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ASCO SPECIAL ARTICLE

Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update

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This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at *www.asco.org/supportive-care-guidelines*.

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ABSTRACT

Purpose
To provide an updated joint ASCO/Infectious Diseases Society of America (IDSA) guideline on antimicrobial prophylaxis for adult patients with immunosuppression associated with cancer and its treatment.

Methods
ASCO and IDSA convened an update Expert Panel and conducted a systematic review of relevant studies from May 2011 to November 2016. The guideline recommendations were based on the review of evidence by the Expert Panel.

Results
Six new or updated meta-analyses and six new primary studies were added to the updated systematic review.

Recommendations
Antibacterial and antifungal prophylaxis is recommended for patients who are at high risk of infection, including patients who are expected to have profound, protracted neutropenia, which is defined as < 100 neutrophils/μL for > 7 days or other risk factors. Herpes simplex virus–seropositive patients undergoing allogeneic hematopoietic stem-cell transplantation or leukemia induction therapy should receive nucleoside analog-based antiviral prophylaxis, such as acyclovir. *Pneumocystis jirovecii* prophylaxis is recommended for patients receiving chemotherapy regimens that are associated with a $> 3.5\%$ risk for pneumonia as a result of this organism (eg, those with ≥ 20 mg prednisone equivalents daily for ≥ 1 month or on the basis of purine analog usage). Treatment with a nucleoside reverse transcription inhibitor (eg, entecavir or tenofovir) is recommended for patients at high risk of hepatitis B virus reactivation. Recommendations for vaccination and avoidance of prolonged contact with environments that have high concentrations of airborne fungal spores are also provided within the updated guideline. Additional information is available at *www.asco.org/supportive-care-guidelines*.

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INTRODUCTION

Patients undergoing cytotoxic chemotherapy and hematopoietic stem-cell transplantation (HSCT) are at risk for infection, particularly during the period of neutropenia.[1] Neutrophils are critical for providing host defense against infection, particularly bacterial and fungal infection. The risk of infection increases with the depth and duration of neutropenia, with the greatest risk occurring in patients who experience profound, prolonged neutropenia after chemotherapy, which is most likely to occur in the period before engraftment during HSCT and after induction chemotherapy for acute leukemia.[2] Fever can be an important indicator and is often the only sign or symptom of infection, although clinicians should also be mindful that severely or profoundly neutropenic patients may present with suspected infection in an afebrile state or even hypothermic. Prevention and appropriate management of febrile neutropenia (FN) is important because the rate of major complications (eg, hypotension, acute renal, respiratory, or heart failure) in the context of FN is approximately 25% to 30% and mortality up to 11%.[3,4] In the setting of severe sepsis or septic shock, the hospital mortality rate may be as high as

ASSOCIATED CONTENT

Appendix
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THE BOTTOM LINE

Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update

Guideline Question

What antimicrobial prophylaxis is appropriate for immunosuppressed patients with cancer?

Target Population

Patients receiving treatment of cancer as inpatients or outpatients who are experiencing immune suppression or increased susceptibility to infection.

Target Audience

Oncologists, infectious disease specialists, emergency medicine physicians, nurses, and advanced practice providers who may treat patients with immunosuppression resulting from cancer treatment.

Methods

An Expert Panel convened to update clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Key Recommendations

A summary of antimicrobial prophylaxis recommendations can be found here and in Table 1.

Antimicrobial prophylaxis:

Recommendation 1.1: Risk of febrile neutropenia (FN) should be systematically assessed (in consultation with infectious disease specialists as needed), including patient-, cancer-, and treatment-related factors (Table 2). (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong.)

Recommendation 1.2: Antibiotic prophylaxis with a fluoroquinolone is recommended for patients who are at high risk for FN or profound, protracted neutropenia (eg, most patients with acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or hematopoietic stem-cell transplantation (HSCT) treated with myeloablative conditioning regimens). Antibiotic prophylaxis is not routinely recommended for patients with solid tumors. (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate.)

Recommendation 2.1: Antifungal prophylaxis with an oral triazole or parenteral echinocandin is recommended for patients who are at risk for profound, protracted neutropenia, such as most patients with AML/MDS or HSCT. Antifungal prophylaxis is not routinely recommended for patients with solid tumors. Additional distinctions between recommendations for invasive candidiasis and invasive mold infection are provided within the full text of the guideline. (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate.)

Recommendation 2.2: Prophylaxis is recommended, eg, trimethoprim-sulfamethoxazole (TMP-SMX), for patients receiving chemotherapy regimens associated with $>$ 3.5% risk for pneumonia from *Pneumocystis jirovecii* (eg, those with $\geq$ 20 mg prednisone equivalents daily for $\geq$ 1 month or those on the basis of purine analogs). (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong.[7])

Recommendation 3.1: Herpes simplex virus–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive prophylaxis with a nucleoside analog (eg, acyclovir). (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong.[7])

Recommendation 3.2: Treatment with a nucleoside reverse transcription inhibitor (eg, entecavir or tenofovir) is recommended for patients who are at high risk of hepatitis B virus reactivation. (Type: consensus-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate.)

Recommendation 3.3: Yearly influenza vaccination with inactivated vaccine is recommended for all patients receiving chemotherapy for malignancy and all family and household contacts and health care providers. (Type: consensus-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate.)

Recommendation 3.4: The Expert Panel also supports other vaccination recommendations for immunosuppressed adult oncology patients that are contained within the IDSA guideline for vaccination of the immunosuppressed host.[16,62]

(continued on following page)

THE BOTTOM LINE (CONTINUED)

(Type: consensus-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate.)

Additional recommended precautions

Recommendation 4.1: All health care workers should comply with hand hygiene and respiratory hygiene/cough etiquette guidelines to reduce the risk for aerosol- and direct or indirect contact–based transmission of pathogenic microorganisms in the health care setting. (Type: consensus-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong.)

Recommendation 4.2: Outpatients with neutropenia from cancer therapy should avoid prolonged contact with environments that have high concentrations of airborne fungal spores (eg, construction and demolition sites, intensive exposure to soil through gardening or digging, or household renovation). (Type: consensus-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong.)

Please see the complete guideline document that follows this summary for further details and qualifying statements to the recommendations.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

Additional Resources: More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net

50%.[5] In addition to the depth and duration of neutropenia, other factors that contribute to immunosuppression and/or the risk of infection in this patient population include impaired integrity of mucocutaneous barriers—catheters or mucositis; type of treatment or conditioning regimens; metabolic perturbations, such as diabetes or uremia; the presence of immunomodulating viruses; the presence of graft-versus-host disease (GVHD); and perturbation of the microbiome.

Antimicrobial prophylaxis is an intervention that can reduce the risk of infection in immunosuppressed patients; however, as a result of drug-related adverse effects, as well as concerns with antimicrobial resistance, cost considerations, and the physiologic importance to the host of maintaining equilibrium in the diversity and density of the host microbiome, the decision to administer prophylaxis requires balancing benefits and harms. The previous version of this guideline recommended antibacterial and antifungal prophylaxis for higher-risk patients and that there was not a high enough baseline risk of FN and infection-related mortality in lower risk patients to warrant the routine administration of these agents.[6] This version of the guideline includes updated meta-analyses of antimicrobial interventions for prevention of FN.

This update of the 2013 ASCO guidelines for Antimicrobial Prophylaxis for Immunosuppression in Adults Treated for Malignancy is being carried out in partnership with the Infectious Diseases Society of America (IDSA).[6,7] ASCO methodology relies on the analysis of strength and quality of evidence; IDSA employs the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for assessing the quality of evidence and developing evidence-based recommendations.[8] This guideline employs the ASCO methodology and grading system. This guideline cannot be considered a comprehensive resource on the prevention of infection in patients with cancer. For guidance on outpatient management of FN, please consult the recently updated joint ASCO/IDSA guideline, Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy.[9] For recommendations on the use of colony-stimulating factors (CSFs) in patients with solid tumors or lymphoma, refer to Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update.[10] For more specific guidelines on the prevention and treatment of infections in stem-cell transplant recipients, the reader is advised to consult American Society for Blood and Marrow Transplantation/IDSA guidelines.[11] A summary of the key recommendations contained within this guideline can be found in the Bottom Line box.

GUIDELINE QUESTIONS

This clinical practice guideline addresses the following clinical questions:

1. Does antibacterial prophylaxis with a fluoroquinolone, compared with placebo, no intervention, or another class of antibiotic reduce the incidence of and mortality related to FN?
2. Does antifungal (antiyeast or antimold) prophylaxis with an oral triazole or parenteral echinocandin, compared with no prophylaxis or another treatment option, reduce the incidence of and mortality related to FN?

3. Is other prophylaxis, eg, antiviral, more effective than placebo/no treatment for higher-risk immunosuppressed patients with cancer?
4. Are precautions such as neutropenic diet, etc., more effective than no intervention for prophylaxis of infection in afebrile neutropenic outpatients?

METHODS

Guideline Update Development Process

This update of the 2013 ASCO guidelines for Antimicrobial Prophylaxis for Immunosuppression in Adults Treated for Malignancy was performed in partnership with IDSA.[6,7] The Expert Panel (Appendix Table A1, online only) met via teleconference and/or Webinar and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee before publication. In addition, this guideline was reviewed and approved by the IDSA Board of Directors. All funding for the administration of the project was provided by ASCO.

Recommendations were developed by an Expert Panel with multidisciplinary representation, including expertise in medical oncology, hematology, infectious diseases, and nursing. The Expert Panel also included a patient representative and an ASCO guidelines staff member with expertise in health research methodology. A systematic review of Medline conducted with the PubMed search engine—May 2011 to November 2016—was conducted. Articles were selected for inclusion in the systematic review if they were randomized clinical trials of prophylactic interventions for microbial infections that patients with neutropenia or other types of immunosuppression are predisposed to, including bacterial infections, fungal infections caused by *Candida spp and Aspergillus spp*,[12] and some viral infections. Box 1

Table 1. Summary of Recommendations for Antimicrobial Prophylaxis

Type of Prophylaxis	Population	Recommendation	Timing of Prophylaxis
Antibacterial	Patients at high risk of febrile neutropenia (Table 2) or profound, protracted neutropenia	Fluoroquinolone prophylaxis is recommended	During period of expected neutropenia
Antifungal	Patients at high risk of febrile neutropenia (Table 2) or profound, protracted neutropenia Patients with GVHD[14]	Oral triazole or parenteral echinocandin prophylaxis is recommended; a mold-active triazole is recommended when the risk of invasive aspergillosis is > 6%, such as in patients with AML/MDS or during treatment of GVHD[14]	During period of expected neutropenia
	Patients receiving chemotherapy regimens associated with > 3.5% risk for pneumonia from *Pneumocystis jirovecii* (eg, those with ≥ 20 mg prednisone equivalents daily for ≥ 1 month or those on the basis of purine analogs)	Prophylaxis, eg, trimethoprim-sulfamethoxazole (TMP-SMX), is recommended	Postmyeloid reconstitution or engraftment after stem-cell transplantation, particularly in the setting of postengraftment augmented immunosuppression (for the treatment of GVHD)
Antiviral	HSV-seropositive patients undergoing HSCT or leukemia induction therapy	Antiviral prophylaxis with a nucleoside analog is recommended (eg, acyclovir)	Until recovery of the WBC count or resolution of mucositis, whichever occurs later; duration can be extended for persons with frequent recurrent HSV infections or those with GVHD, or can be continued as VZV prophylaxis for up to 1 year
	Patients at substantial risk of reactivation of HBV infection	Treatment with a nucleoside reverse transcription inhibitor (eg, entecavir or tenofovir) is recommended	See updated ASCO HBV Provisional Clinical Opinion[15]
	Any individuals treated with chemotherapy for malignancy and family and household contacts	Administration of inactivated influenza vaccine is recommended for household contacts and health care providers	Optimal timing of vaccination for patients being treated for cancer is not established, but serologic responses may be best between chemotherapy cycles (> 7 days after the last treatment) or > 2 weeks before chemotherapy starts[7] Patients with cancer and their household contacts should be immunized annually[7] Influenza vaccination response seems to be best in HSCT recipients if vaccinated > 6 months after transplantation[7]
	Immunosuppressed adult oncology patients	The Expert Panel also supports other vaccination recommendations for immunosuppressed adult oncology patients that are contained within the IDSA guideline for vaccination of the immunosuppressed host[16]	Not applicable

Abbreviations: AML/MDS, acute myeloid leukemia/myelodysplastic syndrome; GVHD, graft-versus-host disease; HBV, hepatitis B virus; HSCT, hematopoietic stem-cell transplantation; HSV, herpes simplex virus; IDSA, Infectious Diseases Society of America.

lists the definitions for fever and neutropenia that were used by the Expert Panel.

Box 1. Definitions of fever and neutropenia

Fever in neutropenic patients is defined as a single oral temperature of ≥ 38.3°C (101°F) or a temperature of ≥ 38.0°C (100.4°F) sustained over a 1-hour period.[7] Neutropenia is defined as an absolute neutrophil count < 1,000/μL (equivalent to < 1.0×10^9/L), severe neutropenia as absolute neutrophil count < 500/μL (equivalent to < 0.5×10^9/L), and profound neutropenia as < 100/μL (equivalent to < 0.1×10^9/L). The period of neutropenia is considered protracted if it lasts for ≥ 7 days.

Articles were excluded from the systematic review if they were meeting abstracts not subsequently published in peer-reviewed journals; editorials, commentaries, letters, news articles, case reports, or narrative reviews; or published in a non-English language.

The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[13] In addition, a guideline implementation review was conducted. On the basis of the implementation review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation (Methodology Supplement).

Detailed information about the methods used to develop this guideline update is available in the Methodology Supplement at www.asco.org/supportive-care-guidelines, including an overview (eg, panel composition, development process, and revision dates); literature search and data extraction; the recommendation development process (GLIDES and BRIDGE-Wiz); and quality assessment.

Table 2. Factors to Consider in Assessing Risk of a Febrile Neutropenic Episode in Patients Undergoing Cytotoxic Chemotherapy for Malignancy

Factors Related To	Factor	Effect on Risk	
Patient characteristics	Advanced age	Risk increases if age ≥ 65 years[17]	
	Performance status	Risk increases if ECOG performance score ≥ 2[17]	
	Nutritional status	Risk increases if albumin < 35 g/L[18,19]	
	Prior FN episode	Risk in cycles 2-6 is four-fold greater if FN episode occurs in cycle 1[20]	
	Comorbidities	FN odds increase by 27%, 67%, and 125% for one, two, or three or more comorbidities, respectively[17,21]	
Underlying malignancy	Cancer diagnosis	Diagnosis	Reported FN rates (%)
		Acute leukemia/MDS	85.0-95.0[22-25]
		High-grade lymphoma	35.0-71.0*.[26]
		Soft tissue sarcoma	27.0 (95% CI, 19.0 to 34.5)[20,21,27,28]
		NHL/myeloma	26.0 (95% CI, 22.0 to 29.0)[20,21,27,28]
		Germ-cell carcinoma	23.0 (95% CI, 16.6 to 29.0)[20,21,27,28]
		Hodgkin lymphoma	15.0 (95% CI, 6.6 to 24.0)[20,21,27,28]
		Ovarian carcinoma	12.0 (95% CI, 6.6 to 17.7)[20,21,27,28]
		Lung cancers	10.0 (95% CI, 9.8 to 10.7)[20,21,27,28]
		Colorectal cancers	5.5 (95% CI, 5.1 to 5.8)[20,21,27,28]
		Head and neck carcinoma	4.6 (95% CI, 1.0 to 8.2)[20,21,27,28]
		Breast cancer	4.4 (95% CI, 4.1 to 4.7)[20,21,27,28]
		Prostate cancer	1.0 (95% CI, 0.9 to 1.1)[20,21,27,28]
	Cancer stage	Risk increases for advanced stage (≥ 2)[4]	
	Remission status	Risk increases if not in remission[24,29]	
	Cancer treatment response	Risk is lowest if patient has a CR	
		If patient has a PR, FN risk is greater for acute leukemia than for solid tissue malignancies[24]	
		FN risk is higher if persistent, refractory, or progressive disease despite treatment[30,31]	
Treatment of malignancy	Cytotoxic regimen	Risk is higher with regimens that administer:	
		Anthracyclines at doses ≥ 90 mg/m^2	
		Cisplatin at doses ≥ 100 mg/m^2	
		Ifosfamide at doses ≥ 9 g/m^2	
		Cyclophosphamide at doses ≥ 1 g/m^2	
		Etoposide at doses ≥ 500 mg/m^2	
		Cytarabine at doses ≥ 1 g/m^2	
		High dose density	
		Anthracycline + taxane, and cyclophosphamide or gemcitabine, for breast cancer	
	Dose intensity	Increased risk if > 85% of scheduled doses are administered[28,32]	
	Degree and duration of GI and/or oral mucositis	Risk is greatest if NCI mucositis grade is ≥ 3 (GI) or if peak score on OMAS is ≥ 2[25,33,34]	
	Degree and duration of cytopenia	Profound, protracted neutropenia	ANC < 100/μL for ≥ 7 days[35-37]
		Lymphopenia	ALC < 700/μL (ANC surrogate)[27,38]
		Monocytopenia	AMC < 150/μL (ANC surrogate)[39]

Abbreviations: ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; CHOP, cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine (Oncovin), prednisone; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FN, febrile neutropenia; MDS, myelodysplastic syndrome; NCI, National Cancer Institute; NHL, non-Hodgkin lymphoma; OMAS, oral mucositis assessment scale; PR, partial response
*Grade 3 and 4 neutropenia. Treatment included colony-stimulating factors and antimicrobial prophylaxis. Rate of neutropenia varied by chemotherapy regimen.

The ASCO Expert Panel and guidelines staff work with co-chairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO determines the need to update. The Methodology Supplement (available at www.asco.org/supportive-care-guidelines) provides additional information about the ASCO Signals approach to updating.

This is the most recent information as of the publication date. Visit the ASCO Guidelines Web site at www.asco.org/supportive-care-guidelines to submit new evidence.

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Guideline and Conflicts of Interest. The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RECOMMENDATIONS

Table 1 provides a summary of antimicrobial prophylaxis recommendations.

CLINICAL QUESTION 1

Antibacterial Prophylaxis. Does antibacterial prophylaxis with a fluoroquinolone, compared with placebo, no intervention, or another class of antibiotic, reduce the incidence of and mortality as a result of febrile episodes in patients with cancer?

Recommendation 1.1. Risk of FN should be systematically assessed (in consultation with infectious disease specialists as needed), including patient-, cancer-, and treatment-related factors (Table 2). (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong.)

Recommendation 1.2. Antibiotic prophylaxis with a fluoroquinolone is recommended for patients who are at high risk for FN or profound, protracted neutropenia—for example, patients with acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or HSCT treated with myeloablative conditioning regimens. Antibiotic prophylaxis is not routinely recommended for patients with solid tumors. (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate.)

Qualifying Statements.

- Antibacterial prophylaxis is recommended during the expected period of neutropenia in patients who meet the proposed criteria for use.
- Antibacterial prophylaxis is not recommended for patients who are at low risk of profound, protracted neutropenia.
- Antibacterial and antifungal prophylaxis would generally not be indicated when CSF prophylaxis effectively reduces the depth and duration of neutropenia.[6]
- Fluoroquinolone-based antibacterial prophylaxis may have limited utility among matched-related HSCT on the basis of reduced-intensity conditioning regimens.[40]
- Fluoroquinolone resistance rates among community-acquired Enterobacteriaceae isolates in the United States have risen from < 1% to as high as 30% during the decade from the late 1990s to 2009.[41] GI colonization by fluoroquinolone-resistant—and extended-spectrum β-lactamase–positive—gram-negative bacilli has been a risk factor for bacteremic events in the setting of GI mucositis, and fluoroquinolone resistance may result in inappropriate initial empirical antibacterial therapy and increased all-cause mortality.[42,43] A threshold prevalence of fluoroquinolone resistance among *Escherichia coli* isolates above which the protective efficacy of fluoroquinolone prophylaxis may be limited has not been defined.[44]
- The activity of fluoroquinolone prophylaxis on the intestinal microbiome is to select not only for fluoroquinolone-resistant, gram-negative bacilli, but also for *Clostridium difficile* and enterococci.[45] Clinicians must be mindful of the clinical syndromes associated with these pathogens and appropriately tailor their therapeutic approaches.

Literature review update. An updated systematic review of antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients after chemotherapy included 109 studies that compared antibiotic prophylaxis options with each other or placebo or no intervention.[46] A quality assessment conducted by the review authors concluded that the quality of the outcome data was generally moderate to high. Detailed characteristics of included trials are included in the full systematic review publication.[46]

In the subgroup of patients who were at higher risk as defined earlier, quinolone prophylaxis resulted in significant reductions in all-cause mortality (relative risk [RR], 0.57; 95% CI, 0.4 to 0.82) and febrile patients/episodes (RR, 0.79; 95% CI, 0.69 to 0.9). In the lower-risk subgroup of patients with solid tumors, quinolone prophylaxis also resulted in significant reductions in all-cause

mortality (RR, 0.48; CI 95%, 0.26 to 0.88) and febrile patients/episodes (RR, 0.57; 95% CI, 0.43 to 0.76). The number-needed-to-treat to prevent one death from any cause was 29 for the high-risk group compared with 63 for the lower-risk group, and baseline risk of all-cause mortality was approximately 2.5 times higher in the former group. Infection-related mortality was also significantly improved with quinolone prophylaxis in the high-risk group (RR, 0.53; 95% CI, 0.32 to 0.86), whereas this outcome was uncertain in the solid tumors group because of a low number of events. Across subgroups, more adverse events, mostly including nausea and diarrhea, were reported in the treatment group.

Clinical interpretation. Fluoroquinolones were recommended over trimethoprim-sulfamethoxazole (TMP-SMX) in the previous version of this guideline because the former drug class results in fewer adverse events that lead to discontinuation of treatment. Update panel members continue to be supportive of this recommendation on the basis of updated results from the review described above. Two main studies[20,47] provided the majority of the data for that analysis, and no large studies of similar significance have been found in this guideline update. Whereas a significant reduction in FN incidence and mortality was found in both high- and low-risk populations outlined in Clinical Question 1, the benefits (eg, infection prevention and decreased all-cause mortality) did not sufficiently outweigh the harms (emergence of resistance, *C. difficile* infection, antibiotic-associated adverse effects) in patients with solid tumors/lymphoma to justify the recommendation of fluoroquinolone prophylaxis for all patients in this group. The higher incidence of all-cause mortality and the lower number needed to treat led the panel to conclude that the benefits of routine fluoroquinolone prophylaxis would outweigh the harms for high-risk patients who were undergoing treatment for acute leukemia or stem-cell transplantation. Fluoroquinolone prophylaxis may also be recommended for some patients with solid tumors or lymphoma who are expected to experience profound neutropenia for at least 7 days and for whom granulocyte CSF is not being prescribed. Notwithstanding, the US Food and Drug Administration, on July 26, 2016, issued an updated warning to clinicians that advised that fluoroquinolone antibacterial agents have been associated with disabling and potentially permanent adverse effects involving tendons, muscles, joints, peripheral nerves, and the CNS, and that these agents should be reserved for patients with serious bacterial infections for whom the benefits outweigh the harms or for less serious bacterial infections for which there may be no other treatment options.[48] In the context of this guideline, clinicians should consider the desired fluoroquinolone-driven treatment outcome, the subgroup of neutropenic patients in which the treatment outcome is desired, and these updated warnings.

For patients who are intolerant or allergic to fluoroquinolones, cefpodoxime has been used as an alternative agent for neutropenic prophylaxis.[49]

CLINICAL QUESTION 2

Antifungal Prophylaxis. Does antifungal prophylaxis with an oral triazole or parenteral echinocandin, compared with no prophylaxis or another treatment option, reduce the incidence of and mortality as a result of febrile episodes in patients with cancer?

Recommendation 2.1. Antifungal prophylaxis with an oral triazole or parenteral echinocandin is recommended for patients who are at risk for profound, protracted neutropenia, such as most patients with AML/MDS or undergoing HSCT. Prophylaxis is not routinely recommended for patients with solid tumors. (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate.)

Qualifying Statements.

- Antifungal prophylaxis is recommended during the expected period of neutropenia in those patients who are anticipated to have profound, protracted neutropenia and grade III or IV mucositis where the risk for invasive candidiasis is high.
- Clinicians should be able to differentiate the risks for invasive candidiasis from the risks for invasive mold infection. Fluconazole, which is active against yeast but not mold, has for the most part been effective in reducing the risks of the former, but not the latter. Examples of mold-active agents include echinocandins and other azole antifungals, such as posaconozole, voriconozole, or isavuconazole.
- A mold-active triazole is recommended where the risk of invasive aspergillosis is $> 6\%$, such as in patients with AML/MDS during the neutropenic period associated with chemotherapy.
- Invasive mold infection risk is now observed to be greater in late-stage postallogeneic SCT, and a mold-active antifungal should be considered in this context (eg, posaconazole) and/or in the context of GVHD.[14,50-53]
- Antifungal prophylaxis is not recommended for patients who are at low risk of profound, protracted neutropenia.
- Antibacterial and antifungal prophylaxis would generally not be indicated when CSF prophylaxis effectively reduces the depth and duration of neutropenia.[6]

Recommendation 2.2. Prophylaxis is recommended, eg, TMP-SMX—for patients receiving chemotherapy regimens associated with $> 3.5\%$ risk for pneumonia from *Pneumocystis jirovecii* (eg, those with ≥ 20 mg prednisone equivalents daily for ≥ 1 month or those on the basis of purine analogs. (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong.)

Qualifying Statement.

- Alternatives such as dapsone, aerosolized pentamidine, or atovaquone are options for individuals who may be hypersensitive to sulfonamides or unable to tolerate TMP-SMX for other reasons.

Literature review update and analysis. An updated Cochrane review, which included 29 trials of antifungal prophylaxis and three trials of empirically administered antifungals in patients with cancer with neutropenia found no significant difference between antifungals and placebo or no treatment of all-cause mortality at approximately 3 months (RR, 0.94; 95% CI, 0.81 to 1.09); however, there was a significant effect for death related to fungal infection (RR, 0.52; 95% CI, 0.38 to 0.71) and invasive infections (RR, 0.50; 95% CI, 0.39 to 0.64).[54] Results of a subgroup analysis of recipients of allogeneic HSCT demonstrated no significant difference in all-cause mortality (RR, 0.71; 95% CI, 0.49 to 1.04) using follow-up numbers from Gotzsche et al.[54] Baseline rates of fungal infections in the control groups were 7.6% (all patients receiving HSCT and chemotherapy) and 20% (patients

receiving HSCT only). In a subgroup analysis, Robenshtok et al[55] did not find a significant difference in all-cause mortality for autologous and allogeneic HSCT combined (RR, 0.67; 95% CI, 0.42 to 1.09) or patients with acute leukemia (RR, 0.88; 95% CI, 0.74 to 1.06); however, a difference was found in fungal-related mortality for allogeneic HSCT (RR, 0.52; 95% CI, 0.27 to 0.99).

Evidence is emerging about the risk of infection with newer cancer therapy options. A retrospective review of the medical records of 740 patients with melanoma who received immune checkpoint blockers found that serious infection occurred in 54 patients (7.3%). The main risk factors for infection were the receipt of corticosteroids and/or infliximab.[56] The Expert Panel also noted that, according to manufacturers, serious *pneumocystis jirovecii pneumonia* infections occurred in 0.6% of 317 patients who were treated with copanlisib monotherapy[57] and in < 1% of patients who were treated with idelalisib.[58]

Clinical interpretation. The previous version of this guideline recommended antifungal prophylaxis when there is a substantial risk for invasive fungal infection. This revised guideline reaffirms this recommendation, including antifungal prophylaxis with an oral triazole or parenteral echinocandin in the case of a population level risk of *Candida* infection > 10% and a mold-active triazole when the population level risk of aspergillosis is > 6%.[6] The panel recognized that significant heterogeneity exists between patient groups that are dependent on disease and treatment-related variation but concluded that this risk level would generally apply to patients undergoing induction therapy for acute leukemia or HSCT because of their higher likelihood of experiencing a profound, protracted period of neutropenia. The panel considered the potential reduction in fungal-related mortality when reaching consensus on this recommendation. The recommendation for PJP prophylaxis remains unchanged from the previous version of this guideline. The Expert Panel will consider prophylaxis for patients undergoing therapy with phosphatidylinositol-3-kinase inhibitors (eg, idelalisib or copanlisib) in the next iteration of this guideline, pending additional supporting evidence. In addition, the panel noted that PJP prophylaxis may be considered in the setting of prolonged corticosteroid use (> 20 mg/d for > 4 weeks) to treat immune-related adverse events associated with checkpoint inhibitors and other immunotherapies, pending additional supporting evidence.[56]

CLINICAL QUESTION 3

Antiviral Prophylaxis. Does antiviral prophylaxis reduce the incidence of immunosuppression-related viral infections in patients with cancer compared with no prophylaxis or another treatment option?

Recommendation 3.1. Herpes simplex virus–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive antiviral prophylaxis with a nucleoside analog (eg, acyclovir). (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong.[7])

Recommendation 3.2. Treatment with a nucleoside reverse transcription inhibitor (eg, entecavir or tenofovir) is recommended for patients at high risk of hepatitis B virus reactivation.[59,60] (Type: consensus-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate.)

Qualifying Statement.

- Recommendations related to universal testing and in-depth treatment algorithms for hepatitis B virus are included in the ASCO Provisional Clinical Opinion on Hepatitis B Virus Screening for Patients With Cancer Before Therapy.[15]

Recommendation 3.3. Yearly influenza vaccination with inactivated quadrivalent vaccine is recommended for all patients receiving chemotherapy for malignancy. Optimal timing of vaccination for patients being treated for cancer is not established, but serologic responses may be best between chemotherapy cycles (> 7 days after the last treatment)or > 2 weeks before chemotherapy starts. Influenza vaccination is also recommended for all family and household contacts and health care providers. Individuals older than 65 years should receive the high-dose vaccine. Currently, there are insufficient data to recommend the high-dose vaccine in compromised hosts younger than 65 years. (Type: consensus-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate.)

Recommendation 3.4. The Expert Panel also supports other vaccination recommendations for immunosuppressed adult oncology patients that are contained within the IDSA guideline for vaccination of the immunosuppressed host.[16] (Type: consensus-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate.)

Qualifying Statement.

- It is anticipated that recommendations for the new inactivated recombinant subunit shingles vaccine in compromised hosts will be issued by the US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices in the coming year.[61]

Literature review update and analysis. The previous version of this guideline endorsed the recommendations from the US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices[62] and other organizations that all patients undergoing treatment of malignancy and all family and household contacts receive the seasonal influenza vaccination, given that many patients mount adequately protective immunologic responses to inactivated influenza vaccine as well as the well-documented safety of the vaccine in these patients. This updated version of the guideline continues to endorse this recommendation (Table 1).

CLINICAL QUESTION 4

Do additional precautions, such as hand hygiene, air filtration, or a neutropenic diet, reduce the risk of infection in neutropenic patients with cancer compared with no or other additional precautions?

Recommendation 4.1. All health care workers should comply with hand hygiene and respiratory hygiene/cough etiquette guidelines to reduce the risk for aerosol- and direct or indirect contact–based transmission of pathogenic micro-organisms in the health care setting. (Type: consensus-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong.)

Recommendation 4.2. Outpatients with neutropenia from cancer therapy should avoid prolonged contact with environments that have high concentrations of airborne fungal spores (eg, construction and demolition sites, intensive exposure to soil through gardening or digging, or household renovation). (Type: evidence-based; benefits outweigh harms; Evidence quality: strong; Strength of recommendation: strong.)

Literature review update and analysis. According to the previous version of this guideline, recommendations for hand hygiene reflect the endorsement of the practices deemed prudent by the US Centers for Disease Control and Prevention.[6,63] Recommendation 4.2 is based on retrospective reports and the panel opinion regarding prudent practices. Studies included in the previous version of this review of high-efficiency particulate air–filtered protected environments, respiratory masks, footwear exchange, and dietary interventions did not demonstrate any significant differences in outcomes, although protected environments may play a limited role in the prevention of airborne acquisition of infections, such as invasive mold, in the event that the patient remains in the protected environment and does not import an infection from previous exposure. Included in this update is a new meta-analysis of neutropenic diets—that is, diets that generally include cooked foods and restrict raw fruit, vegetables, fish meat, and soft cheese, which did not show a protective benefit with intervention.[64]

Clinical interpretation. The Expert Panel continues to endorse the ASCO recommendations from the previous version of this guideline, including recommendations from the US Centers for Disease Control and Prevention for hand hygiene and the prevention of infection in outpatient settings and recommendations against interventions, such as footwear exchange, protected environments, respiratory or surgical masks, neutropenic diet, or nutritional supplements, for which evidence of clinical benefit is lacking.

DISCUSSION

This updated guideline includes the latest evidence on prophylaxis for immunosuppressed adult patients undergoing treatment of malignancy. Updated systematic reviews and meta-analyses and new single studies did not include any new information that would alter the recommendations for antibiotic or antifungal prophylaxis included in the previous version of this review. Prophylaxis recommendations are stratified by high- and low-risk categories, and antibiotic and antifungal prophylaxis is recommended for higher-risk patients on the basis of patient- and treatment-related factors. For this updated version of the guideline, antiviral prophylaxis recommendations are also included and good practice recommendations related to vaccinations are outlined. This guideline does not provide a detailed discussion of monotherapies, combination therapies, and multiagent therapies. For this information, the reader is referred to the Surviving Sepsis Campaign guideline.[65,66] In addition, this guideline does not provide recommendations for specific agents and dosing schedules as a result of our inability to continuously update these guidelines as new agents are approved or as new evidence is published.

With the addition of few new studies to the evidence base, the Expert Panel continued to endorse previous recommendations with minor modifications noted within the guideline text; ASCO will continue to monitor the literature for new information and update this guideline at regular intervals.

PATIENT AND CLINICIAN COMMUNICATION

Recommendations throughout this document are aimed at a target audience of oncologists, infectious disease specialists, emergency medicine physicians, nurses, and advanced practice providers. The patient representative included in our Expert Panel highlighted the importance of communication between these clinicians and both inpatients and outpatients with regard to education about safety practices, what patients need to be aware of to communicate with clinicians, and expectations of patient/caregiver responsibilities once discharged. Across the recommendations contained within this guideline, the patient representative highlighted that infection prophylaxis information should be provided to patients and caregivers, including details from the recommendations that are related to hand hygiene, respiratory hygiene/cough etiquette, and avoidance of prolonged contact with environments that have high concentrations of airborne fungal spores. Patients frequently have questions about neutropenic diets or nutritional supplements; therefore, recommendations related to these topics should be included in patient materials.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving poor-quality care than other Americans.[67-70] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform the treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCCs)—is challenging. Patients with MCCs are a complex and heterogeneous population, which makes it difficult to account for all possible permutations to develop specific recommendations for care. In addition, the best

available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCCs, any treatment plan must take into account the complexity and uncertainty created by the presence of MCCs and highlight the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of the recommended care for the target index condition, clinicians should review all other chronic conditions that are present in the patient and take into account those conditions when formulating the treatment and follow-up plan.

In light of the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

The burden of a cancer diagnosis extends beyond the physical and psychological impacts of the disease; the social and financial impact of cancer, cancer treatment, and supportive care on the patient and family can be profound for patients worldwide.[71] Out-of-pocket expenses incurred by patients in accessing care can range widely and can affect patients' financial well-being significantly.[72] In particular, for patients with cancer who experience extreme financial toxicity, such as bankruptcy, these financial effects can be associated with increased mortality.[73] The financial consequences associated with diagnostic and treatment choices for patients with cancer with FN rarely are associated with significant costs; however, the cost implications of mismanagement of a patients with cancer with FN who subsequently requires intensive care or prolonged hospital stays can be substantial. Whereas discussions about the costs of cancer supportive care commonly focus on balancing the potential to save and extend lives with the costs to society or payers, the low cost of most interventions discussed in this guideline and their potential impact on infectious complications suggest that they have a favorable cost-benefit ratio even without formal evaluations.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

Submit new evidence or access more information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net.

Related ASCO Guidelines

- Recommendations for the Use of WBC Growth Factors Update.[10] (http://ascopubs.org/doi/10.1200/JCO.2015.62.3488)
- Central Venous Catheter Care for the Patient With Cancer.[74] (http://ascopubs.org/doi/10.1200/jco.2012.45.5733)
- Hepatitis B Virus Screening for Patients With Cancer Before Therapy.[15] http://ascopubs.org/doi/10.1200/JCO.2015.61.3745
- Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy.[9] http://ascopubs.org/doi/10.1200/JCO.2017.77.6211

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

1. Sievers EL, Dale DC, Bolyard AA, et al: Types of severe chronic neutropenia. https://www.neutropenia.ca/about/types-of-neutropenia?phpMyAdmin=8c01cfac7abc247071277b7622ac9394
2. Bow E, Wingard JR: Overview of neutropenic fever syndromes. https://www.uptodate.com/contents/overview-of-neutropenic-fever-syndromes
3. Carmona-Bayonas A, Jiménez-Fonseca P, Virizuela Echaburu J, et al: Prediction of serious complications in patients with seemingly stable febrile neutropenia: Validation of the Clinical Index of Stable Febrile Neutropenia in a prospective cohort of patients from the FINITE study. J Clin Oncol 33: 465-471, 2015
4. Kuderer NM, Dale DC, Crawford J, et al: Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 106: 2258-2266, 2006
5. Legrand M, Max A, Peigne V, et al: Survival in neutropenic patients with severe sepsis or septic shock. Crit Care Med 40:43-49, 2012
6. Flowers CR, Seidenfeld J, Bow EJ, et al: Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 31:794-810, 2013
7. 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 52:e56-e93, 2011
8. Brożek JL, Akl EA, Compalati E, et al: Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. Allergy 66:588-595, 2011
9. 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 36:1443-1453, 2018
10. Smith TJ, Bohlke K, Lyman GH, et al: Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 33:3199-3212, 2015
11. Tomblyn M, Chiller T, Einsele H, et al: Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: A global perspective. Preface. Bone Marrow Transplant 44:453-455, 2009
12. Agrawal S, Jones B, Barnes R, et al: A practical critique of antifungal treatment guidelines for haemato-oncologists. Crit Rev Microbiol 38:203-216, 2012
13. Shiffman RN MG, Michel G, Rosenfeld RM, et al: Building better guidelines with BRIDGE-Wiz: Development and evaluation of a software assistant to promote clarity, transparency, and implementability. J Am Med Inform Assoc 19:94-101, 2012
14. Ullmann AJ, Lipton JH, Vesole DH, et al: Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 356: 335-347, 2007
15. Hwang JP, Somerfield MR, Alston-Johnson DE, et al: Hepatitis B virus screening for patients with cancer before therapy: American Society of Clinical Oncology provisional clinical opinion update. J Clin Oncol 33:2212-2220, 2015
16. Rubin LG, Levin MJ, Ljungman P, et al: 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 58: e44-e100, 2014
17. Lyman GH, Abella E, Pettengell R: Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. Crit Rev Oncol Hematol 90:190-199, 2014
18. Lyman GH, Dale DC, Friedberg J, et al: Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: A nationwide study. J Clin Oncol 22:4302-4311, 2004
19. Intragumtornchai T, Sutheesophon J, Sutcharitchan P, et al: A predictive model for life-threatening neutropenia and febrile neutropenia after the first course of CHOP chemotherapy in patients with aggressive non-Hodgkin's lymphoma. Leuk Lymphoma 37:351-360, 2000
20. Cullen MH, Billingham LJ, Gaunt CH, et al: Rational selection of patients for antibacterial prophylaxis after chemotherapy. J Clin Oncol 25: 4821-4828, 2007
21. Hosmer W, Malin J, Wong M: Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer. Support Care Cancer 19:333-341, 2011
22. Bow EJ: Infectious complications in patients receiving cytotoxic therapy for acute leukemia: History, background, and approaches to management, in Wingard JR, Bowden RA (eds): Management of Infection in Oncology Patients. London, United Kingdom, Martin Dunitz, 2003, pp 71-104
23. Gardner A, Mattiuzzi G, Faderl S, et al: Randomized comparison of cooked and noncooked diets in patients undergoing remission induction therapy for acute myeloid leukemia. J Clin Oncol 26: 5684-5688, 2008
24. Klastersky J, Paesmans M, Rubenstein EB, et al: The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 18:3038-3051, 2000
25. Bow EJ, Meddings JB: Intestinal mucosal dysfunction and infection during remission-induction therapy for acute myeloid leukaemia. Leukemia 20: 2087-2092, 2006
26. Romaguera JE, Fayad L, Rodriguez MA, et al: High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 23:7013-7023, 2005
27. Ray-Coquard I, Borg C, Bachelot T, et al: Baseline and early lymphopenia predict for the risk of febrile neutropenia after chemotherapy. Br J Cancer 88:181-186, 2003
28. Pettengell R, Schwenkglenks M, Leonard R, et al: Neutropenia occurrence and predictors of reduced chemotherapy delivery: Results from the INC-EU prospective observational European neutropenia study. Support Care Cancer 16:1299-1309, 2008
29. Talcott JA, Finberg R, Mayer RJ, et al: The medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. Arch Intern Med 148: 2561-2568, 1988
30. Bow EJ, Kilpatrick MG, Scott BA, et al: Acute myeloid leukemia in Manitoba. The consequences of standard "7 + 3" remission-induction therapy followed by high dose cytarabine postremission consolidation for myelosuppression, infectious morbidity, and outcome. Cancer 74:52-60, 1994
31. Talcott JA, Siegel RD, Finberg R, et al: Risk assessment in cancer patients with fever and neutropenia: A prospective, two-center validation of a prediction rule. J Clin Oncol 10:316-322, 1992
32. Schwenkglenks M, Jackisch C, Constenla M, et al: Neutropenic event risk and impaired chemotherapy delivery in six European audits of breast cancer treatment. Support Care Cancer 14:901-909, 2006
33. Sonis ST, Oster G, Fuchs H, et al: Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol 19:2201-2205, 2001
34. Bodey GP, Buckley M, Sathe YS, et al: Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64:328-340, 1966
35. Blay JY, Chauvin F, Le Cesne A, et al: Early lymphopenia after cytotoxic chemotherapy as a risk factor for febrile neutropenia. J Clin Oncol 14: 636-643, 1996
36. Bodey GP, Rodriguez V, Chang HY, et al: Fever and infection in leukemic patients: A study of 494 consecutive patients. Cancer 41:1610-1622, 1978
37. Hughes WT, Armstrong D, Bodey GP, et al: 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 34: 730-751, 2002
38. Oguz A, Karadeniz C, Ckitak EC, et al: Which one is a risk factor for chemotherapy-induced febrile neutropenia in childhood solid tumors: Early lymphopenia or monocytopenia? Pediatr Hematol Oncol 23:143-151, 2006
39. Aapro MS, Cameron DA, Pettengell R, et al: EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 42:2433-2453, 2006
40. Heidenreich D, Kreil S, Nolte F, et al: Allogeneic hematopoietic cell transplantation without fluconazole and fluoroquinolone prophylaxis. Ann Hematol 95:287-293, 2016
41. Spellberg B, Doi Y: The rise of fluoroquinolone-resistant *Escherichia coli* in the community: Scarier than we thought. J Infect Dis 212:1853-1855, 2015
42. Lautenbach E, Metlay JP, Bilker WB, et al: Association between fluoroquinolone resistance and mortality in *Escherichia coli* and *Klebsiella pneumoniae* infections: The role of inadequate empirical antimicrobial therapy. Clin Infect Dis 41:923-929, 2005
43. Trecarichi EM, Tumbarello M, Spanu T, et al: Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by *Escherichia coli* in patients with hematological malignancies. J Infect 58:299-307, 2009
44. Blijlevens NM, Logan RM, Netea MG: The changing face of febrile neutropenia-from monotherapy to moulds to mucositis. Mucositis: From febrile neutropenia to febrile mucositis. J Antimicrob Chemother 63:i36-i40, 2009 (suppl 1)
45. Bow EJ: Fluoroquinolones, antimicrobial resistance and neutropenic cancer patients. Curr Opin Infect Dis 24:545-553, 2011
46. Gafter-Gvili A, Fraser A, Paul M, et al: Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev 1:CD004386, 2012

47. Bucaneve G, Micozzi A, Menichetti F, et al: Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 353: 977-987, 2005

48. US Food and Drug Administration: FDA updates warnings for fluoroquinolone antibiotics. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm513183.htm

49. Wojenski DJ, Barreto JN, Wolf RC, et al: Cefpodoxime for antimicrobial prophylaxis in neutropenia: A retrospective case series. Clin Ther 36: 976-981, 2014

50. Blennow O, Remberger M, Klingspor L, et al: Randomized PCR-based therapy and risk factors for invasive fungal infection following reduced-intensity conditioning and hematopoietic SCT. Bone Marrow Transplant 45:1710-1718, 2010

51. Klingspor L, Saaedi B, Ljungman P, et al: Epidemiology and outcomes of patients with invasive mould infections: A retrospective observational study from a single centre (2005-2009). Mycoses 58: 470-477, 2015

52. Kontoyiannis DP, Marr KA, Park BJ, et al: Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) database. Clin Infect Dis 50:1091-1100, 2010

53. Sun Y, Meng F, Han M, et al: Epidemiology, management, and outcome of invasive fungal disease in patients undergoing hematopoietic stem cell transplantation in China: A multicenter prospective observational study. Biol Blood Marrow Transplant 21:1117-1126, 2015

54. Gøtzsche PC, Johansen HK: Routine versus selective antifungal administration for control of fungal infections in patients with cancer. Cochrane Database Syst Rev 2014:CD000026, 2014

55. Robenshtok E, Gafter-Gvili A, Goldberg E, et al: Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: Systematic review and meta-analysis. J Clin Oncol 25: 5471-5489, 2007

56. Del Castillo M, Romero FA, Argüello E, et al: The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. Clin Infect Dis 63:1490-1493, 2016

57. US Food and Drug Administration: Aliqopa (copanlisib): Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209936s000lbl.pdf

58. Gilead Sciences: Zydelig: Highlights of prescribing information. http://www.gilead.com/~/media/CF1E73FFB80B42E2A39F9F5758DB3001.ashx

59. Huang H, Li X, Zhu J, et al: Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: A randomized clinical trial. JAMA 312:2521-2530, 2014

60. Mozessohn L, Chan KK, Feld JJ, et al: Hepatitis B reactivation in HBsAg-negative/HBcAb-positive patients receiving rituximab for lymphoma: A meta-analysis. J Viral Hepat 22:842-849, 2015

61. US Centers for Disease Control and Prevention: Advisory committee on immunization practices. https://www.cdc.gov/vaccines/acip/index.html

62. Kim DK RL, Riley LE, Hunter P: Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older: United States, 2018. MMWR Morb Mortal Wkly Rep 67:158-160, 2018

63. Boyce JM, Pittet D: Guideline for hand hygiene in health-care settings: Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force—Society for Healthcare Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. MMWR Recomm Rep 51:1-45, 2002; quiz CE1-CE4

64. Sonbol MB, Firwana B, Diab M, et al: The effect of a neutropenic diet on infection and mortality rates in cancer patients: A meta-analysis. Nutr Cancer 67:1230-1238, 2015

65. Rhodes A, Evans LE, Alhazzani W, et al: Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock—2016. Crit Care Med 45:486-552, 2017

66. IDSA Sepsis Task Force: IDSA position statement: Why IDSA did not endorse the Surviving Sepsis Campaign guidelines. Clin Infect Dis 66: 1631-1635, 2018

67. American Cancer Society: Cancer facts and figures for African Americans 2016-2018. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-facts-and-figures-for-african-americans/cancer-facts-and-figures-for-african-americans-2016-2018.pdf

68. US National Cancer Institute: SEER cancer statistics review, 1975-2013. http://seer.cancer.gov/csr/1975_2013/

69. US Cancer Statistics Working Group: United States cancer statistics: 1999–2012 incidence and mortality Web-based report. http://www.cdc.gov/uscs

70. Mead H, Cartwright-Smith L, Jones K, et al. Racial and Ethnic Disparities in U.S. Health Care: A Chartbook. New York, NY, The Commonwealth Fund, 2008

71. Jemal A, Bray F, Center MM, et al: Global cancer statistics. CA Cancer J Clin 61:69-90, 2011

72. Ramsey S, Blough D, Kirchhoff A, et al: Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. Health Aff (Millwood) 32: 1143-1152, 2013

73. Ramsey SD, Bansal A, Fedorenko CR, et al: Financial insolvency as a risk factor for early mortality among patients with cancer. J Clin Oncol 34:980-986, 2016

74. Schiffer CA, Mangu PB, Wade JC, et al: Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 31:1357-1370, 2013

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Appendix

Table A1. Expert Panel Membership

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