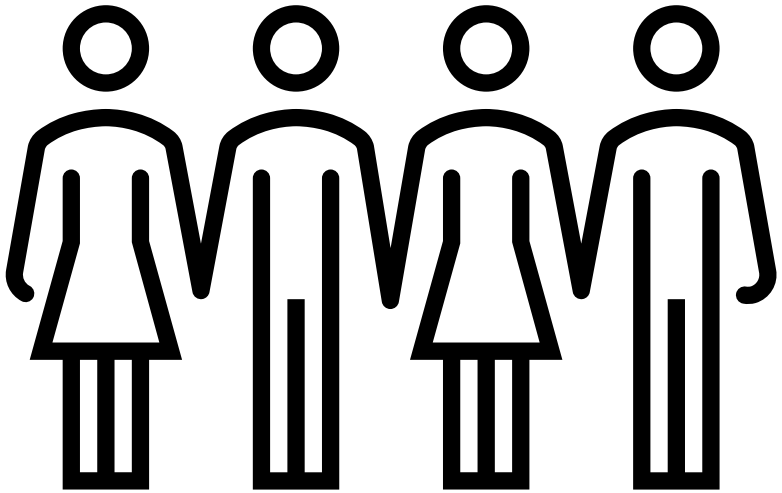
PRESENTATION OUTLINE

Background

- Definition
- Prevalence and disease burden
- Validated risk stratification tools

Management options

- Prevention
- Empiric therapy
- Escalation/De-escalation



BACKGROUND

Definition, prevalence, disease burden, guidelines, risk stratification tools

DEFINITIONS

Fever

- A single oral temperature of 38.3°C or higher OR 38.0°C or higher over 1 hour
- In the absence of an obvious cause

Neutropenia

- Absolute neutrophil count (ANC) less than 500 neutrophils/mcL OR
- ANC less than 1000 neutrophils/mcL and a predicted decline to 500 neutrophils/mcL or less over the next 48 hours

"Profound" Neutropenia: ANC less than 100 neutrophils/mcL
(Manual reading of the blood smear is required)

Sources: Freifeld AG, et al. *Clin Infect Dis*. 2011;52(4):e56-e93.

PREVALENCE AND DISEASE BURDEN

- FN occurs frequently in patients who receive chemotherapy
  - 10-50% of solid tumor patients with neutropenia
  - 80% of hematologic malignancies with neutropenia
  - Rate of 7.83 cases/1000 cancer patients and 43.3 cases/1000 patients with hematological malignancy
- Rate of major complications in the context of FN: approximately 25-30%
  - Hypotension, acute renal failure, respiratory failure, heart failure
- Mortality rate ranges up to 11%

Sources: Al-Tawfiq JA, et al. *J Infect Public Health*. 2019;12(3):364-366.
Taplitz RA, et al. *J Clin Oncol*. 2018;36(14):1443-1453.

GUIDELINES AND RISK STRATIFICATION TOOLS

- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
  - Prevention and Treatment of Cancer-Related Infections, 2021
  - Hematopoietic Growth Factors, 2022
- Infectious Diseases Society of America (IDSA) and American Society of Clinical Oncology (ASCO)
  - Clinical Practice outline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer, 2010
  - Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression, 2018
  - Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy, 2018

	NCCN Guidelines®	IDSA + ASCO
Risk Stratification Tools	• Multinational Association of Supportive Care in Cancer (MASCC) • Clinical Index of Stable Febrile Neutropenia (CISNE)	• MASCC • Talcott's group • CISNE

Sources: Taplitz RA, et al. *J Clin Oncol*. 2018;36(14):1443-1453.

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021.

MASCC (Scores ≥ 21 indicate a low risk for medical complications)	CISNE (Low risk = 0 points, intermediate risk = 1 to 2 points, and high risk ≥ 3 points)	Talcott (Group IV is low risk)
• Burden of FN with no or mild symptoms • No hypotension • No chronic obstructive pulmonary disease • Solid tumor or hematologic malignancy with no previous fungal infection • No dehydration requiring parenteral fluids • Burden of FN with moderate symptoms • Outpatient status • Age < 60 years	• Eastern Cooperative Oncology Group performance status ≥ 2 • Chronic obstructive pulmonary disease • Chronic cardiovascular disease • National Cancer Institute Common Toxicity Criteria mucositis of grade ≥ 2 • Monocytes < 200/mcL • Stress-induced hyperglycemia	• Group I: Inpatient (at the time of fever onset) • Group II: Outpatients with acute comorbidity requiring, by itself, hospitalization • Group III: Outpatients without comorbidity but with uncontrolled cancer • Group IV: Outpatients with cancer controlled and without comorbidity

Source: Taplitz RA, et al. *J Clin Oncol*. 2018;36(14):1443-1453

ASSESSMENT QUESTION #1

Pharmacy Technicians

Which of the following meets the definition of febrile neutropenia?

a) Single oral temperature of <37°C (98.6°F) and an absolute neutrophil count <500/µL
b) Single oral temperature of >37°C (98.6°F) and an absolute neutrophil count >500/µL
c) Single oral temperature of <38.3°C (101°F) and an absolute neutrophil count >500/µL
d) Single oral temperature of >38.3°C (101°F) and an absolute neutrophil count <500/µL

ASSESSMENT QUESTION #1

Pharmacy Technicians

Which of the following meets the definition of febrile neutropenia?

a) Single oral temperature of <37°C (98.6°F) and an absolute neutrophil count <500/µL
b) Single oral temperature of >37°C (98.6°F) and an absolute neutrophil count >500/µL
c) Single oral temperature of <38.3°C (101°F) and an absolute neutrophil count >500/µL
d) **Single oral temperature of >38.3°C (101°F) and an absolute neutrophil count <500/µL**

ASSESSMENT QUESTION #2

Pharmacists and Nurses

Which of the following is not a validated tool for risk stratification in cancer patients?

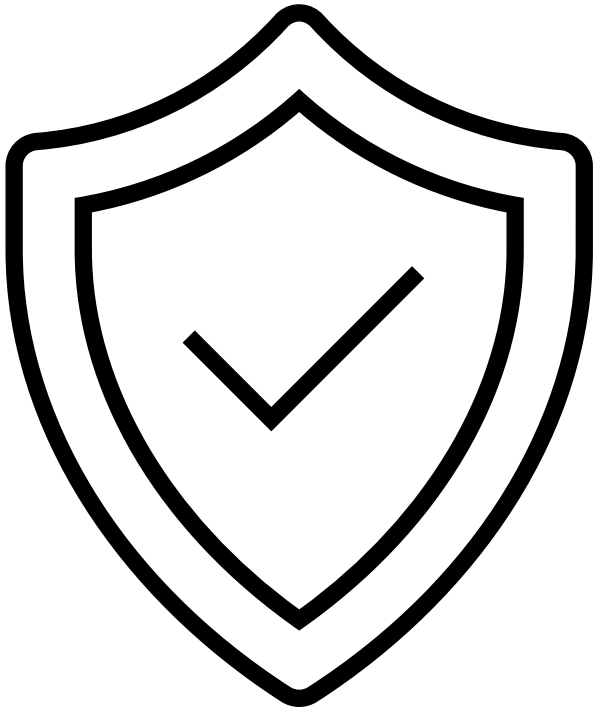
a) NCCN
b) MASCC
c) CISNE
d) Talcott's group

ASSESSMENT QUESTION #2

Pharmacists and Nurses

Which of the following is not a validated tool for risk stratification in cancer patients?

a) **NCCN**
b) MASCC
c) CISNE
d) Talcott's group



PREVENTION OF INFECTIOUS DISEASES

Antibacterial Prophylaxis, Antifungal Prophylaxis, *Pneumocystis jirovecii* Prophylaxis, Vaccines and G-CSF

ANTIBACTERIAL PROPHYLAXIS

1. Candidates

- Intermediate – high risk patients including ANC < 100 neutrophils/µl for > 7 days
- Should be systemically assessed in consultation with infectious disease specialist as needed
  - Patient characteristics
    - Advanced age (65 years or greater)
    - Eastern Cooperative Oncology Group performance score of 2 or greater
    - Albumin <35 g/L
    - Cycles 2-6
    - Comorbidities
    - Cancer diagnosis with high risk of FN (acute leukemia/myelodysplastic syndrome (MDS) and high-grade lymphoma highest)
    - Cancer stage (2 or higher)
    - Cytotoxic regimen, dose intensity, degree
    - Duration of cytopenia (ANC <100/mcL for 7 or more days)

Source: Taplitz RA, et al. *J Clin Oncol*. 2018;36(14):1443-1453.

ANTIBACTERIAL PROPHYLAXIS

2. Agents
   - Fluoroquinolone (FQ)
   - If intolerant to FQ, consider TMP/SMX or oral third-generation cephalosporin
3. Duration
   - During the expected period of neutropenia
4. Outcomes studied:
   - Mortality, morbidity, infection rates, fever

Sources: Freifeld AG, et al. *Clin Infect Dis*. 2011;52(4):e56-e93.

FLUOROQUINOLONE STUDIES

- Gafter-Gvili, et al: Meta-analysis of 95 RCTs
  - Neutropenic patients undergoing cytotoxic therapy
  - **Significantly decreased the risk of all-cause death, infection-related mortality, fever, clinically documented infections and bacteremia**
- Gafter-Gvili, et al: Systemic review and meta-analysis of 109 trials
  - Neutropenic patients with hematologic cancer following chemotherapy
  - **Significantly reduced all-cause mortality**
- Engels EA, et al.: Meta-analysis of 18 trials
  - Neutropenic cancer patients following chemotherapy
  - FQs reduced gram-negative infections by about 80%, Gram-positive infections and fungal infections not significantly affected, **did not affect infection-related mortality rates**
- Cullen M, et al.: RCT of 1565 patients
  - Patients with solid tumors and lymphomas
  - Reduced in febrile episodes and hospitalizations in FQ, but **incidence of severe infections, infection-related mortality and overall mortality were similar between both groups**

Sources: Gafter-Gvili, et al. *Ann Intern Med*. 2005;142(12 Pt 1):979-995. Gafter-Gvili, et al. *Cochrane Database Syst Rev*. 2012;1(1):CD004386.
Engels EA, et al. *J Clin Oncol*. 1998;16(3):1179-1187. Cullen M, et al. *N Engl J Med*. 2005;353(10):988-998.

ANTIBACTERIAL AGENTS

Agents	Dose	Clinical Pearls

Ciprofloxacin	• 500-750 mg PO every 12 hours or 400 mg IV every 8-12 hours	• FQ Black Box Warning:
		  • Tendon rupture
		  • Peripheral neuropathy
		  • CNS effects
		  • Exacerbation of myasthenia gravis
		• Moxifloxacin has insufficient activity against Pseudomonas
		• Prophylaxis may increase bacterial resistance and superinfection
		• Renal dose adjustments are required

Levofloxacin	• 500-750 mg PO or IV daily	
Moxifloxacin	• 400 mg PO or IV daily	

ANTIFUNGAL PROPHYLAXIS

Guidelines	NCCN Guidelines	IDSA/ASCO

Candidates	• Intermediate to high risk patients including neutropenia for >7 days
	  • Patients with chronic severe neutropenia (ANC <500 neutrophils/mcL) are at substantial risk for invasive aspergillosis
	• Secondary prophylaxis in patients with prior chronic disseminated candidiasis or with invasive filamentous fungal infection during subsequent cycles of chemotherapy
		• Patients with <100 neutrophils/mcL for >7 days
		• Patients at risk of *Candida* infection >10%
		• Patients at risk of invasive aspergillosis >6%
		  • Patients who are undergoing intensive chemotherapy for AML/MDS

Agents	• Posaconazole is a Category 1 treatment option for AML/MDS • Fluconazole, voriconazole, an echinocandin (micafungin, caspofungin or anidulafungin), or amphotericin B products are Category 2B recommended treatment options	Fluconazole, itraconazole, voriconazole, posaconazole, micafungin and caspofungin
Duration	Until resolution of neutropenia	During the expected period of neutropenia
Outcomes studied	Incidence of invasive aspergillosis, rate of invasive fungal infections, survival benefit	Death related to fungal infection, invasive infections

Taplitz RA, et al. *J Clin Oncol*. 2018;36(14):1443-1453.

ANTIFUNGAL PROPHYLAXIS STUDY

	Cornely OA, et al.
Type of study	• Multicenter, randomized study
Interventions	• Posaconazole vs fluconazole or itraconazole as prophylaxis for neutropenia resulting from chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome
Results	• 602 patients randomized • Absolute risk reduction of invasive fungal infections: 6% by posaconazole • Fewer posaconazole patients had invasive aspergillosis ($P<0.001$) • Survival was significantly longer among recipients of posaconazole ($P=0.04$) • Serious adverse events (GI tract disturbances) were higher in posaconazole group ($P=0.01$)
Conclusion	• **Posaconazole prevented invasive fungal infections more effectively than did either fluconazole or itraconazole and improved overall survival**

Source: Cornely OA, et al. *N Engl J Med.* 2007;356(4):348-359.

ANTIFUNGAL AGENTS - AZOLES

Agents	Dose	Clinical Pearls
Fluconazole	• Adults with normal renal function: 400 mg IV/PO daily	• Most Candida species • Inactive against molds
Isavuconazonium sulfate	• Loading dose (LD) 372 mg IV/PO every 8 hours x 6 doses then maintenance dose (MD) 372 mg IV/PO daily	• **Anti-mold properties** • May shorten QTc interval • Moderate inhibitor of CYP3A4
Itraconazole	• 400 mg PO daily; LD 200 mg PO TID x 3 days, then MD 200 mg PO BID	• **Anti-mold properties** • Negative inotropic properties • H2 blockers and proton pump inhibitors (PPIs) may inhibit absorption of capsule formulation
Posaconazole	• IV injection and delayed-release (DR) tablet: LD 300 mg DR tablet PO BID or 300 mg IV BID on Day 1 and then MD 300 mg PO daily • Oral suspension prophylaxis: 200 mg TID • Oral suspension treatment: 200 mg QID	• **Anti-mold properties** • Refractory infection in several invasive fungal disease (not FDA-approved) • PPIs decrease plasma concentration with oral suspension
Voriconazole	*Prophylaxis:* 200 mg BID PO *Invasive aspergillosis*: LD: 6 mg/kg IV or 400 mg PO BID x 2 doses on Day 1. MD: 4 mg/kg IV BID *Candidemia:* LD: 6 mg/kg IV or 400 mg PO BID x 2 doses on Day 1. MD: 3-4 mg/kg IV BID	• **Anti-mold properties** • IV formulation: caution in renally impaired patients • Visual disturbances and hallucinations • Bioavailability with food

Sources: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021.

ANTIFUNGAL AGENTS

Echinocandins

Agents	Dose	Clinical Pearls
Liposomal amphotericin B	• 3-5 mg/kg IV daily	• **Anti-mold properties** • Reduced infusional and renal toxicity compared to amphotericin B deoxycholate
★ Caspofungin	• 70 mg IV x 1 dose, then 50 mg IV daily	• **Anti-mold properties** • Primary therapy for candidemia and invasive candidiasis • Poor CNS and eye penetration • Excellent safety profile
★ Micafungin	• 100 mg IV daily for candidemia and 50-100 mg/d IV as prophylaxis	

Sources: Hicheri, et al. *Clin Microbiol Infect.* 2012;18 Suppl 2:1-15.

PNEUMOCYSTIS JIROVECII

- Candidates: Patients with acute lymphoblastic leukemia (ALL), receiving chemotherapy regimens associated with >3.5% risk for pneumonia from *Pneumocystis jirovecii* (corticosteroid treatment equivalent of 20 mg or more of prednisone daily for 4 weeks or more or those on purine analogs), receiving idelalisib +/- rituximab, or receiving temozolomide and radiotherapy
- Agent: Trimethoprim/sulfamethoxazole
- Duration: Throughout anti-leukemic therapy for patients with ALL. Varies depending on the chemotherapeutic agent

Agents	Dose	Spectrum	Considerations
Trimethoprim/ sulfamethoxazole (TMP/SMX)	• Prophylaxis (PJP): Single or double strength daily or double strength 3 times per week • Treatment: 15 mg/kg/d in divided doses every 6-8 hours based on trimethoprim component	• Activity against P. jirovecii and other relevant pathogens, including Toxoplasma gondii and Nocardia	• Highly effective as prophylaxis against P. jirovecii • Renal insufficiency, myelosuppression, hepatotoxicity and hyperkalemia

Sources: Freifeld AG, et al. *Clin Infect Dis*. 2011;52(4):e56-e93.

ANTIVIRAL PROPHYLAXIS: HERPES SIMPLEX VIRUS (HSV)

- Results from reactivation of latent virus
  - Occurs in 60-80% of patients with acute leukemia undergoing induction or re-induction therapy who are seropositive for HSV
- Candidates:
  - HSV-seropositive patients who are receiving chemotherapy for acute leukemia
- Agents:
  - Acyclovir, famciclovir, or valacyclovir
- Duration:
  - During the period of neutropenia and longer depending on risk
- Other viruses:
  - Prophylaxis for other viruses may be necessary in patients undergoing stem cell transplant or in patients on certain agents, such as alemtuzumab

Sources: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021.

ANTIVIRAL AGENTS

Agents	Dose	Clinical Pearl
Acyclovir	• 400-800 mg PO BID	• Hydration to avoid nephropathy with high dose • Dosing based on ideal body weight
Famciclovir	• 250 mg PO BID	• No data for oncologic-related prophylaxis
Valacyclovir	• 500 mg PO BID or TID	

Sources: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021.

VACCINES

- NCCN Guidelines panel recommends that patients with cancer receive the **influenza, pneumococcal, meningococcal and HPV** vaccines
- Persons receiving chemotherapy or radiation therapy for malignancies should **not receive live vaccines** for *at least 3 months* after cessation and until they are presumed to be immunocompetent
- Covid-19 vaccines for the immunocompromised
  - mRNA vaccines are preferred
  - Third primary shot (mRNA vaccine) 4 weeks after the 2nd dose
  - 2nd booster dose (mRNA vaccine) after at least 4 months of the first booster dose
- Household members of an immunocompromised patient
  - Stay up to date with vaccines
  - Do not receive a live flu vaccine unless healthy, not pregnant and 2-49 years old
  - If the immunocompromised patient had a stem cell transplant in the last 2 months, has graft versus host disease, or severe combined immunodeficiency, do not receive the live flu vaccine

Sources: Am Fam Physician. 2014;90(9):664-666.
CDC. Covid-19. Accessed March 2022.

COVID-19: TIXAGEVIMAB AND CILGAVIMAB

- Emergency Use Authorization (EUA) granted on 12/8/2021
- Pre-exposure prophylaxis for those who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure
  - With moderate to severe immune compromise or in whom vaccination is not recommended
  - For those who received a COVID-19 vaccine, to be administered at least two weeks after vaccination
- Mechanism of action
  - Recombinant human IgG1k monoclonal antibodies
  - Bind to nonoverlapping epitopes of the spike protein receptor-binding domain of SARS-CoV-2, blocking attachment to the human ACE2 receptor
- Dosing:
  - Tixagevimab 300 mg and cilgavimab 300 mg as a single dose administered intramuscularly in 2 separate syringes consecutively

Source: *JAMA*. 2022;327(4):384-385

GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF)

GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF)

- ✓Hematopoietic growth factors can promote proliferation and differentiation of hematopoietic progenitors into mature blood cells
- ✓Myeloid growth factors (MGFs), such as G-CSF, reduce the incidence of FN in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy
- ✓Benefits: reduces the incidence, duration and severity of FN; decreases the subsequent rates of infection and hospitalization; improves the delivery of full-dose intensity chemotherapy
- ✓Risks: bone pain, splenic rupture, increased bleomycin-induced pulmonary toxicity
- ✓Examples: Filgrastim, pegfilgrastim

Source: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors. Version 1.2022.

STUDIES REGARDING THE USE OF G-CSF

- Prophylactic use of G-CSF
  - A systematic review of RCTs by Kuderer NM, et al. showed that the use of G-CSF was associated with reduced FN and infection-related mortality
  - A RCT by Kosaka Y, et al. showed that the use of pegfilgrastim was associated with lower incidences of FN and hospitalizations
- G-CSF in patients who have FN
  - Double-blind, placebo-controlled trial by Waher DW, et al.
  - Interventions: Filgrastim vs placebo
  - Results:
    - Reduction in the median number of days of neutropenia (P=0.01), but not days of fever
    - Prolonged hospitalization was decreased (P=0.02), same median number of hospitalization days while on the study
  - Conclusion: No mortality benefits to use of G-CSF in treatment of FN

Sources: Freifeld AG, et al. *Clin Infect Dis*. 2011;52(4):e56-e93.
Kuderer NM, et al. *J Clin Oncol*. 2007;25(21):3158-3167.
Kosaka Y, et al. *Supp Care Canc*. 2015;23(4):1137-1143. Maher DW, et al. *Ann Intern Med*. 1994;12(7):492-501.

PROPHYLACTIC USE OF GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF)

Not recommended for treatment of established fever and neutropenia

Primary prophylaxis

- G-CSF administration within 5 days of beginning chemotherapy
- G-CSF is recommended in patients with high risk (>20%) of developing FN
- G-CSF can be considered in patients with intermediate (10-20%) risk of developing FN
- G-CSF is not recommended in patients with low (<10%) risk of developing FN

Secondary prophylaxis

- G-CSF administration prior to second and subsequent chemotherapy cycles
- Patients who has had febrile neutropenia or dose-limiting neutropenic event during the previous treatment cycle
  - Received G-CSF in the previous treatment cycle → consider chemotherapy treatment change
  - Did not receive G-CSF in the previous treatment cycle → consider G-CSFs

Source: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors. Version 1.2022.

PROPHYLACTIC USE OF GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF)

Risk stratification

- Disease
- Chemotherapy regimen (High-dose therapy, dose-dense therapy, standard-dose therapy)
  - Chemotherapy regimens for which clinical trial data show an incidence of FN greater than 20% in chemotherapy-naïve patients are considered *high risk*
- Patient Risk factors
  - Older age (>65 years)
  - Prior exposure to chemotherapy or radiation therapy
  - Persistent neutropenia
  - Bone marrow involvement by the tumor
  - Poor performance status
  - Recent surgery and/or open wounds
  - Renal or liver dysfunction
  - HIV infection
  - Chronic immunosuppression in the post-transplant setting
- Treatment intent (curative vs palliative)

ASSESSMENT QUESTION #3

Pharmacy Technicians

Which of the following agents is considered an antifungal?

a) Tenofovir
b) Fluconazole
c) Cefepime
d) Levofloxacin

ASSESSMENT QUESTION #3

Pharmacy Technicians

Which of the following agents is considered an antifungal?

a) Tenofovir
b) **Fluconazole**
c) Cefepime
d) Levofloxacin

ASSESSMENT QUESTION #4

Pharmacists and Nurses

Which of the following agents is the preferred antimicrobial agent used for prevention of *Pneumocystis jirovecii* infection?

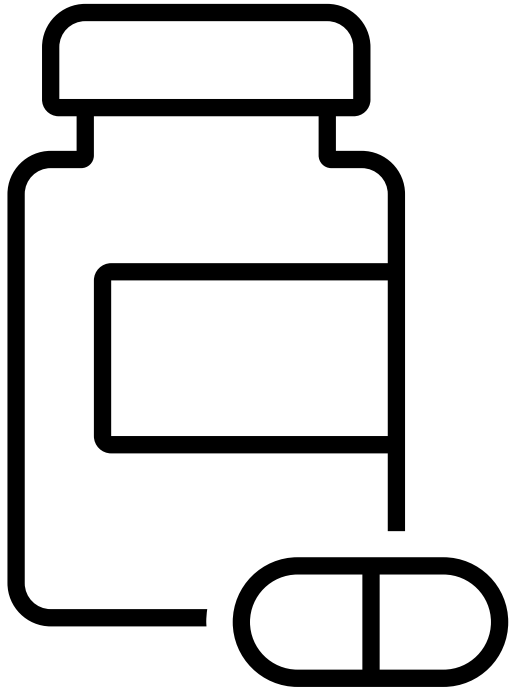
a) Entecavir
b) Fluconazole
c) Meropenem
d) Trimethoprim/sulfamethoxazole

ASSESSMENT QUESTION #4

Pharmacists and Nurses

Which of the following agents is the preferred antimicrobial agent used for prevention of *Pneumocystis jirovecii* infection?

a) Entecavir
b) Fluconazole
c) Meropenem
d) **Trimethoprim/sulfamethoxazole**



MANAGEMENT OF FN

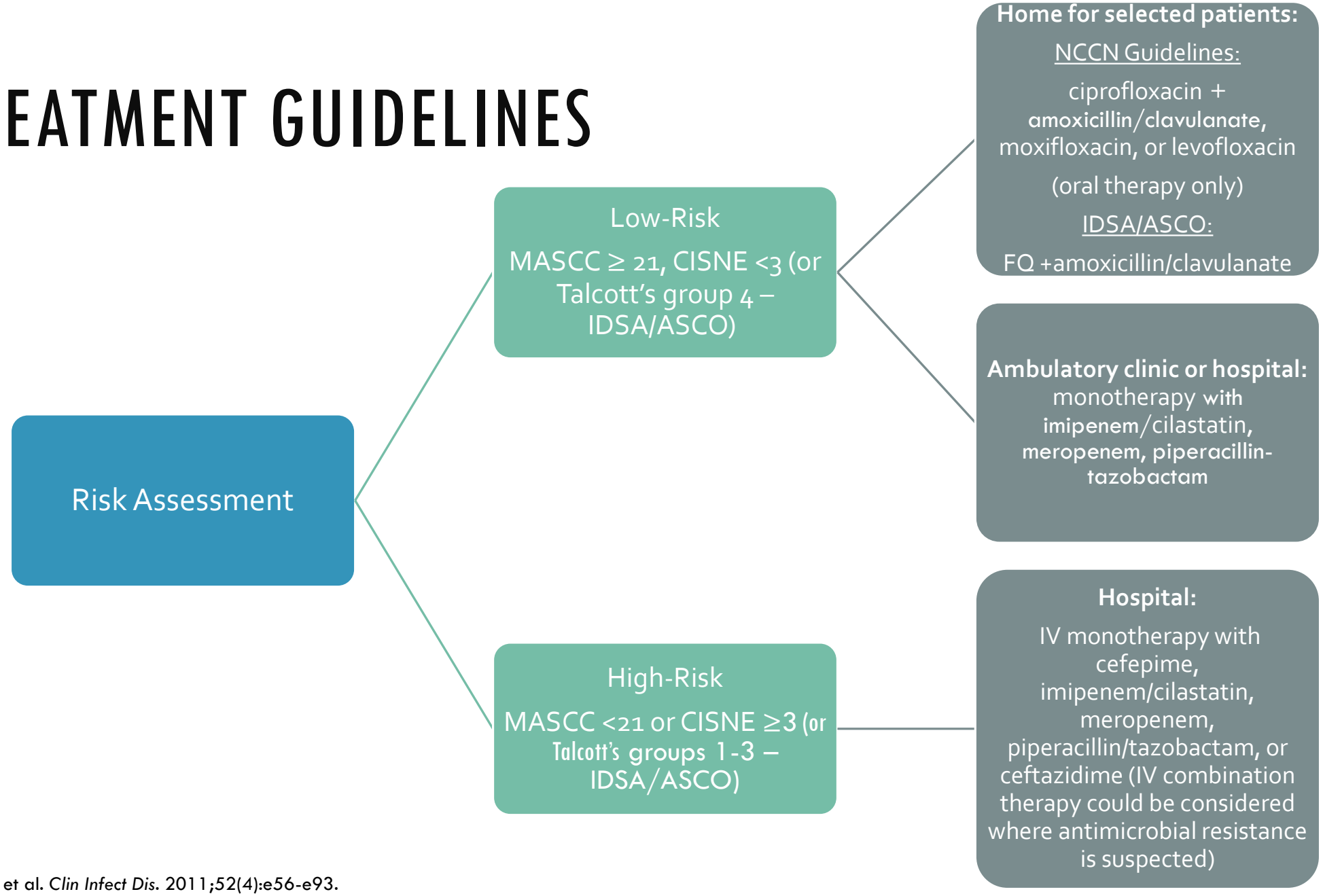
Initial evaluation, low risk patients, outpatient management, use of vancomycin, reevaluation and empiric fungal therapies

INITIAL EVALUATION

1. Determine the potential sites and causative organisms of infection
2. Assess the patient's risk of developing an infection-related complication
3. Initial laboratory/radiology evaluation
   - Complete blood count, liver function tests, renal function tests, measurement of electrolytes, total bilirubin
   - Oxygen saturation and urinalysis
   - Chest radiographs
4. Cultures should be obtained *before* the administration of antibiotics
   - **One set obtained peripherally and another from a central venous catheter**
   - Both sets obtained peripherally
   - Both sets obtained through the catheter
5. Start empiric antibiotics within 1 hour after triage from initial presentation
   - Patient's infection risk, antimicrobial susceptibilities of pathogens isolated locally, most common potentially infecting organisms, potential sites of infection, clinical instability, drug allergy, recent antibiotic use

Sources: Freifeld AG, et al. *Clin Infect Dis*. 2011;52(4):e56-e93.

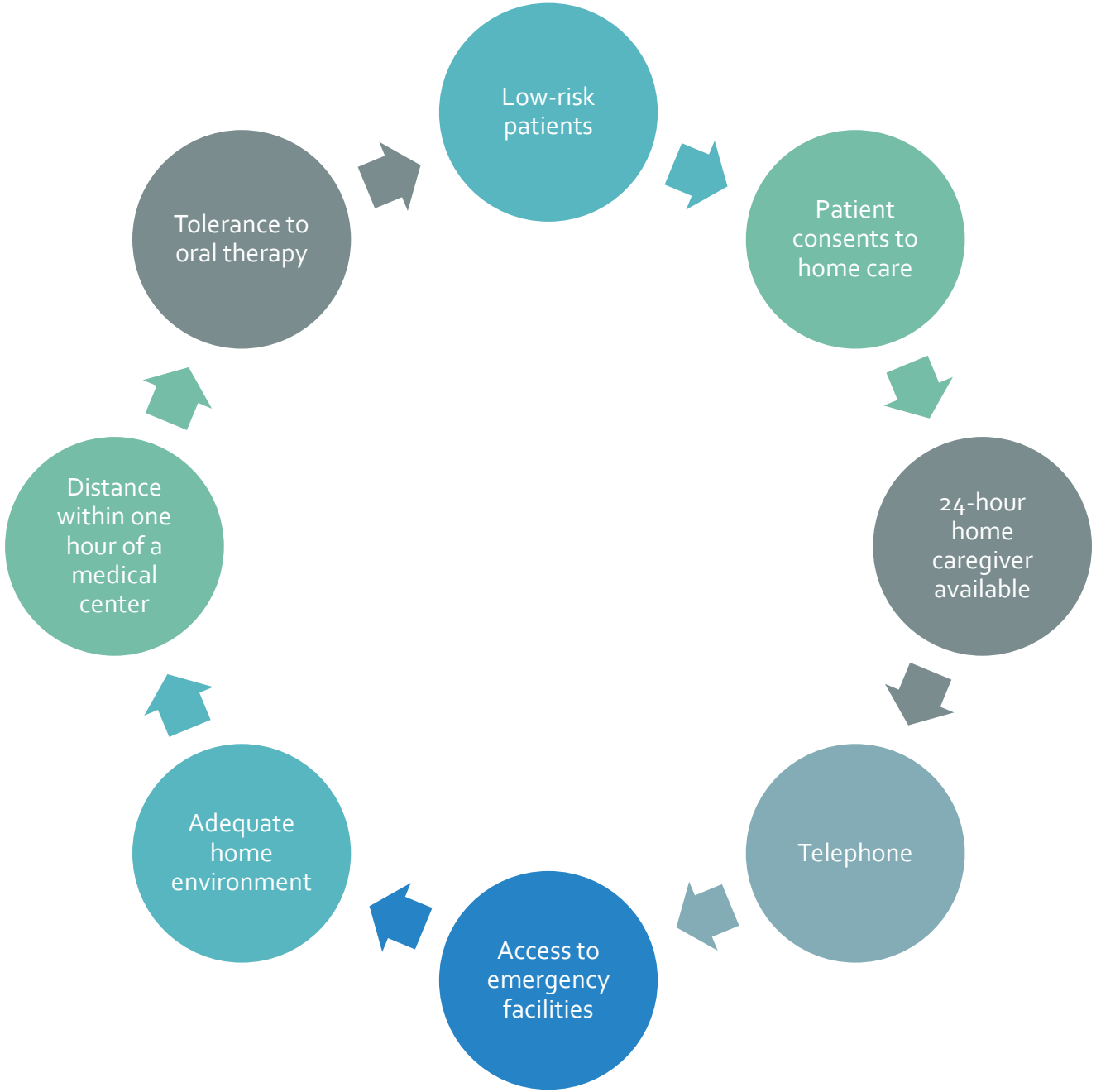
TREATMENT GUIDELINES



Sources: Freifeld AG, et al. *Clin Infect Dis*. 2011;52(4):e56-e93.

WHO CAN RECEIVE OUTPATIENT MANAGEMENT?

- Low-risk patients may be treated in the hospital with oral or IV antibiotics, in an ambulatory clinic, or at home
- Observation period of 2 to 12 hours
- Telephone follow up performed within 12 to 24 hours



Source: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021.

OUTPATIENT ORAL MEDICATION

Ciprofloxacin + amoxicillin/ Clavulanate	Levofloxacin	Moxifloxacin
Only for patients who have not received a quinolone as prophylaxis Choice should be based on reliable Gram-negative bacillary activity of the antibiotic that also includes P. aeruginosa and local antibacterial susceptibilities		
• Ciprofloxacin by itself does not provide adequate Gram-positive coverage • Amoxicillin/ clavulanate can be switched to clindamycin for penicillin-allergic patients	No activity against anaerobes	• Insufficient activity against pseudomonas • Has a longer half-life, which allows for once-daily dosing • In a double-blind, randomized trial by Kern WV, et al., moxifloxacin monotherapy demonstrated equivalence to ciprofloxacin + amoxicillin/ clavulanate combination therapy
On the contrary, IDSA/ASCO guidelines recommend **all fluoroquinolones be combined with amoxicillin/clavulanate** (or clindamycin if allergic to penicillins)		

Sources: Kern WV, et al. *J Clin Oncol*. 2013;31(9):1149-1156.

EMPIRIC INTRAVENOUS ANTIBIOTIC THERAPY

- **Monotherapy with an antipseudomonal beta-lactam is preferred**

Agents	Dose	Clinical Pearls
Cefepime	• 2 g IV every 8 hours	• Not active against most anaerobes and Enterococcus spp. • Mental status changes may occur • CNS penetration
Ceftazidime	• 2 g IV every 8 hours	• *Poor Gram-positive activity* • Not active against most anaerobes and Enterococcus spp. • CNS penetration
Piperacillin/ tazobactam	• 3.375 g IV every 6 hours (mild-moderate infections) or • 4.5 g IV every 6 hours (severe infections) over 30 minutes	• Anaerobic coverage • Use for suspected intra-abdominal source • Not recommended for CNS infections
Imipenem/ cilastatin sodium	• 500 mg IV every 6 hours	• Anaerobic coverage • Extended-spectrum beta-lactamase(ESBL) and serious Enterobacter infections • Use for suspected intra-abdominal source • CNS infection (meropenem) • Carbapenems may lower seizure threshold
Meropenem	• 1-2 g IV every 8 hours or 500 mg every 6 hours	

Source: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021.

WHEN TO ADD VANCOMYCIN TO THE EMPIRIC REGIMEN

- A prospective, randomized trial by European Organization for Research and Treatment of Cancer (EORTC)
  - Vancomycin as a part of initial empiric therapy
  - Vancomycin group associated with decreased fever days, but not mortality
    - Increased nephrotoxicity and hepatotoxicity
- A systematic review and meta-analysis of RCTs by Paul M, et al.
  - Antibiotics with Gram-positive coverage
  - No significant difference in mortality and overall treatment success
  - Intervention arm associated with significantly more adverse events, especially nephrotoxicity

→ **Empiric Gram-positive coverage does not provide mortality benefits and is associated with more adverse events**

Sources: EORTC. *J Infect Dis*. 1991;163(5):951-958.
Paul M, et al. *J Antimicrob Chemother*. 2005;55(4):436-444.

WHEN TO ADD VANCOMYCIN TO THE EMPIRIC REGIMEN

- **Empiric vancomycin use is reserved for patients at high risk for serious gram-positive infection**
- Clinically apparent, serious IV catheter-related infection
- Blood cultures positive for gram-positive bacteria before susceptibility testing is finalized
- Known colonization with penicillin/cephalosporin-resistant pneumococci or MRSA
- Clinical instability, pending the results of cultures
- Soft tissue infection
- Severe mucositis, if FQ prophylaxis has been given and ceftazidime is being used as empirical therapy

Sources: Freifeld AG, et al. *Clin Infect Dis*. 2011;52(4):e56-e93.
Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021.

WHEN TO ADD AMINOGLYCOSIDES TO THE EMPIRIC REGIMEN

- Broaden gram-negative activity in the empiric regimen
- Can be used in patients who are clinically unstable or are at high risk of resistant organisms

Agents	Dose	Clinical Pearl
Amikacin	• 15-20 mg/kg daily	• Consider traditional dosing in renal impairment
Gentamicin	• 5-7 mg/kg daily	
Tobramycin	• 5-7 mg/kg daily	

Sources: Madiajagane R, et al. *Natl Med J India*. 1993;6(2):67-70.
Torfoss D, et al. *J Antimicrob Chemother*. 2007;59(4):711-717.
Kiel PJ, et al. 2008;15(2):131-136.

WHEN TO MODIFY THE INITIAL EMPIRIC THERAPY

Organisms	Modifications
Methicillin-resistant Staphylococcus aureus (MRSA)	• Consider early addition of vancomycin, linezolid, or daptomycin
Vancomycin-resistant enterococcus (VRE)	• Consider early addition of linezolid or daptomycin
Extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria	• Consider early use of a carbapenem
Carbapenemase-producing organisms, including Klebsiella pneumoniae carbapenemase (KPC)	• Consider early use of meropenem-vaborbactam, ceftazidime-avibactam, or imipenem-cilastatin-relbactam

- If susceptible bacteria are not recovered from the patient after 2-3 days, the Gram-positive active agent should be discontinued
- Daptomycin should not be used for pneumonia, as it will be inactivated by pulmonary surfactant
- Adding an aminoglycoside to a broad-spectrum beta-lactam active against *P. aeruginosa* is not beneficial in regard to survival, adverse events and fungal super-infections

Sources: Tamma PD, et al. IDSA. 2022
Taplitz RA, et al. *J Clin Oncol*. 2018;36(14):1443-1453.
Paul M, et al. *Cochrane Database Syst Rev*. 2013;2013(6):CD003038

EMPIRIC ANTIFUNGAL THERAPY

WHEN TO CONSIDER EMPIRIC ANTIFUNGAL THERAPY IN PERSISTENT FN

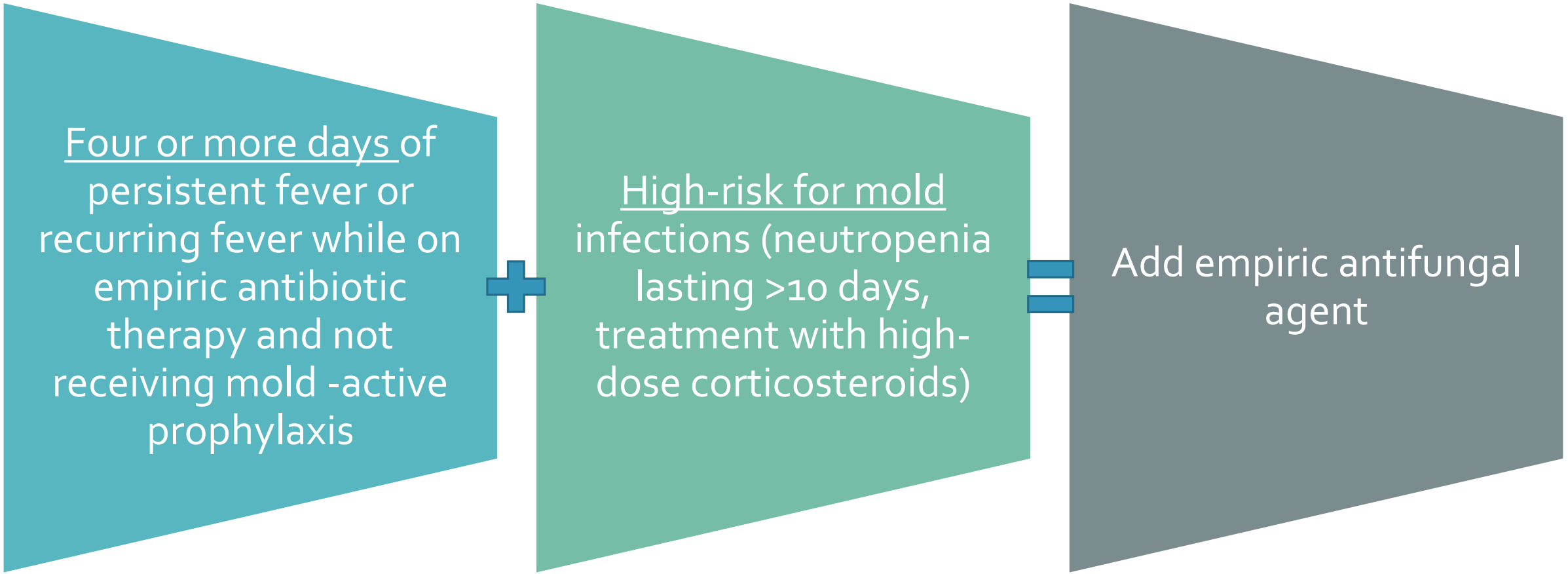
- Persistently febrile neutropenia without early detection of invasive fungal infections

NCCN Guidelines	IDSA/ASCO
• Timing varies with risk of invasive mold • High risk for mold -initiate after 4 or more days of persistent fever unless receiving active mold-active prophylaxis	• Empiric antifungal therapy after 4 or more days of persistent or recurrent fever and duration of neutropenia is expected to be > 7 days • Preemptive[1] antifungal therapy is acceptable as an alternative in a sub-set of patients

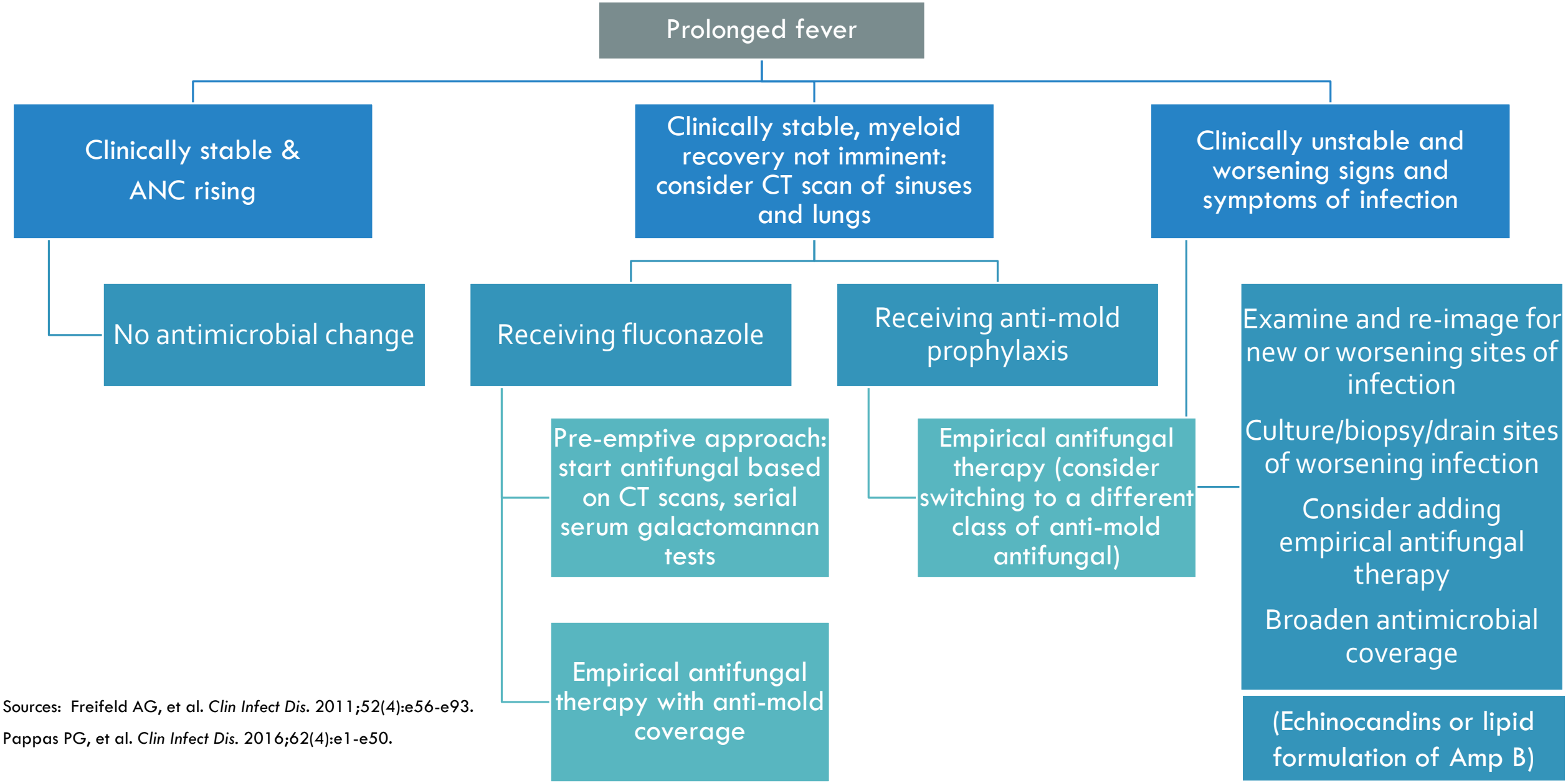
[1] Preemptive therapy is a targeted therapy for patients with additional findings suggestive of invasive fungal infection. Limited literature exists to support its use; more research is needed.
Empiric antifungal therapy, on the other hand, is non-targeted therapy for all patients with febrile neutropenia

Sources: Freifeld AG, et al. *Clin Infect Dis*. 2011;52(4):e56-e93.
Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021.

NCCN GUIDELINES FOR EMPIRIC ANTIFUNGAL THERAPY



IDSA/ASCO GUIDELINES FOR RE-EVALUATION



Sources: Freifeld AG, et al. *Clin Infect Dis.* 2011;52(4):e56-e93.

Pappas PG, et al. *Clin Infect Dis.* 2016;62(4):e1-e50.

ASSESSMENT QUESTION #5

Pharmacy Technicians

Which of the following agents is an antipseudomonal beta lactam antibiotic used in the management of febrile neutropenia?

a) Diphenhydramine
b) Acetaminophen
c) Ceftazidime
d) Levofloxacin

ASSESSMENT QUESTION #5

Pharmacy Technicians

Which of the following agents is an antipseudomonal beta lactam antibiotic used in the management of febrile neutropenia?

a) Diphenhydramine
b) Acetaminophen
c) **Ceftazidime**
d) Levofloxacin

ASSESSMENT QUESTION #6

Pharmacists and Nurses

Which of the following criteria would make a patient eligible for vancomycin empiric therapy?

a) Clinical instability, pending the results of cultures
b) Blood cultures positive for gram-negative bacteria before final identification
c) Known colonization with MSSA
d) Urinary tract infection

ASSESSMENT QUESTION #6

Pharmacists and Nurses

Which of the following criteria would make a patient eligible for vancomycin empiric therapy?

a) **Clinical instability, pending the results of cultures**
b) Blood cultures positive for gram-negative bacteria before final identification
c) Known colonization with MSSA
d) Urinary tract infection

Follow-up, persistent fever, duration of treatment

RE-EVALUATION

FOLLOW-UP

- Daily evaluation by a health care professional
  - Response to empiric antimicrobial therapy
    - Fever trends and changes in signs and/or symptoms of infections
- Time to defervesce ranges from 2 to 7 days
- Overall response to initial empiric antimicrobial therapy should be evaluated 3 to 5 days from initiation of empiric therapy
- Duration of therapy of targeted infections:
  - Skin and soft tissue: 5-14 days
  - Bloodstream infection
    - Gram-negative and Gram-positive: 7-14 days
    - *S. aureus*: 4 weeks after first negative blood culture
    - Yeast: 2 weeks or longer after first negative blood culture
  - Bacterial sinusitis: 7-14 days
  - Bacterial pneumonia: 5-14 days
  - Fungal: minimum of 2 weeks after first negative culture
  - Mold (eg, *Aspergillus*): minimum of 12 weeks
  - Viral: 7-10 days for HSV/VZV

Source: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021.

Re-evaluating patients receiving empiric therapy

Responding, clinically stable patients

- No change to the initial regimen necessary
- Can discontinue agent for Gram-positive-resistant infections if pathogen was not recovered
- Can discontinue antibiotics if febrile for at least 24 hours and ANC recovery is achieved

Febrile but otherwise hemodynamically stable patients

- Can be safely watched unless persistent/recurrent fever after 4-7 days without mold-active prophylaxis

Non-responding, clinically unstable patients

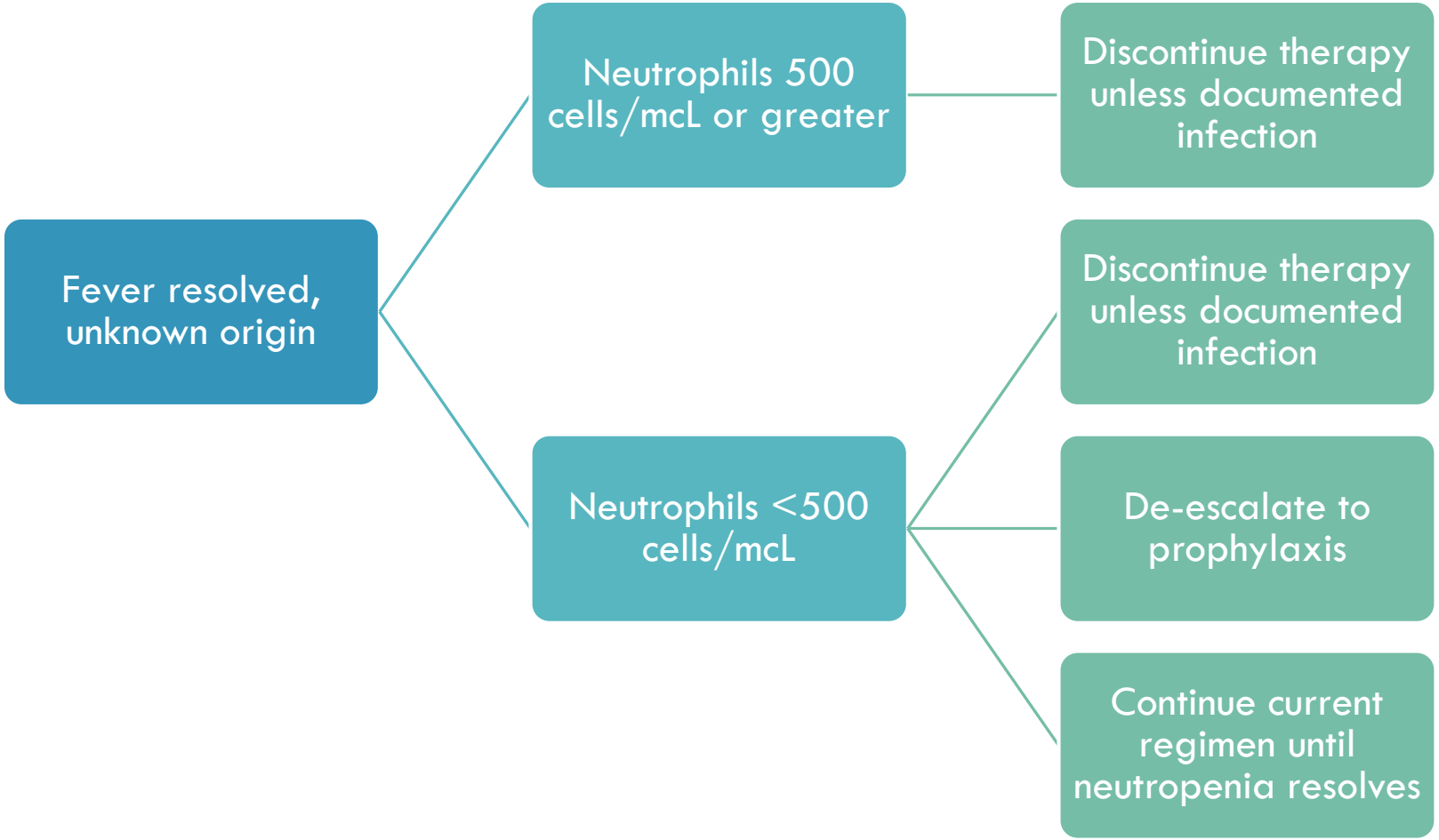
- Radiographic, culture and clinical examination data, fever trends
- Consult an infectious disease specialist
- Antimicrobial regimen broadened to include anaerobes, resistant gram-negative rods and resistant gram-positive organisms
- Antifungal therapy for fever continuing for 4 or more days

Patients with documented infections

- Targeted treatment

Source: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021.

DURATION OF THERAPY



Source: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021.

DURATION OF EMPIRIC THERAPY

Type of study	**Investigator-driven, superiority, open-label, randomized, controlled phase 4 clinical trial**
Location	6 academic hospitals in Spain
Inclusion	Adults with hematological malignancies or hematopoietic stem-cell transplantation recipients, with high-risk febrile neutropenia
Intervention	Empiric antimicrobial therapy (EAT) withdrawn after 72 h or more of apyrexia plus clinical recovery vs treatment withdrawn after neutrophil count was also 500 cells/mcL or higher
Results	• 709 patients were included • EAT free days higher in the experimental group (P=0.026) • 341 adverse events in the experimental group vs 295 in the control group (P=0.057) - mostly mild or moderate
Conclusion	EAT can be safely withdrwwn after 72 h or more of apyrexia irrespective of ANC recovery

Source: Aguilar-Guisado M, et al. *Lancet Haematol* 2017;4(12):e573-e583.

REFERENCES

- 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-e583. doi:10.1016/S2352-3026(17)30211-9
- Al-Tawfiq JA, Hinedi K, Khairallah H, et al. Epidemiology and source of infection in patients with febrile neutropenia: A ten-year longitudinal study. *J Infect Public Health*. 2019;12(3):364-366. doi:10.1016/j.jiph.2018.12.006
- Center for Disease Control and Prevention. COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/index.html. Accessed March 30, 2021.
- Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356(4):348-359. doi:10.1056/NEJMoa061094
- Cullen M, Steven N, Billingham L, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med*. 2005;353(10):988-998. doi:10.1056/NEJMoa050078
- Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. *J Clin Oncol*. 1998;16(3):1179-1187. doi:10.1200/JCO.1998.16.3.1179
- Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis*. 2011;52(4):e56-e93. doi:10.1093/cid/cir073
- Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients [published correction appears in Ann Intern Med. 2006 May 2;144(9):704]. *Ann Intern Med*. 2005;142(12 Pt 1):979-995. doi:10.7326/0003-4819-142-12_part_1-200506210-00008
- Gafter-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev*. 2012;1(1):CD004386. Published 2012 Jan 18. doi:10.1002/14651858.CD004386.pub3
- Hicheri Y, Cook G, Cordonnier C. Antifungal prophylaxis in haematology patients: the role of voriconazole. *Clin Microbiol Infect*. 2012;18 Suppl 2:1-15. doi:10.1111/j.1469-0691.2012.03772.x
- Kern WV, Marchetti O, Drgona L, et al. Oral antibiotics for fever in low-risk neutropenic patients with cancer: a double-blind, randomized, multicenter trial comparing single daily moxifloxacin with twice daily ciprofloxacin plus amoxicillin/clavulanic acid combination therapy--EORTC infectious diseases group trial XV. *J Clin Oncol*. 2013;31(9):1149-1156. doi:10.1200/JCO.2012.45.8109
- Kiel PJ, Lo M, Stockwell D, Patel GP. An evaluation of amikacin nephrotoxicity in the hematology/oncology population. *Am J Ther*. 2008;15(2):131-136. doi:10.1097/MJT.0b013e31815adfde
- Kosaka Y, Rai Y, Masuda N, et al. Phase III placebo-controlled, double-blind, randomized trial of pegfilgrastim to reduce the risk of febrile neutropenia in breast cancer patients receiving docetaxel/cyclophosphamide chemotherapy. *Support Care Cancer*. 2015;23(4):1137-1143. doi:10.1007/s00520-014-2597-1
- Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. *J Clin Oncol*. 2007;25(21):3158-3167. doi:10.1200/JCO.2006.08.8823
- Madiajagane R, Maitreyan V, Sagar TG, Shanta V. Antibiotics in febrile neutropenia: a randomized prospective comparison of two combinations. *Natl Med J India*. 1993;6(2):67-70.
- Maher DW, Lieschke GJ, Green M, et al. Filgrastim in patients with chemotherapy-induced febrile neutropenia. A double-blind, placebo-controlled trial. *Ann Intern Med*. 1994;121(7):492-501. doi:10.7326/0003-4819-121-7-199410010-00004
- Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. Version 1.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed [March 30, 2022]. To view the most recent and complete version of the guideline, go online to NCCN.org
- Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors. Version 1.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed [March 30, 2022]. To view the most recent and complete version of the guideline, go online to NCCN.org.
- Paul M, Borok S, Fraser A, Vidal L, Leibovici L. Empirical antibiotics against Gram-positive infections for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2005;55(4):436-444. doi:10.1093/jac/dki028
- Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1-e50. doi:10.1093/cid/civ933
- Paul M, Dickstein Y, Schlesinger A, Grozinsky-Glasberg S, Soares-Weiser K, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. *Cochrane Database Syst Rev*. 2013;2013(6):CD003038. Published 2013 Jun 29. doi:10.1002/14651858.CD003038.pub2
- Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host [published correction appears in Clin Infect Dis. 2014 Jul 1;59(1):144]. *Clin Infect Dis*. 2014;58(3):309-318. doi:10.1093/cid/cit816
- Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa) [published online ahead of print, 2022 Apr 19]. *Clin Infect Dis*. 2022;ciac268. doi:10.1093/cid/ciac268
- Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(14):1443-1453. doi:10.1200/JCO.2017.77.6211
- Tixagevimab and Cilgavimab (Evusheld) for Pre-Exposure Prophylaxis of COVID-19. *JAMA*. 2022;327(4):384-385. doi:10.1001/jama.2021.24931
- Torfoss D, Høiby EA, Tangen JM, et al. Tobramycin once versus three times daily, given with penicillin G, to febrile neutropenic cancer patients in Norway: a prospective, randomized, multicentre trial. *J Antimicrob Chemother*. 2007;59(4):711-717. doi:10.1093/jac/dkm003
- Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group and the National Cancer Institute of Canada-Clinical Trials Group [published correction appears in J Infect Dis 1991 Oct;164(4):832]. *J Infect Dis*. 1991;163(5):951-958.

THANK YOU!!

Soo Jin Koo, PharmD | PGY-1 Pharmacy Resident
Atlantic Health System
Soojin.koo@atlantichealth.org