Executive Summary: Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[9] Kent A. Sepkowitz,[2] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]

[1]Department of Medicine, University of Nebraska Medical Center, Omaha, Nebraska; [2]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York; [3]Department of Pediatrics, University of Rochester Medical Center, Rochester, New York; [4]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research, Seattle, Washington; [5]Division of Infectious Diseases, City of Hope National Medical Center, Duarte, California; [6]Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas M.D. Anderson Cancer Center, Houston, Texas; [7]Department of Medicine, University of Minnesota, Minneapolis, Minnesota; [8]Division of Hematology/Oncology, University of Florida, Gainesville, Florida; and [9]Departments of Medical Microbiology and Internal Medicine, the University of Manitoba, and Infection Control Services, Cancer Care Manitoba, Winnipeg, Manitoba, Canada

This document updates and expands the initial Infectious Diseases Society of America (IDSA) Fever and Neutropenia Guideline that was published in 1997 and first updated in 2002. It is intended as a guide for the use of antimicrobial agents in managing patients with cancer who experience chemotherapy-induced fever and neutropenia.

Recent advances in antimicrobial drug development and technology, clinical trial results, and extensive clinical experience have informed the approaches and recommendations herein. Because the previous iteration of this guideline in 2002, we have a developed a clearer definition of which populations of patients with cancer may benefit most from antibiotic, antifungal, and antiviral prophylaxis. Furthermore, categorizing neutropenic patients as being at high risk or low risk for infection according to presenting signs and symptoms, underlying cancer, type of therapy, and medical comorbidities has become essential to the treatment algorithm. Risk stratification is a recommended starting point for managing patients with fever and neutropenia. In addition, earlier detection of invasive fungal infections has led to debate regarding optimal use of empirical or preemptive antifungal therapy, although algorithms are still evolving.

What has not changed is the indication for immediate empirical antibiotic therapy. It remains true that all patients who present with fever and neutropenia should be treated swiftly and broadly with antibiotics to treat both gram-positive and gram-negative pathogens.

Finally, we note that all Panel members are from institutions in the United States or Canada; thus, these guidelines were developed in the context of North American practices. Some recommendations may not be as applicable outside of North America, in areas where differences in available antibiotics, in the predominant pathogens, and/or in health care–associated economic conditions exist. Regardless of venue, clinical vigilance and immediate treatment are the universal keys to managing neutropenic patients with fever and/or infection.

EXECUTIVE SUMMARY

Fever during chemotherapy-induced neutropenia may be the only indication of a severe underlying infection, because signs and symptoms of inflammation typically are attenuated. Physicians must be keenly aware of the infection risks, diagnostic methods, and antimicrobial therapies required for management of febrile patients through the neutropenic period. Accordingly, algorithmic approaches to fever and neutropenia, infection prophylaxis, diagnosis, and treatment have been

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Correspondence: Dr Alison G. Freifeld, Immunocompromised Host Program, Dept of Medicine, University of Nebraska Medical Center, Omaha, NE 68198-5400 (afreifeld@unmc.edu).

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established during the past 40 years, guided and modified by clinical evidence and experience over time.

The Infectious Diseases Society of America Fever and Neutropenia Guideline aims to provide a rational summation of these evolving algorithms. Summarized below are the recommendations made in the 2010 guideline update. A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found in the full text of the guideline.

GUIDELINE RECOMMENDATIONS FOR THE EVALUATION AND TREATMENT OF PATIENTS WITH FEVER AND NEUTROPENIA

I. What Is the Role of Risk Assessment and What Distinguishes High-risk and Low-risk Patients with Fever and Neutropenia?

Recommendations

1. Assessment of risk for complications of severe infection should be undertaken at presentation of fever (**A-II**). Risk assessment may determine the type of empirical antibiotic therapy (oral vs intravenous [IV]), venue of treatment (inpatient vs outpatient), and duration of antibiotic therapy (**A-II**).

2. Most experts consider high-risk patients to be those with anticipated prolonged (>7 days duration) and profound neutropenia (absolute neutrophil count [ANC] ⩽100 cells/mm^3 following cytotoxic chemotherapy) and/or significant medical co-morbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes. Such patients should be initially admitted to the hospital for empirical therapy (**A-II**).

3. Low-risk patients, including those with anticipated brief (⩽7 days duration) neutropenic periods or no or few co-morbidities, are candidates for oral empirical therapy (**A-II**).

4. Formal risk classification may be performed using the Multinational Association for Supportive Care in Cancer (MASCC) scoring system (**B-I**).

i. High-risk patients have a MASCC score <21 (**B-I**). All patients at high risk by MASCC or by clinical criteria should be initially admitted to the hospital for empirical antibiotic therapy if they are not already inpatients (**B-I**).

ii. Low-risk patients have a MASCC score ⩾21 (**B-I**). Carefully selected low-risk patients may be candidates for oral and/or outpatient empirical antibiotic therapy (**B-I**).

II. What Specific Tests and Cultures Should be Performed during the Initial Assessment?

Recommendations

5. Laboratory tests should include a complete blood cell (CBC) count with differential leukocyte count and platelet count; measurement of serum levels of creatinine and blood urea nitrogen; and measurement of electrolytes, hepatic transaminase enzymes, and total bilirubin (**A-III**).

6. At least 2 sets of blood cultures are recommended, with a set collected simultaneously from each lumen of an existing central venous catheter (CVC), if present, and from a peripheral vein site; 2 blood culture sets from separate venipunctures should be sent if no central catheter is present (**A-III**). Blood culture volumes should be limited to <1% of total blood volume (usually ~70 mL/kg) in patients weighing <40 kg (**C-III**).

7. Culture specimens from other sites of suspected infection should be obtained as clinically indicated (**A-III**).

8. A chest radiograph is indicated for patients with respiratory signs or symptoms (**A-III**).

III. In Febrile Patients With Neutropenia, What Empiric Antibiotic Therapy Is Appropriate and in What Venue?

Recommendations

General Considerations

9. High-risk patients require hospitalization for IV empirical antibiotic therapy; monotherapy with an anti-pseudomonal β-lactam agent, such as cefepime, a carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam, is recommended (**A-I**). Other antimicrobials (aminoglycosides, fluoroquinolones, and/or vancomycin) may be added to the initial regimen for management of complications (eg, hypotension and pneumonia) or if antimicrobial resistance is suspected or proven (**B-III**).

10. Vancomycin (or other agents active against aerobic gram-positive cocci) is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia (**A-I**). These agents should be considered for specific clinical indications, including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability.

11. Modifications to initial empirical therapy may be considered for patients at risk for infection with the following antibiotic-resistant organisms, particularly if the patient's condition is unstable or if the patient has positive blood culture results suspicious for resistant bacteria (**B-III**). These include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), extended-spectrum β-lactamase (ESBL)–producing gram-negative bacteria, and carbapenemase-producing organisms, including *Klebsiella pneumoniae* carbapenemase (KPC). Risk factors include previous infection or colonization with the organism and treatment in a hospital with high rates of endemicity.

i. MRSA: Consider early addition of vancomycin, linezolid, or daptomycin (**B-III**).

ii. VRE: Consider early addition of linezolid or daptomycin (**B-III**).

iii. ESBLs: Consider early use of a carbapenem (**B-III**).

iv. KPCs: Consider early use of polymyxin-colistin or tigecycline (**C-III**).

12. Most penicillin-allergic patients tolerate cephalosporins, but those with a history of an immediate-type hypersensitivity reaction (eg, hives and bronchospasm) should be treated with a combination that avoids β-lactams and carbapenems, such as ciprofloxacin plus clindamycin or aztreonam plus vancomycin (**A-II**).

13. Afebrile neutropenic patients who have new signs or symptoms suggestive of infection should be evaluated and treated as high-risk patients (**B-III**).

14. Low-risk patients should receive initial oral or IV empirical antibiotic doses in a clinic or hospital setting; they may be transitioned to outpatient oral or IV treatment if they meet specific clinical criteria (**A-I**).

i. Ciprofloxacin plus amoxicillin-clavulanate in combination is recommended for oral empirical treatment (**A-I**). Other oral regimens, including levofloxacin or ciprofloxacin monotherapy or ciprofloxacin plus clindamycin, are less well studied but are commonly used (**B-III**).

ii. Patients receiving fluoroquinolone prophylaxis should not receive oral empirical therapy with a fluoroquinolone (**A-III**).

iii. Hospital re-admission or continued stay in the hospital is required for persistent fever or signs and symptoms of worsening infection (**A-III**).

IV. When and How Should Antimicrobials be Modified During the Course of Fever and Neutropenia?

Recommendations

15. Modifications to the initial antibiotic regimen should be guided by clinical and microbiologic data (**A-II**).

16. Unexplained persistent fever in a patient whose condition is otherwise stable rarely requires an empirical change to the initial antibiotic regimen. If an infection is identified, antibiotics should be adjusted accordingly (**A-I**).

17. Documented clinical and/or microbiological infections should be treated with antibiotics appropriate for the site and for the susceptibilities of any isolated organisms (**A-I**).

18. If vancomycin or other coverage for gram-positive organisms was started initially, it may be stopped after 2 days if there is no evidence for a gram-positive infection (**A-II**).

19. Patients who remain hemodynamically unstable after initial doses with standard agents for neutropenic fever should have their antimicrobial regimen broadened to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria and fungi (**A-III**).

20. Low-risk patients who have initiated IV or oral antibiotics in the hospital may have their treatment approach simplified if they are clinically stable (**A-I**).

i. An IV-to-oral switch in antibiotic regimen may be made if patients are clinically stable and gastrointestinal absorption is felt to be adequate (**A-I**).

ii. Selected hospitalized patients who meet criteria for being at low risk may be transitioned to the outpatient setting to receive either IV or oral antibiotics, as long as adequate daily follow-up is ensured (**B-III**). If fever persists or recurs within 48 h in outpatients, hospital re-admission is recommended, with management as for high-risk patients (**A-III**).

21. Empirical antifungal coverage should be considered in high-risk patients who have persistent fever after 4–7 days of a broad-spectrum antibacterial regimen and no identified fever source (**A-II**).

V. How Long Should Empirical Antibiotic Therapy be Given?

Recommendations

22. In patients with clinically or microbiologically documented infections, the duration of therapy is dictated by the particular organism and site; appropriate antibiotics should continue for at least the duration of neutropenia (until ANC is $\geq$ 500 cells/mm^3) or longer if clinically necessary (**B-III**).

23. In patients with unexplained fever, it is recommended that the initial regimen be continued until there are clear signs of marrow recovery; the traditional endpoint is an increasing ANC that exceeds 500 cells/mm^3 (**B-II**).

24. Alternatively, if an appropriate treatment course has been completed and all signs and symptoms of a documented infection have resolved, patients who remain neutropenic may resume oral fluoroquinolone prophylaxis until marrow recovery (**C-III**).

VI. When Should Antibiotic Prophylaxis be Given, and With What Agents?

Recommendations

25. Fluoroquinolone prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (ANC $\leq$100 cells/mm^3 for $>$7 days) (**B-I**). Levofloxacin and ciprofloxacin have been evaluated most comprehensively and are considered to be roughly equivalent, although levofloxacin is preferred in situations with increased risk for oral mucositis-related invasive viridans group streptococcal infection. A systematic strategy for monitoring the development of fluoroquinolone resistance among gram-negative bacilli is recommended (**A-II**).

26. Addition of a gram-positive active agent to fluoroquinolone prophylaxis is generally not recommended (**A-I**).

27. Antibacterial prophylaxis is not routinely recommended for low-risk patients who are anticipated to remain neutropenic for $<$7 days (**A-III**).

VII. What Is the Role of Empirical or Pre-emptive Antifungal Therapy and Which Antifungal Should be Used?

Recommendations

High risk

28. Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be >7 days **(A-I).** Data are insufficient to recommend a specific empirical antifungal agent for a patient already receiving anti-mold prophylaxis, but switching to a different class of anti-mold antifungal that is given intravenously should be considered **(B-III)**.

29. Preemptive antifungal management is acceptable as an alternative to empirical antifungal therapy in a subset of high-risk neutropenic patients. Those who remain febrile after 4–7 days of broad-spectrum antibiotics but are clinically stable, have no clinical or chest and sinus computed tomography (CT) signs of fungal infection, have negative serologic assay results for evidence of invasive fungal infection, and have no recovery of fungi (such as *Candida* or *Aspergillus* species) from any body site may have antifungal agents withheld **(B-II)**. Antifungal therapy should be instituted if any of these indicators of possible invasive fungal infection are identified.

Low Risk

30. In low-risk patients, the risk of invasive fungal infection is low, and therefore routine use of empirical antifungal therapy is not recommended **(A-III).**

VIII. When Should Antifungal Prophylaxis be Given and With What Agents?

Recommendations

High risk

31. Prophylaxis against *Candida* infection is recommended in patient groups in whom the risk of invasive candidal infection is substantial, such as allogeneic hematopoietic stem cell transplant (HSCT) recipients or those undergoing intensive remission-induction or salvage-induction chemotherapy for acute leukemia **(A-I)**. Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin are all acceptable alternatives.

32. Prophylaxis against invasive *Aspergillus* infections with posaconazole should be considered for selected patients ⩾13 years of age who are undergoing intensive chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) in whom the risk of invasive aspergillosis without prophylaxis is substantial **(B-I)**.

33. Prophylaxis against *Aspergillus* infection in pre-engraftment allogeneic or autologous transplant recipients has not been shown to be efficacious. However, a mold-active agent is recommended in patients with prior invasive aspergillosis **(A-III)**, anticipated prolonged neutropenic periods of at least 2 weeks **(C-III),** or a prolonged period of neutropenia immediately prior to HSCT **(C-III)**.

Low Risk

34. Antifungal prophylaxis is not recommended for patients in whom the anticipated duration of neutropenia is <7 days **(A-III).**

IX. What Is the Role of Antiviral Prophylaxis and What Virus Infections Require Antiviral Treatment?

Recommendations

35. Herpes simplex virus (HSV)–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive acyclovir antiviral prophylaxis **(A-I).**

36. Antiviral treatment for HSV or varicella-zoster virus (VZV) infection is only indicated if there is clinical or laboratory evidence of active viral disease **(C-III).**

37. Respiratory virus testing (including testing for influenza, parainfluenza, adenovirus, respiratory syncytial virus [RSV], and human metapneumovirus) and chest radiography are indicated for patients with upper respiratory symptoms (eg, coryza) and/or cough **(B-III).**

38. Yearly influenza vaccination with inactivated vaccine is recommended for all patients being treated for cancer **(A-II).** Optimal timing of vaccination is not established, but serologic responses may be best between chemotherapy cycles (>7 days after the last treatment) or >2 weeks before chemotherapy starts **(B-III).**

39. Influenza virus infection should be treated with neuraminidase inhibitors if the infecting strain is susceptible **(A-II)**. In the setting of an influenza exposure or outbreak, neutropenic patients presenting with influenza-like illness should receive treatment empirically **(C-III).**

40. Routine treatment of RSV infection in neutropenic patients with upper respiratory disease should not be given **(B-III).**

X. What Is the Role of Hematopoietic Growth Factors (G-CSF or GM-CSF) in Managing Fever and Neutropenia?

Recommendations

41. Prophylactic use of myeloid colony-stimulating factors (CSFs; also referred to as hematopoietic growth factors) should be considered for patients in whom the anticipated risk of fever and neutropenia is ⩾20% **(A-II).**

42. CSFs are not generally recommended for treatment of established fever and neutropenia **(B-II)**.

XI. How are Catheter-Related Infections Diagnosed and Managed in Neutropenic Patients?

Recommendation

43. Differential time to positivity (DTP) >120 min of qualitative blood cultures performed on specimens simultaneously drawn from the CVC and a vein suggests a central line–associated blood stream infection (CLABSI) **(A-II).**

44. For CLABSI caused by *S. aureus*, *P. aeruginosa,* fungi, or mycobacteria, catheter removal is recommended in addition to systemic antimicrobial therapy for at least 14 days **(A-II).** Catheter removal is also recommended for tunnel infection or port pocket site infection, septic thrombosis, endocarditis, sepsis with hemodynamic instability, or bloodstream infection that persists despite ⩾72 h of therapy with appropriate antibiotics **(A-II)**.

45. For documented CLABSI caused by coagulase-negative staphylococci, the catheter may be retained using systemic therapy with or without antibiotic lock therapy **(B-III).**

46. Prolonged treatment (4–6 weeks) is recommended for complicated CLABSI, defined as the presence of deep tissue infection, endocarditis, septic thrombosis **(A-II)** or persistent bacteremia or fungemia occurring >72 h after catheter removal in a patient who has received appropriate antimicrobials (**A-II** for *S. aureus*, **C-III** for other pathogens).

47. Hand hygiene, maximal sterile barrier precautions, and cutaneous antisepsis with chlorhexidine during CVC insertion are recommended for all CVC insertions **(A-I).**

XII. What Environmental Precautions Should be Taken When Managing Febrile Neutropenic Patients?

Recommendations

48. Hand hygiene is the most effective means of preventing transmission of infection in the hospital **(A-II).**

49. Standard barrier precautions should be followed for all patients, and infection-specific isolation should be used for patients with certain signs or symptoms **(A-III).**

50. HSCT recipients should be placed in private (ie, single-patient) rooms **(B-III).** Allogeneic HSCT recipients should be placed in rooms with >12 air exchanges/h and high-efficiency particulate air (HEPA) filtration **(A-III)**.

51. Plants and dried or fresh flowers should not be allowed in the rooms of hospitalized neutropenic patients **(B-III)**.

52. Hospital work exclusion policies should be designed to encourage health care workers (HCWs) to report their illnesses or exposures **(A-II)**.

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances

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