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Antibiotic Resistance in the Patient With Cancer: Escalating Challenges and Paths Forward

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Abstract: Infection is the second leading cause of death in patients with cancer. Loss of efficacy in antibiotics due to antibiotic resistance in bacteria is an urgent threat against the continuing success of cancer therapy. In this review, the authors focus on recent updates on the impact of antibiotic resistance in the cancer setting, particularly on the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp.*). This review highlights the health and financial impact of antibiotic resistance in patients with cancer. Furthermore, the authors recommend measures to control the emergence of antibiotic resistance, highlighting the risk factors associated with cancer care. A lack of data in the etiology of infections, specifically in oncology patients in United States, is identified as a concern, and the authors advocate for a centralized and specialized surveillance system for patients with cancer to predict and prevent the emergence of antibiotic resistance. Finding better ways to predict, prevent, and treat antibiotic-resistant infections will have a major positive impact on the care of those with cancer. *CA Cancer J Clin* 2021;0:1-17. © 2021 The Authors. *CA: A Cancer Journal for Clinicians* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Keywords: antibiotic resistance, antibiotics, bacterial infections, cancer

Introduction

Bacterial resistance to penicillin was encountered in patients¹ within 2 years after mass production of the antibiotic began in 1945.^{2,3} Since then, the emergence of antibiotic resistance has been reported against virtually all antibiotics developed to date.⁴ Organizations such as the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) have recognized antimicrobial resistance (AMR) as a global threat.^{5,6} The misuse and overuse of antibiotics is a significant driver for increasing antibiotic resistance.^{4,7} If the scientific community fails to manage and replenish our antibiotic supply, nearly 10 million extra deaths are predicted by 2050 due to drug-resistant infections.⁸⁻¹⁰ In a postantibiotic era, many interventions that we currently take for granted will be threatened. These include medical advances that have occurred in general surgery,¹¹ treatment of immunocompromised patients,¹² organ transplant recipients,¹³ and patients with prosthetic implants.¹⁴ Importantly, increasing levels of antibiotic resistance are already having a profound impact on the care of patients with cancer.¹⁵ *End cancer as we know it* is a major priority of the Biden Administration¹⁶ as well as medical societies,¹⁷ but achieving that goal will also require action against drug-resistant microbes.

Infections are common in patients with cancer, and they depend upon effective antibiotics to both prevent and treat bacterial infections. Antibiotic failure in patients with cancer increases the frequency of sepsis, sepsis-related mortality, and sepsis-associated

costs of care.¹⁸⁻²³ Thus it is not surprising that oncologists have been among the first to point out the clinical impact of increasing antibacterial resistance. For example, a recent study in the United Kingdom reported that 46% of the oncologists in the United Kingdom are worried that chemotherapy as a treatment for cancer will be difficult as a result of drug-resistant infections.²⁴ Optimizing the use of current antibiotics and discovery of novel antibiotics are critically important to protect patients with cancer from antibiotic-resistant infections in the future because antibiotic resistance threatens to undo much of the hard-won progress against cancer.²⁵

Antibiotic resistance is defined as the ability of microorganisms to survive when exposed to antibiotics that usually would kill them or prevent their growth.²⁶ Some of the key factors contributing to antibiotic resistance are misuse of antibiotics in humans and animals, use of antibiotics in animal and food industries, lack of rapid diagnosis procedures, and the presence of antibiotics in the environment.²⁷ Antibiotic resistance can be intrinsic or acquired due to various genetic mechanisms. We have highlighted the major mechanisms of antibiotic resistance in Table 1.²⁸⁻⁴¹ Some mechanisms can lead to antibiotic resistance in 1 or 2 classes of antibiotics, whereas others result in multidrug-resistant (MDR) isolates, which are characterized by exhibiting resistance to ≥ 3 different classes of antibiotics.^{42,43} In 2008, Rice et al designated 6 groups of bacteria (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) that were commonly associated with antibiotic resistance in the hospital environment and referred to them as ESKAPE pathogens.⁴⁴ In this review, we focus on recent updates regarding antibiotic-resistant ESKAPE infections, including risk factors, antibiotic use, management, and prevention of antibiotic resistance in patients with cancer.

The Use of Antibiotics and the Burden of Antibiotic Resistance in Patients With Cancer

Infections are one of the most frequent complications seen in patients with cancer,⁴⁵ and a patient with cancer has a 3 times greater risk of dying from a fatal infection than a patient without cancer.⁴⁶ Infections are thought to play a primary or associated role in the cause of death in approximately 50% of patients with hematological malignancies or solid tumors,⁴⁷ even if drug-resistant infections are rarely recorded as the official cause of death on death certificates.⁴⁸ Bacteria are the most common cause of infections in patients with cancer.^{47,49} Risks of developing an infection include disruption of anatomic barriers,⁵⁰ surgery,⁵¹ chemotherapy-related and radiation-related neutropenia,⁵² and stem cell transplantation.⁵³ More

recently, an increased risk of infection is reportedly caused by toxicity mitigation strategies using newer immunotherapies against cancer.⁵⁴⁻⁵⁶ Under neutropenic conditions, patients with cancer are subjected to prolonged treatment of antibiotics prophylactically and empirically.^{57,58} However, widespread and prolonged use of broad-spectrum antibiotics to reduce mortality and morbidity from infections in patients with cancer are likely contributors to the emergence of resistance.⁵⁹⁻⁶¹ In addition, patients with cancer are vulnerable to health care-acquired infections as a major source of antibiotic-resistant organisms.^{32,62,63} We have summarized several studies in which ESKAPE pathogens were isolated from patients with cancer since 2015 in Table 2.^{31,59-62,64-74} These illustrate the prevalence of MDR in different ESKAPE pathogens and highlight that prior antibiotic exposure and hospital-acquired infections are the major risk factors for developing antibiotic resistance in patients with cancer. For Figure 1, we derived data from the National Healthcare Safety Network (NHSN) 2015 to 2017 adult and pediatric antibiotic resistance reports^{75,76} to illustrate differences between the percentage of central line-associated bloodstream infections by ESKAPE pathogens that tested nonsusceptible to selected antimicrobial agents. Vancomycin resistance in *E. faecium* and fluoroquinolone nonsusceptibility in *Escherichia coli* appear to be significantly higher in adult oncology patients compared with pediatric patients.

Antibiotic Resistance Is Related to Unfavorable Outcomes in Patients With Cancer

Antibiotic resistance leads to detrimental effects in patients with cancer, who rely on antibiotics to prevent and treat infections. Although cancer survivorship has increased with the success of modern cancer care, current therapeutic approaches continue to make these patients vulnerable to infections.⁷⁷⁻⁷⁹ A meta-analysis by Teillant et al found that, in postchemotherapy infections, 26.8% of pathogens were identified as resistant to the standard prophylactic antibiotics that had been prescribed. That study forecasted that a reduction in antibiotic efficacy of 30% to 70% would result in nearly 4000 to 10000 additional infections and 500 to 1000 additional deaths per year in the United States among patients who go through chemotherapy for hematological malignancies.¹⁵

Multiple studies demonstrate the impact of increasing resistance on outcomes in this vulnerable population.⁸⁰⁻⁸² Bodro et al reported increased persistence of bacteremia (25% vs 9.7%), metastatic infection (8% vs 4%), and early case-fatality rates (23% vs 11%) among patients with cancer who had infections caused by antibiotic-resistant ESKAPE pathogens compared with other bacterial pathogens. Risk

TABLE 1. Antibiotic-Resistance Mechanisms in ESKAPE Bacteria^a

RESISTANCE TYPE (Blair 2015 ²⁸)	EXAMPLES OF MOLECULAR MECHANISMS (Bax & Griffin 2012 ²⁹)	EFFECTED ANTIBIOTICS CLASSES (Kapoor 2017 ³⁰)	EXAMPLES OF ANTIBIOTIC-RESISTANT ISOLATES FROM PATIENTS WITH CANCER (REFERENCE)
Antibiotic inactivation	<ul style="list-style-type: none"> • β-Lactamases • Aminoglycoside-modifying enzymes 	<ul style="list-style-type: none"> • Penicillins • Aminoglycosides 	<ul style="list-style-type: none"> • ESBL-producing <i>K. pneumoniae</i> (Zhang 2016³¹)^b • ESBL-producing <i>E. coli</i> (Cornejo-Luarez 2015³²) • CRE <i>K. pneumoniae</i> (Satlin 2027³³)^c • Carbapenem-resistant <i>A. baumannii</i> (Bodro 2014³⁴) • Methicillin-resistant <i>S. aureus</i> (MRSA) (Bodro 2014³⁴)
Antibiotic target modification	<ul style="list-style-type: none"> • Alteration of the peptidoglycan synthesis pathway • Mutations in DNA gyrase 	<ul style="list-style-type: none"> • Glycopeptides • Fluoroquinolones 	<ul style="list-style-type: none"> • Metallo-β-lactamase-producing <i>P. aeruginosa</i> (Toleman 2004³⁵) • Vancomycin-resistant <i>E. faecium</i> (Alatorre-Fernandez et al. 2017⁶⁵)
Antibiotic efflux	<ul style="list-style-type: none"> • Ribosomal mutations • Overexpression of multidrug-resistant pumps 	<ul style="list-style-type: none"> • Tetracyclines and Fluoroquinolones 	<ul style="list-style-type: none"> • Fluoroquinolone-resistant clinical isolates of <i>E. coli</i> (Conrad 1996³⁷) • Efflux pump-overexpressing <i>K. pneumoniae</i> and <i>E. coli</i> (Hamed 2018³⁸)
Reduced permeability of antibiotic	<ul style="list-style-type: none"> • Downregulation or mutations in porin proteins 	<ul style="list-style-type: none"> • Penicillins • Cephalosporins 	<ul style="list-style-type: none"> • <i>K. pneumoniae</i> with porin deletions (Satlin 2013³⁹)

Abbreviations: CRE, carbapenem-resistant *Enterobacteriales*-like; ESBL, extended-spectrum β -lactamase.

^aESKAPE indicates *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.

^bESBLs break down and destroy some commonly used antibiotics, including penicillins and cephalosporins (Centers for Disease Control and Prevention 2019⁴⁰).

^cCRE-like *E. coli* and *K. pneumoniae* develop resistance to the group of antibiotics called carbapenems (Centers for Disease Control and Prevention 2019⁴¹).

TABLE 2. Antibiotic Resistance in Patients With Cancer: Highlights From the Last 5 Years

POPULATION STUDIED	RESISTANT MICROORGANISMS	RISK FACTORS FOR DEVELOPMENT OF ANTI-BIOTIC RESISTANCE	INTERPRETATIONS	REFERENCE
BSI episodes in patients with cancer (January 1995 to May 2015)	<i>Enterococcus faecium</i> (EF)	<ul style="list-style-type: none"> Prolonged antibiotic exposure 	<ul style="list-style-type: none"> 403 Episodes of EF BSIs from 21,695 positive blood cultures Increase in BSIs due to EF infections observed from 2005 to 2015 	Tedim 2017 ⁶⁰
Hematologic neutropenic patients (July 2009 to July 2012)	<i>Enterococcus faecium</i>	<ul style="list-style-type: none"> Previous hospitalization 	<ul style="list-style-type: none"> Ampicillin-resistant EF (AREfm) colonization was detected in 32 of 52 patients (61.4%) 	Sanchez-Diaz 2016 ⁶⁴
BSIs in patients with hematologic malignancies (January 2008 to December 2012)	<i>Enterococcus faecium</i>	<ul style="list-style-type: none"> Levofloxacin extended prophylaxis Prophylactic antibiotics 	<ul style="list-style-type: none"> Multidrug-resistant (MDR) clones of AREfm in intestine of patients with cancer increase the development of bacteremia 58 Episodes of EF BSI episodes from a total of 15,095 blood cultures 	Alatorre-Fernandez 2017 ⁶⁵
BSIs in malignant hematology and oncology patients (2008-2014)	<i>Enterococcus faecium</i>	<ul style="list-style-type: none"> Vancomycin therapy during the previous 3 mo Prior antibiotic exposure 	<ul style="list-style-type: none"> Higher mortality was associated with vancomycin-resistant isolates 96 Patients with EF BSIs were included in the study Higher 30-d mortality was associated with vancomycin-resistant isolates 	Xie 2020 ⁵⁹
BSIs in patients with hematologic malignancies (January 2012 to December 2014)	<i>Pseudomonas aeruginosa</i> (PA)	<ul style="list-style-type: none"> Previous hospitalization Prior use of fluoroquinolones 	<ul style="list-style-type: none"> 64 Patients with PA BSIs were studied 37.5% Isolates were MDR 	Tofas 2020 ⁶¹
BSIs in patients with hematologic malignancies and hematopoietic cell transplant recipients (January 2012 to March 2018)	<i>Pseudomonas aeruginosa</i>	<ul style="list-style-type: none"> Fluoroquinolone prophylaxis 	<ul style="list-style-type: none"> PA is an important pathogen in patients who have hematologic malignancies associated with high mortality 55 Episodes of PA bacteremia among 51 patients Fluoroquinolone prophylaxis was associated with non-susceptibility to meropenem, but not to anti-pseudomonal β-lactams or aminoglycosides 	Hakki 2019 ⁶⁶
BSIs in neutropenic patients with cancer (January 2006 to May 2018)	<i>Pseudomonas aeruginosa</i>	<ul style="list-style-type: none"> Prior therapy with piperacillin-tazobactam Prior anti-pseudomonal carbapenem use Fluoroquinolone prophylaxis HAIs 	<ul style="list-style-type: none"> 1217 Episodes of BSI due to PA across 34 centers in 12 countries The rate of MDR increased significantly over the study period 	Gudiol 2020 ⁶⁷
Respiratory infections in patients with lung cancer (September 2017 to October 2018)	<i>Klebsiella pneumoniae</i> (KP)		<ul style="list-style-type: none"> KP was identified in 27 of 47 patients who had lung cancer with respiratory infection 51.4% KP isolates were MDR and the dominant strain causing lung infection in patients with lung cancer in the study 	Ding 2020 ⁶⁸
Patients who had cancer with BSIs, HAIs, and intra-abdominal infections (February to July 2013)	<i>Klebsiella pneumoniae</i>	<ul style="list-style-type: none"> History of systemic steroid Combination antimicrobial therapy 	<ul style="list-style-type: none"> In total, 230 consecutive cases of KP infection were studied 12.6% of hypervirulent KP isolates produced extended-spectrum β-lactamase 	Zhang 2016 ³¹

TABLE 2. (Continued)

POPULATION STUDIED	RESISTANT MICROORGANISMS	RISK FACTORS FOR DEVELOPMENT OF ANTIBIOTIC RESISTANCE	INTERPRETATIONS	REFERENCE
BSIs in malignant hematology and oncology patients (January 2014 to September 2018)	<i>Klebsiella pneumoniae</i>	<ul style="list-style-type: none"> Carbapenem exposure within 30 d before the onset of BSIs 	<ul style="list-style-type: none"> 89 patients with KP bacteremia were included in the study Carbapenem-resistant KP caused more mortality than carbapenem-susceptible KP (55.0% vs 15.9%; $P = .001$) 	Liu 2019 ⁶⁹
Patients with cancer (2006 to March 2015)	<i>Methicillin-resistant Staphylococcus aureus</i> (MRSA)	<ul style="list-style-type: none"> HAIs 	<ul style="list-style-type: none"> 21.1% of MRSA was documented from 450 patients reported with <i>S. aureus</i> infection Protective factors for mortality included catheter removal and initiation of adequate treatment for <i>S. aureus</i> <48 h after positive blood cultures 	Bello-Chavolla 2018 ⁷⁰
Patients with erythrodermic cutaneous T-cell lymphoma (CTCL) (2012–2016)	<i>Staphylococcus aureus</i>		<ul style="list-style-type: none"> Of 50 events, 17 (34%) were due to MRSA The MRSA prevalence was high in patients with erythrodermic CTC 	Engge 2020 ⁷¹
Patients with cancer (June 2014 to March 2016)	Methicillin-resistant <i>Staphylococcus aureus</i>		<ul style="list-style-type: none"> 120 isolates (40 community-acquired and 80 hospital-acquired MRSA) were included in the study Patients with community-acquired MRSA showed remarkable ability to acquire MDR after irradiation 	Shehata 2019 ⁷²
Patients with cancer (July 2017 to January 2018)	<i>Acinetobacter baumannii</i> (AB)		<ul style="list-style-type: none"> 48 AB isolates were recovered from 520 blood samples Carbapenemases were identified as the main mechanism of carbapenem resistance in AB 	Wasfi 2020 ⁷³
Patients with cancer—outbreak initiated from a single patient (March 2011)	<i>Acinetobacter baumannii</i>	<ul style="list-style-type: none"> HAIs 	<ul style="list-style-type: none"> 66 AB strains (62.3%) were considered infection, and 40 (37.7%) were considered colonization 	Cornejo-Juarez 2020 ⁶²
Patients with malignant hematology (January 2014 to June 2015)	<i>Acinetobacter baumannii</i>	<ul style="list-style-type: none"> Previous carbapenem exposure Previous hospitalization 	<ul style="list-style-type: none"> Highlighted the threat that represents the transfer of colonized patients with MDR strains between institutions 40 Patients with AB bacteremia were identified, accounting for 2.9% (40 of 1358) of bacteremia cases Patients who had carbapenem-resistant AB infections had significantly longer hospital stays 	Wang 2017 ⁷⁴

Abbreviations: BSIs, bloodstream infections; HAIs, hospital-acquired infections.

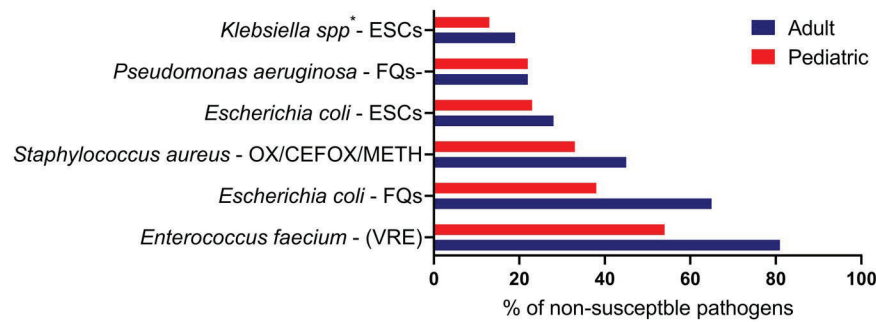


FIGURE 1. Antibiotic Resistance Is Common in Patients With Cancer. This bar graph displays the percentage of pathogens reported from adult and pediatric central line-associated bloodstream infections (CLABSIs) that tested nonsusceptible (NS) to selected antimicrobial agents in hospital oncology units in the United States from 2015 to 2017. Data for the graph were obtained from the National Healthcare Safety Network 2015 to 2017 adult and pediatric antibiotic resistance reports. **Klebsiella* spp. include *K. oxytoca* and *K. pneumoniae*. ESCs indicates extended-spectrum cephalosporins (cefepime, cefotaxime, ceftazidime, or ceftriaxone); FQs, fluoroquinolones (ciprofloxacin or levofloxacin); OX/CEFOX/METH, oxacillin, ceftaxime, or methicillin; VRE, vancomycin-resistant *Enterococcus*.

factors that were associated with having an antibiotic-resistant infection included comorbidities, prior antibiotic therapy, having a urinary catheter, and a urinary tract source of infection. Those authors identified a wide variety of pathogens, including: methicillin-resistant *S. aureus* (MRSA), extended-spectrum β -lactamase (ESBL)-producing *K. pneumoniae*, carbapenem-resistant *A. baumannii*, carbapenem-resistant and quinolone-resistant *P. aeruginosa*, and de-repression of chromosomal β -lactamase and ESBL-producing *Enterobacter* species.³⁴

A study in 2015 found that 58 of 282 deaths (23%) among patients with cancer who required intensive care were caused by hospital-acquired infections. In 51 of those 58 cases (88%), an MDR pathogen was identified. The overall prevalence of MDR pathogens was nearly 40% in microorganisms collected from patients who were admitted to the intensive care unit. Of the identified MDR pathogens, 20% were caused by *E. coli* (94.4% of these were ESBL producers), 12% were caused by *S. aureus* (90.6% of these were MRSA), 12% were caused by *E. faecium* (18.7% were vancomycin resistant), and 6% were caused by *A. baumannii* (all were MDR).³²

In 109 patients with hematological diseases who were undergoing chemotherapy, overall survival at 30 days was analyzed in those who had Gram-negative bloodstream infections (BSIs). In patients who had infections caused by MDR bacteria, survival was significantly lower compared with the survival of those who had infections caused by non-MDR isolates (85.6% vs 55.9%; $P < .001$).⁸³ In addition, numerous recent studies support the association of antibiotic resistance with unfavorable outcomes in patients with both hematological malignancies and solid tumors.⁸⁴⁻⁸⁸ The impact of resistance is not limited to the adult population. In a tertiary children's hospital from 2010 to 2014, carbapenem-resistant versus carbapenem-susceptible BSI was associated with a longer duration of bacteremia (mean, 3.8 vs 1.7 days), a higher risk for intensive care unit hospitalization (44.4% vs

10.1%), and a higher mortality rate (33% vs 5.8%) in patients with hematological malignancies and after hematopoietic stem cell transplantation.⁸⁹

Infections with antibiotic-resistant bacteria have been studied less in patients with solid tumors than in those with hematological malignancies.⁹⁰ This could be because of a lower incidence of BSIs reported in solid tumors compared with hematological malignancies in neutropenic patients with cancer.⁹¹ One main difference in infections between solid and hematological malignancies is the source of infection: pneumonia and urinary tract infections were frequent among patients with solid tumors, whereas endogenous sources and catheter-related BSIs were frequent in patients with hematological malignancies.⁹¹ The risk of infection in patients with solid tumors can be increased by factors such as chemotherapy-related or radiation therapy-related neutropenia, disruption of anatomic barriers from medical devices and surgical or diagnostic procedures, and obstruction due to primary or metastatic tumors, resulting in postobstructive pneumonia, lung abscess, or urinary tract infections. Common sites of infection in patients with solid tumors include BSIs related to neutropenia and postsurgical site infections in breast, bone, central nervous system, and skin.⁴⁵ Recent epidemiologic data highlight the high prevalence of MDR pathogens in these patients.⁹²⁻⁹⁴ One study reported that patients older than 70 years with solid tumors had more frequent infections because of MDR organisms compared with patients younger than 70 years.⁸⁷ Another study demonstrated that patients with solid tumors were more susceptible to bacteremic cholangitis caused by *Enterobacteriaceae* and *E. faecium*, highlighting the emergence of MDR as a special concern, especially in patients who have a second episode of bacteremia.⁹⁵ AMR can become important even during the diagnostic evaluation of solid tumors. For example, recent literature has demonstrated complications such as increased hospitalization and death due to antibiotic-resistant infections after prostate

biopsies.^{96,97} Extensive use of fluoroquinolone prophylaxis may be associated with an increase in resistant *E. coli* strains, which can result in infections after prostate biopsies⁹⁸; as a result, broad-spectrum and longer duration of prophylaxis is recommended.^{96,99} Importantly, targeted antibiotic prophylaxis with prebiopsy screening has reduced the number of infections after the biopsy.^{100,101}

Cancer and antibiotic resistance also converge to worsen health disparities. Certain communities of color in the United States, including African American, Latinx, and indigenous communities, experience higher cancer incidence and lower survival rates for many types of cancers. Many complex factors drive these disparities.¹⁰² Similarly, experts have identified many reasons to suspect a disparate impact of AMR, including differences regarding the use of prescribed and nonprescribed antibiotics, barriers to medical care, higher rates of foreign travel to regions with high AMR burden, and more likely employment in food animal production.¹⁰³ Taken together, the joint epidemics of cancer and AMR can contribute significantly to persistent health inequities.

AMR and the Cost of Treating Cancer

The decline of antibiotic effectiveness due to AMR has imposed a massive burden on health care costs, with an increase in hospital admissions.¹⁰⁴ Antibiotic resistance is estimated to cost nearly \$20 billion in health care and \$35 billion a year in lost productivity in the US economy.^{4,105} The cost of treating infections in patients with cancer adds a significant amount to the overall cost of cancer treatment. For example, of all-cause health care costs during first-line chemotherapy, neutropenia-related costs accounted for 32.2% in patients with non-small lung cancer who were diagnosed with febrile neutropenia.¹⁰⁶ On the basis of a study published with 91,560 and 16,859 cancer-related neutropenia hospitalizations among adults and children, respectively, the cost of cancer-related neutropenia hospitalization was \$24,770 per stay for adults and \$26,000 per stay for children in the United States.¹⁰⁷ Tori et al reported that the cost of treatment for an episode of febrile neutropenia after chemotherapy, on average, was from \$50,000 to \$60,000 in 2020.¹⁰⁸

Although studies have estimated the increased cost of health care caused by AMR, the direct costs of AMR related to cancer therapy have rarely been studied. In 2004, Watters et al reported the cost associated with the treatment of patients with head and neck cancer who become colonized or infected with MRSA after major surgical procedures. Patients who were colonized or infected with MRSA had up to a 3 times more prolonged hospital stay compared with those who were not positive for MRSA. Furthermore, the authors reported that the cost of antibiotics increased by £2470 per patient because of MRSA.¹⁰⁹

Strategies for Preventing Antibiotic Resistance in Patients With Cancer

Prevention of Infection—Minimizing Antibiotic Usage

Antibiotic prophylaxis is a common practice for preventing infections and infection-related complications under neutropenic conditions in patients who have cancer.^{110,111} With neutropenic conditions, patients are prone to develop fever (febrile neutropenia), indicating possible infection. The mortality rate can go up to 11% in patients who have cancer with febrile neutropenia^{112,113} and can be as high as 50% during severe sepsis conditions.¹¹⁴ According to some studies, prophylactic use of quinolones reduces the incidence of fever, probable infections, hospitalizations,^{115,116} and the overall mortality rate.^{110,117} These gains must be balanced with observations that patients with cancer who receive prolonged antibiotic prophylaxis are at risk for developing breakthrough antibiotic-resistant infections.^{67,118–120} Previous antibiotic exposure has been recognized as one of the main risk factors for AMR development in some patients with cancer.^{59–61,67} In fact, there remains ongoing debate in clinical oncology settings about the overall use or duration of quinolone prophylaxis in some patients with cancer because the procedure failed to reduce overall mortality and increased the emergence of resistant strains in some studies.^{121–124}

Minimizing infections provides an opportunity to reduce the use of antibiotics in patients with cancer who have neutropenia or those undergoing surgeries and other invasive procedures. The CDC, the American Cancer Society, and the National Comprehensive Cancer Network provide guidance to patients with cancer, caregivers, and their health care teams to prevent infections in patients who have cancer. These include educating patients and caregivers about day-to-day good practices to prevent infections or to detect infections early.^{125–127}

Antibiotic or chemotherapy administration can result in gut microbiota dysbiosis, altering the diversity of bacteria.^{128–130} Dysbiosis in the gut microbiota can increase the risk for resistance bacteria in the microbiota,¹³¹ invasive infections,⁵⁰ post-transplant complications (such as graft-versus-host disease in those who undergo hematopoietic stem cell transplantation),¹³² and reduced efficacy in patients who have cancer treated with immunotherapy.¹³³ Monitoring gut microbiota for its composition, administering protective commensal bacteria to reduce antibiotic-resistant infections, and promoting a healthy microbiome could be promising approaches for preventing antibiotic resistance, minimizing antibiotic use, and leading to positive outcomes in these patients.^{134–136}

Another area of concern for patients with cancer is the recognition that there is geographical variability in antibiotic

resistance. Resistance to antibiotics frequently originates in one locality, only to spread to others. For example, vancomycin-resistant *Enterococci* was identified in 1987 in Europe and, within 10 years, it represented >25% of *Enterococci* associated with BSIs in hospitalized patients in the United States.¹³⁷ A study by Arcilla et al in 2017 found that 34.3% of 1847 travelers who were ESBL-negative before traveling from the Netherlands had acquired ESBL *Enterobacterales* during their international travel, with examples of transmission within households.¹³⁸ Furthermore, medical tourists travel between health facilities in locations with different rates of antibiotic resistance, potentially disseminating resistant pathogens.¹³⁹ With international travel poised to rebound after COVID-19, vulnerable groups such as patients with cancer should remain aware of infectious risks, including information on the prevalence of drug-resistant pathogens that might be present in the locations to which they travel.

Promoting the appropriate use of antibiotics among health care practitioners and patients will prevent the misuse and overuse of antibiotics as well as decreasing costs.¹⁴⁰⁻¹⁴² Most importantly, this will allow for continued use of the existing antibiotic armamentarium.¹⁴³⁻¹⁴⁵ The required duration of antibiotic therapy is inexact and has been disputed in oncology settings, leading to unnecessarily extended courses of antibiotics and heterogeneity of use between practice sites.¹⁴⁶⁻¹⁴⁸ Well defined guidelines are required after comprehensive studies to establish the optimal duration of antibiotic administration to reduce antibiotic overuse in oncology settings.¹⁴⁹ For example, vancomycin has been shown to be inappropriately prescribed as empirical treatment resulting in vancomycin resistance.¹⁵⁰ Fever and neutropenia guidelines published by the Infectious Diseases Society of America indicate that vancomycin is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia and should be considered for specific clinical indications. Furthermore, these guidelines emphasize the importance of discontinuing vancomycin in the absence of Gram-positive organisms.¹⁵¹ Antibiotic de-escalation and discontinuation should be considered when the patient is stabilized or the causative agent is determined to reduce overuse.¹⁵² Early discontinuation of empirical antibacterial therapy in patients with fever of unknown origin has been demonstrated to be safe,^{153,154} and emerging data indicate that continuation of empirical antibiotics until absolute neutrophil count recovery could be unnecessary.^{155,156} De-escalating and discontinuation strategies have been successfully demonstrated in high-risk neutropenic patients who have cancer, with a significant reduction in antibiotic use.¹⁵⁷⁻¹⁵⁹

Antibiotic Stewardship to Optimize Antibiotic Use

Antimicrobial stewardship has been defined as selection of the best antimicrobial treatment at the optimal dose and

duration, resulting in the best clinical outcome for treating and preventing infection with minimal toxicity and a minimal effect on subsequent resistance.^{160,161}

In health care settings, antimicrobial stewardship teams, ideally led by infectious diseases physicians in partnership with infectious diseases pharmacists, clinical microbiologists, and infection preventionists, are charged with this important initiative. Antimicrobial stewardship is especially important for patients with cancer and/or those undergoing hematopoietic stem cell transplantation, who are prone to serious infections and receive multiple courses of antimicrobial therapy during the treatment process.¹⁶² These patients may have the most potential to benefit from antibiotic stewardship because past antibiotic exposure is a critical risk factor for developing an antibiotic-resistant infection. As discussed above, patients who have cancer with antibiotic-resistant infections have worse outcomes than those who have antibiotic-susceptible infections.¹⁶³ Rosa et al evaluated patient outcomes related to antibiotic stewardship in those with hematological malignancies and solid tumors. Their study indicated that adherence to antibiotic stewardship was independently associated with lower mortality.¹⁶⁴ However, according to a review published by Pillinger et al in 2020, these patient populations are frequently excluded from studies of antibiotic stewardship, and more efforts are needed to determine the broader impact of different stewardship strategies in this vulnerable patient population.¹⁶⁵ Nevertheless, several other studies in hospital-wide intervention programs have demonstrated the impact of antibiotic stewardship on decreasing antibiotic resistance system wide and reducing antimicrobial expenditures.¹⁶⁶⁻¹⁷⁰ Although more data in this patient population are needed, it is reasonable to conclude that decreases in infections caused by antibiotic-resistant pathogens in a health care system would translate to improved outcomes across a diverse range of patient populations. The Centers for Medicare and Medicaid Services require acute care hospitals and long-term care facilities to have antibiotic stewardship programs in place, but their impact is uneven because many hospitals lack sufficient resources to fully implement stewardship protocols.¹⁷¹ Only recently has stewardship become a focus in outpatient settings, where high levels of inappropriate antibiotic prescriptions persist. Recently implemented *Core Elements of Outpatient Antibiotic Stewardship* by the CDC focus on a framework for antibiotic stewardship for outpatient clinicians and facilities that routinely provide antibiotic treatment.¹⁷² Increased resources will be critical to the universal adoption of stewardship, and patients at greatest risk for increased morbidity and mortality because of antibiotic-resistant infections—such as those with cancer—have the most to gain.¹⁷³

Other than health care settings, it is important to focus on more general areas that contribute to the occurrence of antibiotic-resistant bacteria. Agriculture, such as the livestock and poultry industries,¹⁷⁴ is one important area of concern. These industries consume large quantities of antibiotics to protect animals from infection and also to promote growth.^{175,176} According to the *2019 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* by the US Food and Drug Administration, 54% of nearly 11 metric tons of antibiotics used in animal agriculture are medically important, such as tetracyclines and penicillins.¹⁷⁴ Antibiotic-resistant bacteria occurring in these settings can be transmitted to humans.¹⁷⁷⁻¹⁷⁹ Although no studies have been performed to correlate antibiotic resistance in farm animals and patients with cancer, it is likely that such patients could face complications because of colonization of antibiotic-resistant species in their intestines. Tackling antibiotic resistance will require a sustained, multifaceted approach in numerous segments of society.

Antibiotic-Resistance Surveillance Systems for Patients With Cancer: Prediction and Prevention of Outbreaks

The CDC has defined surveillance as systematic, ongoing collection, analysis, and interpretation of health data essential for planning, implementing, and evaluating public health practice integrated closely with timely dissemination to those who need the data.¹⁸⁰ Various countries have developed their own guidelines for the surveillance of antibiotic-resistant bacteria.¹⁸¹⁻¹⁸³ Surveillance of AMR involves the tracking and analysis of antibiotic-susceptibility test results in bacteria isolated from clinical samples. These results, combined with clinical and demographic data obtained from patients, enable clinicians to provide meaningful interventions to reduce the burden of antibiotic resistance.¹⁸⁴ Surveillance data can be used for predictions. The data from surveillance, merged with other risk factors, can be used to develop prediction models for antibiotic-resistance development in clinically relevant bacterial pathogens. In 2020, Gudiol et al developed a clinical prediction model available online that could identify neutropenic patients with cancer who are at high risk of bloodstream infections because of MDR *P. aeruginosa*, centered on parameters such as patient age and prior antibiotic use. Although the study has not been replicated yet by other groups, the investigators reported good prediction results in patients with cancer from across 34 centers in 12 countries, indicating that the model may benefit these patients by improving the administration of specific empirical antibiotic treatment and that it may also help optimize the effectiveness of antibiotic stewardship programs.⁶⁷ A comprehensive and predictive model of ESKAPE pathogens theoretically could be a useful tool for predicting the emergence of antibiotic resistance in oncology settings and driving the efficient

utilization of antibiotics. The CDC has increased antibiotic-resistance surveillance in accordance with the first *National Action Plan for Combating Antibiotic Resistant Bacteria*, but significant gaps in our knowledge remain.¹⁸⁵ For example, adult and pediatric antibiotic-resistance reports issued from 2015 to 2017 by the NHSN highlighted health care-associated infections from 17 adult and 8 pediatric oncology facilities only. The number of oncology facilities that reported data was relatively low compared with the total number of health care facilities that reported data in the NHSN (5626 adult centers and 2545 pediatric centers).^{75,76} Furthermore, the report separately revealed the percentage of antibiotic non-susceptible pathogens recorded from oncology units, as summarized in Figure 1. A comparison of the percentage of non-susceptible pathogens between adult and pediatric oncology units reveals higher levels of vancomycin-resistant *E. faecium* and fluoroquinolone-resistant *E. coli*. However, similar data were not found for oncology facilities from previous reports by the NHSN, so comparisons from previous years could not be made.¹⁸⁶⁻¹⁸⁹ Having chronological surveillance data on antibiotic resistance in oncology settings will be critical for tracking trends and linking rates of resistance to interventions made in these patients. Ongoing and future efforts by the CDC will help in this regard.

Future Innovations in Antibiotics and Their Impact on Resistance

Although several international and governmental organizations have helped fund new efforts, such as CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator), to spur the development of innovative antibiotics,¹⁹⁰ several expert reports have warned that antibiotic business models are uniquely broken and require significant reform to bring innovative new antibacterials to patients.¹⁹¹⁻¹⁹⁵ Because physicians frequently reserve new antibiotics as a last resort treatment for infections, this results in a low volume of sales.⁴ An analysis by Towse et al in 2017 estimated that the cost of developing an antibiotic is approximately US\$1581 million, whereas the average annual revenue from an antibiotic's sales is roughly \$46 million.¹⁹⁶ This results in significant obstacles for the pharmaceutical industry to developing new antibiotics.⁴ A predictable return on investment for antibiotic development will likely require the support of the federal government enacting policies that could help prevent the collapse of the antibiotic pipeline. Financial incentives for antibiotic innovation should target drugs that will provide the most clinical benefit for patients with the most significant unmet medical needs.¹⁹⁷

The vast majority of antibiotics used clinically are broad-spectrum. Broad-spectrum antibiotics are usually active against multiple bacterial species, not just the specific pathogen that might be targeted in a particular patient scenario.¹⁹⁸

One major drawback of broad-spectrum antibiotics is the development of AMR not only in pathogenic bacteria but also in the non-pathogenic commensal bacteria that comprise the normal microbiome.¹⁹⁹ The development of narrow-spectrum antibiotics is considered an attractive approach to overcoming antibiotic-resistant bacterial infections because more specific antibiotics can reduce the selection pressure in non-targeted pathogens.^{200,201} Examples of experimental narrow-spectrum antibiotics for ESKAPE pathogens include bacteriophages,^{202,203} monoclonal antibodies,²⁰⁴ bacteriocins,^{205,206} and antisense molecules, such as peptide-conjugated phosphorodiamidate morpholino oligomers.²⁰⁷⁻²⁰⁹ Bacteriophages are bacterial viruses that infect bacterial cells, which can cause the bacterium to lyse.²¹⁰ Bacteriophages are specific for bacteria and selectively attach to specific receptors on the surface of the host cell.²¹¹ Similar to phages, human monoclonal antibodies also can be developed for specific bacteria and can be targeted by the immune system.^{212,213} Bacteriocins are peptides of different sizes produced by various bacteria that exhibit bactericidal activity against other bacteria.^{205,214} Bacteriocins bind various receptors on the surface of the target bacteria to trigger bactericidal effects.²¹⁵ Phosphorodiamidate morpholino oligomers are designed to target mRNA and block translation of the gene of interest.²⁰⁷ Continuing advances in the rapid identification of pathogens will enable the opportunity of using narrow-spectrum antibiotics. Recent developments in diagnostic tests, such as next-generation sequencing,^{36,216-218} matrix-assisted laser desorption ionization–time-of-flight mass spectrometry,²¹⁹ and rapid antigen testing,²²⁰ have made

the prospect of pathogen-specific therapy a viable strategy. Additional policies are needed to strengthen diagnostic innovation and clinical integration of diagnostics, including better outcomes studies to inform clinical use and justify appropriate reimbursement.²²¹ Recently, the Infectious Diseases Society of America issued new guidelines to treat antimicrobial-resistant, Gram-negative infections focusing on the efficiency of different antibiotics according to the etiology of the infection. These guidelines provide preferred or alternative antibiotic treatment options with dosages for ESBL-producing *Enterobacterales*, carbapenem-resistant *Enterobacterales*, and difficult-to-treat *P. aeruginosa* according to the source of infection.²²²

Conclusion

Drug-resistant infections are growing in number and cost and significantly threaten our ability to care for patients with cancer. The cancer community—patients, loved ones, clinicians, and scientists—have successfully advocated for significant investments in research and public health strategies to prevent cancer and increase therapeutic options, with the goal of saving and extending lives.²²³ Because antibiotic resistance threatens to undo much of this hard-won progress, cancer advocates should consider focusing their considerable political power on this public health crisis. Cancer and infectious diseases experts must unite to drive the federal policy changes necessary to prevent, diagnose, and treat drug-resistant infections and to protect the gains that have been made against cancer over the past few decades. ■

References

- Spink WW, Ferris V. Penicillin-resistant staphylococci: mechanisms involved in the development of resistance. *J Clin Invest.* 1947;26:379-393. doi:10.1172/JCI101820
- Aminov RI. A brief history of the antibiotic era: lessons learned and challenges for the future. *Front Microbiol.* 2010;1:134. doi:10.3389/fmicb.2010.00134
- Hamilton KW. Miracle Cure: The Creation of Antibiotics and the Birth of Modern Medicine. *Emerging Infect Dis.* 2019;25:196. doi:10.3201/eid2501.181184
- Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T.* 2015;40:277-283.
- Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019 (2019 AR Threats Report). Accessed February 25, 2021. [cdc.gov/drugresistance/biggest-threats.html](https://www.cdc.gov/drugresistance/biggest-threats.html).
- World Health Organization. Global action plan on antimicrobial resistance. 2021. Accessed February 25, 2021. [who.int/publications/i/item/9789241509763](https://www.who.int/publications/i/item/9789241509763)
- Goossens H, Ferech M, Vander Stichele R, Elseviers M, ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet.* 2005;365:579-587. doi:10.1016/S0140-6736(05)17907-0
- O'Neill J. Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. Review on Antimicrobial Resistance; 2014. Accessed February 25, 2021. amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf
- de Kraker ME, Stewardson AJ, Harbarth S. Will 10 million people die a year due to antimicrobial resistance by 2050? *PLoS Med.* 2016;13:e1002184. doi:10.1371/journal.pmed.1002184
- Hollis A, Ahmed Z. Preserving antibiotics, rationally. *N Engl J Med.* 2013;369:2474-2476. doi:10.1056/NEJMp1311479
- Cohen ME, Salmasian H, Li J, et al. Surgical antibiotic prophylaxis and risk for postoperative antibiotic-resistant infections. *J Am Coll Surg.* 2017;225:631-638.e3. doi:10.1016/j.jamcollsurg.2017.08.010
- DeNegre AA, Ndeffo Mbah ML, Myers K, Fefferman NH. Emergence of antibiotic resistance in immunocompromised host populations: a case study of emerging antibiotic resistant tuberculosis in AIDS patients. *PLoS One.* 2019;14:e0212969. doi:10.1371/journal.pone.0212969
- Bartoletti M, Giannella M, Tedeschi S, Viale P. Multidrug-resistant bacterial infections in solid organ transplant candidates and recipients. *Infect Dis Clin North Am.* 2018;32:551-580. doi:10.1016/j.idc.2018.04.004

14. Ravi S, Zhu M, Luey C, Young SW. Antibiotic resistance in early peri-prosthetic joint infection. *ANZ J Surg.* 2016;86:1014-1018. doi:10.1111/ans.13720
15. Teillant A, Gandra S, Barter D, Morgan DJ, Laxminarayan R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *Lancet Infect Dis.* 2015;15:1429-1437. doi:10.1016/S1473-3099(15)00270-4
16. Gourd E. Biden determined to “end cancer as we know it.” *Lancet Oncol.* 2021;22:759. doi:10.1016/S1470-2045(21)00282-5
17. Ma J, Jemal A, Fedewa SA, et al. The American Cancer Society 2035 challenge goal on cancer mortality reduction. *CA Cancer J Clin.* 2019;69:351-362. doi:10.3322/caac.21564
18. Vazquez-Lopez R, Rivero Rojas O, Ibarra Moreno A, et al. Antibiotic-resistant septicemia in pediatric oncology patients associated with post-therapeutic neutropenic fever. *Antibiotics (Basel).* 2019;8:106. doi:10.3390/antibiotics8030106
19. Williams MD, Braun LA, Cooper LM, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care.* 2004;8:R291-R298. doi:10.1186/cc2893
20. Montassier E, Bataud E, Gastinne T, Potel G, de La Cochetiere MF. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. *Eur J Clin Microbiol Infect Dis.* 2013;32:841-850. doi:10.1007/s10096-013-1819-7
21. Moghnieh R, Estaitieh N, Mugharbil A, et al. Third generation cephalosporin resistant Enterobacteriaceae and multidrug resistant Gram-negative bacteria causing bacteremia in febrile neutropenia adult cancer patients in Lebanon, broad spectrum antibiotics use as a major risk factor, and correlation with poor prognosis. *Front Cell Infect Microbiol.* 2015;5:11. doi:10.3389/fcimb.2015.00011
22. Trecarichi EM, Tumbarello M. Antimicrobial-resistant Gram-negative bacteria in febrile neutropenic patients with cancer: current epidemiology and clinical impact. *Curr Opin Infect Dis.* 2014;27:200-210. doi:10.1097/QCO.000000000000038
23. Thorpe KE, Joski P, Johnston KJ. Antibiotic-resistant infection treatment costs have doubled since 2002, now exceeding \$2 billion annually. *Health Aff (Millwood).* 2018;37:662-669. doi:10.1377/hlthaff.2017.1153
24. The Longitude Prize. Effectiveness of Cancer Treatments Threatened by Rising Antibiotic Resistance. Accessed November 24, 2020. longitudeprize.org/resources/effectiveness-cancer-treatments-threatened-rising-antibiotic-resistance
25. Lee CR, Cho IH, Jeong BC, Lee SH. Strategies to minimize antibiotic resistance. *Int J Environ Res Public Health.* 2013;10:4274-4305. doi:10.3390/ijerph10094274
26. Li B, Webster TJ. Bacteria antibiotic resistance: new challenges and opportunities for implant-associated orthopedic infections. *J Orthop Res.* 2018;36:22-32. doi:10.1002/jor.23656
27. Giacomini E, Perrone V, Alessandrini D, Paoli D, Nappi C, Degli Esposti L. Evidence of antibiotic resistance from population-based studies: a narrative review. *Infect Drug Resist.* 2021;14:849-858. doi:10.2147/IDR.S289741
28. Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ. Molecular mechanisms of antibiotic resistance. *Nat Rev Microbiol.* 2015;13:42-51. doi:10.1038/nrmicro3380
29. Bax R, Griffin D. Introduction to antibiotic resistance. *Handb Exp Pharmacol.* 2012;211:1-12. doi:10.1007/978-3-642-28951-4_1
30. Kapoor G, Saigal S, Elongavan A. Action and resistance mechanisms of antibiotics: a guide for clinicians. *J Anaesthesiol Clin Pharmacol.* 2017;33:300-305. doi:10.4103/joacp.JOACP_349_15
31. Zhang Y, Zhao C, Wang Q, et al. High prevalence of hypervirulent Klebsiella pneumoniae infection in China: geographic distribution, clinical characteristics, and antimicrobial resistance. *Antimicrob Agents Chemother.* 2016;60:6115-6120. doi:10.1128/AAC.01127-16
32. Cornejo-Juarez P, Vilar-Compte D, Perez-Jimenez C, Namendys-Silva SA, Sandoval-Hernandez S, Volkow-Fernandez P. The impact of hospital-acquired infections with multidrug-resistant bacteria in an oncology intensive care unit. *Int J Infect Dis.* 2015;31:31-34. doi:10.1016/j.ijid.2014.12.022
33. Satlin MJ, Chen L, Patel G, et al. Multicenter clinical and molecular epidemiological analysis of bacteremia due to carbapenem-resistant Enterobacteriaceae (CRE) in the CRE epicenter of the United States. *Antimicrob Agents Chemother.* 2017;61:e02349-16. doi:10.1128/AAC.02349-16
34. Bodro M, Gudiol C, Garcia-Vidal C, et al. Epidemiology, antibiotic therapy and outcomes of bacteremia caused by drug-resistant ESKAPE pathogens in cancer patients. *Support Care Cancer.* 2014;22:603-610. doi:10.1007/s00520-013-2012-3
35. Toleman MA, Rolston K, Jones RN, Walsh TR. blaVIM-7, an evolutionarily distinct metallo-beta-lactamase gene in a Pseudomonas aeruginosa isolate from the United States. *Antimicrob Agents Chemother.* 2004;48:329-332. doi:10.1128/AAC.48.1.329-332.2004
36. Kim J, Greenberg DE, Pifer R, et al. VAMPr: VArIant Mapping and Prediction of antibiotic resistance via explainable features and machine learning. *PLoS Comput Biol.* 2020;16:e1007511. doi:10.1371/journal.pcbi.1007511
37. Conrad S, Oethinger M, Kaifell K, Klotz G, Marre R, Kern WV. gyrA mutations in high-level fluoroquinolone-resistant clinical isolates of Escherichia coli. *J Antimicrob Chemother.* 1996;38:443-455. doi:10.1093/jac/38.3.443
38. Hamed SM, Elkhatib WF, El-Mahallawy HA, Helmy MM, Ashour MS, Aboshanab KMA. Multiple mechanisms contributing to ciprofloxacin resistance among Gram negative bacteria causing infections to cancer patients. *Sci Rep.* 2018;8:12268. doi:10.1038/s41598-018-30756-4
39. Satlin MJ, Calfee DP, Chen L, et al. Emergence of carbapenem-resistant Enterobacteriaceae as causes of bloodstream infections in patients with hematologic malignancies. *Leuk Lymphoma.* 2013;54:799-806. doi:10.3109/10428194.2012.723210
40. Centers for Disease Control and Prevention (CDC). ESBL-Producing Enterobacteriales in Healthcare Settings. CDC; 2019. Accessed July 19, 2021. cdc.gov/hai/organisms/ESBL.html
41. Centers for Disease Control and Prevention (CDC). Carbapenem-Resistant Enterobacteriales (CRE). CDC; 2019. Accessed July 19, 2021. cdc.gov/hai/organisms/cre/index.html
42. Centers for Disease Control and Prevention. Antibiotic Resistance & Patient Safety Portal. Accessed May 28, 2021. arpsp.cdc.gov/profile/antibiotic-resistance?tab=antibiotic-resistance
43. Centers for Disease Control and Prevention. Glossary of Terms Related to Antibiotic Resistance. Accessed May 28, 2021. cdc.gov/narms/resources/glossary.html
44. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J Infect Dis.* 2008;197:1079-1081. doi:10.1086/533452

45. Rolston KV. Infections in cancer patients with solid tumors: a review. *Infect Dis Ther.* 2017;6:69-83. doi:10.1007/s40121-017-0146-1
46. Zheng Y, Chen Y, Yu K, et al. Fatal infections among cancer patients: a population-based study in the United States. *Infect Dis Ther.* 2021;10:871-895. doi:10.1007/s40121-021-00433-7
47. Zembower TR. Epidemiology of infections in cancer patients. *Cancer Treat Res.* 2014;161:43-89. doi:10.1007/978-3-319-04220-6_2
48. O'Dowd A. Death certificates should record antimicrobial resistance as cause of deaths, says CMO. *BMJ.* 2018;362:k3832. doi:10.1136/k3832
49. O'Connor D, Bate J, Wade R, et al. Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL2003. *Blood.* 2014;124:1056-1061. doi:10.1182/blood-2014-03-560847
50. Taur Y, Pamer EG. Microbiome mediation of infections in the cancer setting. *Genome Med.* 2016;8:40. doi:10.1186/s13073-016-0306-z
51. Park SY, Kim MS, Eom JS, Lee JS, Rho YS. Risk factors and etiology of surgical site infection after radical neck dissection in patients with head and neck cancer. *Korean J Intern Med.* 2016;31:162-169. doi:10.3904/kjim.2016.31.1.162
52. Rapoport BL. Management of the cancer patient with infection and neutropenia. *Semin Oncol.* 2011;38:424-430. doi:10.1053/j.seminoncol.2011.03.013
53. Alonso CD, Marr KA. Clostridium difficile infection among hematopoietic stem cell transplant recipients: beyond colitis. *Curr Opin Infect Dis.* 2013;26:326-331. doi:10.1097/QCO.0b013e3283630c4c
54. Kyi C, Hellmann MD, Wolchok JD, Chapman PB, Postow MA. Opportunistic infections in patients treated with immunotherapy for cancer. *J Immunother Cancer.* 2014;2:19. doi:10.1186/2051-1426-2-19
55. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol.* 2013;13:862-874. doi:10.1038/nri3552
56. Del Castillo M, Romero FA, Arguello E, Kyi C, Postow MA, Redelman-Sidi G. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. *Clin Infect Dis.* 2016;63:1490-1493. doi:10.1093/cid/ciw539
57. Lustberg MB. Management of neutropenia in cancer patients. *Clin Adv Hematol Oncol.* 2012;10:825-826.
58. Scheler M, Lehrnbecher T, Groll AH, et al. Management of children with fever and neutropenia: results of a survey in 51 pediatric cancer centers in Germany, Austria, and Switzerland. *Infection.* 2020;48:607-618. doi:10.1007/s15010-020-01462-z
59. Xie O, Slavin MA, Teh BW, Bajel A, Douglas AP, Worth LJ. Epidemiology, treatment and outcomes of bloodstream infection due to vancomycin-resistant enterococci in cancer patients in a vanB endemic setting. *BMC Infect Dis.* 2020;20:228. doi:10.1186/s12879-020-04952-5
60. Tedim AP, Ruiz-Garbajosa P, Rodriguez MC, et al. Long-term clonal dynamics of Enterococcus faecium strains causing bloodstream infections (1995-2015) in Spain. *J Antimicrob Chemother.* 2017;72:48-55. doi:10.1093/jac/dkw366
61. Tofas P, Samarkos M, Piperaki ET, et al. Pseudomonas aeruginosa bacteraemia in patients with hematologic malignancies: risk factors, treatment and outcome. *Diagn Microbiol Infect Dis.* 2017;88:335-341. doi:10.1016/j.diagmicrobio.2017.05.003
62. Cornejo-Juarez P, Cevallos MA, Castro-Jaimes S, et al. High mortality in an outbreak of multidrug resistant Acinetobacter baumannii infection introduced to an oncological hospital by a patient transferred from a general hospital. *PLoS One.* 2020;15:e0234684. doi:10.1371/journal.pone.0234684
63. Cornejo-Juarez P, Vilar-Compte D, Garcia-Horton A, Lopez-Velazquez M, Namendys-Silva S, Volkow-Fernandez P. Hospital-acquired infections at an oncological intensive care cancer unit: differences between solid and hematological cancer patients. *BMC Infect Dis.* 2016;16:274. doi:10.1186/s12879-016-1592-1
64. Sanchez-Diaz AM, Cuartero C, Rodriguez JD, et al. The rise of ampicillin-resistant Enterococcus faecium high-risk clones as a frequent intestinal colonizer in oncohaematological neutropenic patients on levofloxacin prophylaxis: a risk for bacteraemia? *Clin Microbiol Infect.* 2016;22:59.e1-59.e8. doi:10.1016/j.cmi.2015.08.008
65. Alatorre-Fernandez P, Mayoral-Teran C, Velazquez-Acosta C, et al. A polyclonal outbreak of bloodstream infections by Enterococcus faecium in patients with hematologic malignancies. *Am J Infect Control.* 2017;45:260-266. doi:10.1016/j.ajic.2016.10.002
66. Hakki M, Humphries RM, Hemarajata P, et al. Fluoroquinolone prophylaxis selects for meropenem-nonsusceptible Pseudomonas aeruginosa in patients with hematologic malignancies and hematopoietic cell transplant recipients. *Clin Infect Dis.* 2019;68:2045-2052. doi:10.1093/cid/ciy825
67. Gudiol C, Albasanz-Puig A, Laporte-Amargos J, et al. Clinical predictive model of multidrug resistance in neutropenic cancer patients with bloodstream infection due to Pseudomonas aeruginosa. *Antimicrob Agents Chemother.* 2020;64:e02494-19. doi:10.1128/AAC.02494-19
68. Ding L, Yang Z, Lu J, et al. Characterization of phenotypic and genotypic traits of Klebsiella pneumoniae from lung cancer patients with respiratory infection. *Infect Drug Resist.* 2020;13:237-245. doi:10.2147/IDR.S229085
69. Liu J, Wang H, Huang Z, et al. Risk factors and outcomes for carbapenem-resistant Klebsiella pneumoniae bacteraemia in onco-hematological patients. *J Infect Dev Ctries.* 2019;13:357-364. doi:10.3855/jidc.11189
70. Bello-Chavolla OY, Bahena-Lopez JP, Garciadiego-Fosass P, et al. Bloodstream infection caused by S. aureus in patients with cancer: a 10-year longitudinal single-center study. *Support Care Cancer.* 2018;26:4057-4065. doi:10.1007/s00520-018-4275-1
71. Emge DA, Bassett RL, Duvic M, Huen AO. Methicillin-resistant Staphylococcus aureus (MRSA) is an important pathogen in erythrodermic cutaneous T-cell lymphoma (CTCL) patients. *Arch Dermatol Res.* 2020;312:283-288. doi:10.1007/s00403-019-02015-7
72. Shehata MMK, Radwan SM, Ali SAM. Effects of gamma-irradiation on antibiotic resistance and diagnostic molecular markers of methicillin-resistant Staphylococcus aureus in Egyptian cancer patients. *Int J Radiat Biol.* 2019;95:1728-1743. doi:10.1080/09553002.2019.1664785
73. Wasfi R, Rasslan F, Hassan SS, Ashour HM, Abd El-Rahman OA. Co-existence of carbapenemase-encoding genes in Acinetobacter baumannii from cancer patients. *Infect Dis Ther.* 2021;10:291-305. doi:10.1007/s40121-020-00369-4
74. Wang X, Zhang L, Sun A, et al. Acinetobacter baumannii bacteraemia in patients with haematological malignancy: a multicentre retrospective study from the Infection Working Party of Jiangsu Society of Hematology. *Eur J Clin Microbiol Infect Dis.* 2017;36:1073-1081. doi:10.1007/s10096-016-2895-2
75. Weiner-Lastinger LM, Abner S, Benin AL, et al. Antimicrobial-resistant pathogens associated with pediatric

- healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015-2017. *Infect Control Hosp Epidemiol.* 2020;41:19-30. doi:10.1017/ice.2019.297
76. Weiner-Lastinger LM, Abner S, Edwards JR, et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015-2017. *Infect Control Hosp Epidemiol.* 2020;41:1-18. doi:10.1017/ice.2019.296
 77. Allam O, Park KE, Chandler L, et al. The impact of radiation on lymphedema: a review of the literature. *Gland Surg.* 2020;9:596-602. doi:10.21037/ggs.2020.03.20
 78. Paskett ED, Stark N. Lymphedema: knowledge, treatment, and impact among breast cancer survivors. *Breast J.* 2000;6:373-378. doi:10.1046/j.1524-4741.2000.99072.x
 79. Moore JX, Akinyemiju T, Bartolucci A, Wang HE, Waterbor J, Griffin R. A prospective study of cancer survivors and risk of sepsis within the REGARDS cohort. *Cancer Epidemiol.* 2018;55:30-38. doi:10.1016/j.canep.2018.05.001
 80. Johnson K, Boucher HW. Editorial commentary: imminent challenges: carbapenem-resistant Enterobacteriaceae in transplant recipients and patients with hematologic malignancy. *Clin Infect Dis.* 2014;58:1284-1286. doi:10.1093/cid/ciu056
 81. Zhao Y, Lin Q, Liu L, et al. Risk factors and outcomes of antibiotic-resistant *Pseudomonas aeruginosa* bloodstream infection in adult patients with acute leukemia. *Clin Infect Dis.* 2020;71(suppl 4):S386-S393. doi:10.1093/cid/ciaa1522
 82. Pouch SM, Satlin MJ. Carbapenem-resistant Enterobacteriaceae in special populations: solid organ transplant recipients, stem cell transplant recipients, and patients with hematologic malignancies. *Virulence.* 2017;8:391-402. doi:10.1080/21505594.2016.1213472
 83. Scheich S, Weber S, Reinheimer C, et al. Bloodstream infections with gram-negative organisms and the impact of multidrug resistance in patients with hematological malignancies. *Ann Hematol.* 2018;97:2225-2234. doi:10.1007/s00277-018-3423-5
 84. Cattaneo C, Di Blasi R, Skert C, et al. Bloodstream infections in hematological cancer patients colonized by multidrug-resistant bacteria. *Ann Hematol.* 2018;97:1717-1726. doi:10.1007/s00277-018-3341-6
 85. Levene I, Castagnola E, Haeusler GM. Antibiotic-resistant Gram-negative bloodstream infections in children with cancer: a review of epidemiology, risk factors, and outcome. *Pediatr Infect Dis J.* 2018;37:495-498. doi:10.1097/INF.0000000000001938
 86. Marin M, Gudiol C, Garcia-Vidal C, Ardanuy C, Carratala J. Bloodstream infections in patients with solid tumors: epidemiology, antibiotic therapy, and outcomes in 528 episodes in a single cancer center. *Medicine (Baltimore).* 2014;93:143-149. doi:10.1097/MD.0000000000000026
 87. Antonio M, Gudiol C, Royo-Cebrecos C, Grillo S, Ardanuy C, Carratala J. Current etiology, clinical features and outcomes of bacteremia in older patients with solid tumors. *J Geriatr Oncol.* 2019;10:246-251. doi:10.1016/j.jgo.2018.06.011
 88. Zhang Y, Zheng Y, Dong F, et al. Epidemiology of febrile neutropenia episodes with Gram-negative bacteria infection in patients who have undergone chemotherapy for hematologic malignancies: a retrospective study of 10 years' data from a single center. *Infect Drug Resist.* 2020;13:903-910. doi:10.2147/IDR.S241263
 89. Vinker-Shuster M, Stepensky P, Temper V, Shayovitz V, Masarwa R, Averbuch D. Gram-negative bacteremia in children with hematologic malignancies and following hematopoietic stem cell transplantation: epidemiology, resistance, and outcome. *J Pediatr Hematol Oncol.* 2019;41:e493-e498. doi:10.1097/MPH.0000000000001556
 90. Gudiol C, Aguado JM, Carratala J. Bloodstream infections in patients with solid tumors. *Virulence.* 2016;7:298-308. doi:10.1080/21505594.2016.1141161
 91. Marin M, Gudiol C, Ardanuy C, et al. Bloodstream infections in neutropenic patients with cancer: differences between patients with hematological malignancies and solid tumours. *J Infect.* 2014;69:417-423. doi:10.1016/j.jinf.2014.05.018
 92. Shrestha G, Wei X, Hann K, et al. Bacterial profile and antibiotic resistance among cancer patients with urinary tract infection in a national tertiary cancer hospital of Nepal. *Trop Med Infect Dis.* 2021;6:49. doi:10.3390/tropicalme6020049
 93. Fentie A, Wondimeneh Y, Balcha A, Amsalu A, Adankie BT. Bacterial profile, antibiotic resistance pattern and associated factors among cancer patients at University of Gondar Hospital, Northwest Ethiopia. *Infect Drug Resist.* 2018;11:2169-2178. doi:10.2147/IDR.S183283
 94. Islas-Munoz B, Volkow-Fernandez P, Ibanes-Gutierrez C, Villamar-Ramirez A, Vilar-Compte D, Cornejo-Juarez P. Bloodstream infections in cancer patients. Risk factors associated with mortality. *Int J Infect Dis.* 2018;71:59-64. doi:10.1016/j.ijid.2018.03.022
 95. Royo-Cebrecos C, Gudiol C, Garcia J, et al. Characteristics, aetiology, antimicrobial resistance and outcomes of bacteraemic cholangitis in patients with solid tumours: a prospective cohort study. *J Infect.* 2017;74:172-178. doi:10.1016/j.jinf.2016.10.008
 96. Boehm K, Siegel FP, Schneidewind L, et al. Antibiotic prophylaxis in prostate biopsies: contemporary practice patterns in Germany. *Front Surg.* 2018;5:2. doi:10.3389/fsurg.2018.00002
 97. Johansen TEB, Zahl PH, Baco E, et al. Antibiotic resistance, hospitalizations, and mortality related to prostate biopsy: first report from the Norwegian Patient Registry. *World J Urol.* 2020;38:17-26. doi:10.1007/s00345-019-02837-0
 98. Derin O, Fonseca L, Sanchez-Salas R, Roberts MJ. Infectious complications of prostate biopsy: winning battles but not war. *World J Urol.* 2020;38:2743-2753. doi:10.1007/s00345-020-03112-3
 99. Sieczkowski M, Gibas A, Wasik A, et al. Drug-eluting biopsy needle as a novel strategy for antimicrobial prophylaxis in transrectal prostate biopsy. *Technol Cancer Res Treat.* 2017;16:1038-1043. doi:10.1177/1533034617722080
 100. Ryu JW, Jung SI, Ahn JH, et al. Povidone-iodine rectal cleansing and targeted antimicrobial prophylaxis using rectal swab cultures in men undergoing transrectal ultrasound-guided prostate biopsy are associated with reduced incidence of postoperative infectious complications. *Int Urol Nephrol.* 2016;48:1763-1770. doi:10.1007/s11255-016-1394-9
 101. Cussans A, Somani BK, Basarab A, Dudderidge TJ. The role of targeted prophylactic antimicrobial therapy before transrectal ultrasonography-guided prostate biopsy in reducing infection rates: a systematic review. *BJU Int.* 2016;117:725-731. doi:10.1111/bju.13402
 102. Zavala VA, Bracci PM, Carethers JM, et al. Cancer health disparities in racial/ethnic minorities in the United States. *Br J Cancer.* 2021;124:315-332. doi:10.1038/s41416-020-01038-6
 103. Nadimpalli ML, Chan CW, Doron S. Antibiotic resistance: a call to action to prevent the next epidemic of inequality. *Nat Med.* 2021;27:187-188. doi:10.1038/s41591-020-01201-9
 104. Dadgostar P. Antimicrobial resistance: implications and costs. *Infect Drug*

- Resist.* 2019;12:3903-3910. doi:10.2147/IDR.S234610
105. Nelson RE, Hatfield KM, Wolford H, et al. National estimates of healthcare costs associated with multidrug-resistant bacterial infections among hospitalized patients in the United States. *Clin Infect Dis.* 2021;72(suppl 1):S17-S26. doi:10.1093/cid/ciaa1581
 106. Stokes ME, Muehlenbein CE, Marciniak MD, et al. Neutropenia-related costs in patients treated with first-line chemotherapy for advanced non-small cell lung cancer. *J Manag Care Pharm.* 2009;15:669-682. doi:10.18553/jmcp.2009.15.8.669
 107. Tai E, Guy GP, Dunbar A, Richardson LC. Cost of cancer-related neutropenia or fever hospitalizations, United States, 2012. *J Oncol Pract.* 2017;13:e552-e561. doi:10.1200/JOP.2016.019588
 108. Tori K, Tansarli GS, Parente DM, Kalligeros M, Ziakas PD, Mylonakis E. The cost-effectiveness of empirical antibiotic treatments for high-risk febrile neutropenic patients: a decision analytic model. *Medicine (Baltimore).* 2020;99:e20022. doi:10.1097/MD.00000000000020022
 109. Watters K, O'Dwyer TP, Rowley H. Cost and morbidity of MRSA in head and neck cancer patients: what are the consequences? *J Laryngol Otol.* 2004;118:694-699. doi:10.1258/0022215042244732
 110. 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:CD004386. doi:10.1002/14651858.CD004386.pub3
 111. Ziegler M, Landsburg D, Pegues D, et al. Fluoroquinolone prophylaxis is highly effective for the prevention of central line-associated bloodstream infections in autologous stem cell transplant patients. *Biol Blood Marrow Transplant.* 2019;25:1004-1010. doi:10.1016/j.bbmt.2018.11.023
 112. Carmona-Bayonas A, Jimenez-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.* 2015;33:465-471. doi:10.1200/JCO.2014.57.2347
 113. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer.* 2006;106:2258-2266. doi:10.1002/cncr.21847
 114. Legrand M, Max A, Peigne V, et al. Survival in neutropenic patients with severe sepsis or septic shock. *Crit Care Med.* 2012;40:43-49. doi:10.1097/CCM.0b013e31822b50c2
 115. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med.* 2005;353:977-987. doi:10.1056/NEJMoA044097
 116. Cullen M, Steven N, Billingham L, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med.* 2005;353:988-998. doi:10.1056/NEJMoA050078
 117. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med.* 2005;142(12 pt 1):979-995. doi:10.7326/0003-4819-142-12_part_1-200506210-00008
 118. Razonable RR, Litzow MR, Khaliq Y, Piper KE, Rouse MS, Patel R. Bacteremia due to viridans group Streptococci with diminished susceptibility to levofloxacin among neutropenic patients receiving levofloxacin prophylaxis. *Clin Infect Dis.* 2002;34:1469-1474. doi:10.1086/340352
 119. Zervos MJ, Hershberger E, Nicolau DP, et al. Relationship between fluoroquinolone use and changes in susceptibility to fluoroquinolones of selected pathogens in 10 United States teaching hospitals, 1991-2000. *Clin Infect Dis.* 2003;37:1643-1648. doi:10.1086/379709
 120. Kern WV, Steib-Bauert M, de With K, et al. Fluoroquinolone consumption and resistance in haematology-oncology patients: ecological analysis in two university hospitals 1999-2002. *J Antimicrob Chemother.* 2005;55:57-60. doi:10.1093/jac/dkh510
 121. Mikulska M, Averbuch D, Tissot F, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. *J Infect.* 2018;76:20-37. doi:10.1016/j.jinf.2017.10.009
 122. Ramasamy K. Reducing infection-related morbidity and mortality in patients with myeloma. *Lancet Oncol.* 2019;20:1633-1635. doi:10.1016/S1470-2045(19)30649-7
 123. Slavin MA, Worth LJ, Seymour JF, Thursky KA. Better sepsis management rather than fluoroquinolone prophylaxis for patients with cancer-related immunosuppression. *J Clin Oncol.* 2019;37:1139-1140. doi:10.1200/JCO.18.01474
 124. Verlinden A, Schroyens WA, Gadiisseur AP. Clinical and microbiological impact of long-term discontinuation of fluoroquinolone prophylaxis in haematological patients with prolonged profound neutropenia. *Eur J Haematol.* 2021;107:377-379. doi:10.1111/ejh.13670
 125. Centers for Disease Control and Prevention. Preventing Infections in Cancer Patients. Accessed November 11, 2020. [cdc.gov/cancer/preventinfections/index.htm](https://www.cdc.gov/cancer/preventinfections/index.htm)
 126. American Cancer Society. Infections in People With Cancer. Accessed November 11, 2020. [cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/infections.html](https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/infections.html)
 127. National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections. Accessed February 26, 2021. [nccn.org/professionals/physician_gls/default.aspx](https://www.nccn.org/professionals/physician_gls/default.aspx)
 128. Montassier E, Gastinne T, Vangay P, et al. Chemotherapy-driven dysbiosis in the intestinal microbiome. *Aliment Pharmacol Ther.* 2015;42:515-528. doi:10.1111/apt.13302
 129. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol.* 2008;6:e280. doi:10.1371/journal.pbio.0060280
 130. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci U S A.* 2011;108(suppl 1):4554-4561. doi:10.1073/pnas.1000087107
 131. Pilmis B, Le Monnier A, Zahar JR. Gut microbiota, antibiotic therapy and antimicrobial resistance: a narrative review. *Microorganisms.* 2020;8:269. doi:10.3390/microorganisms8020269
 132. Holler E, Butzhammer P, Schmid K, et al. Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft-versus-host disease. *Biol Blood Marrow Transplant.* 2014;20:640-645. doi:10.1016/j.bbmt.2014.01.030
 133. Petrelli F, Iaculli A, Signorelli D, et al. Survival of patients treated with antibiotics and immunotherapy for cancer: a systematic review and meta-analysis. *J Clin Med.* 2020;9:1458. doi:10.3390/jcm9051458
 134. Kim SG, Becattini S, Moody TU, et al. Microbiota-derived lantibiotic restores resistance against vancomycin-resistant Enterococcus. *Nature.* 2019;572:665-669. doi:10.1038/s41586-019-1501-z

135. Koh AY. Potential for monitoring gut microbiota for diagnosing infections and graft-versus-host disease in cancer and stem cell transplant patients. *Clin Chem*. 2017;63:1685-1694. doi:10.1373/clinchem.2016.259499
136. Salgia NJ, Bergerot PG, Maia MC, et al. Stool microbiome profiling of patients with metastatic renal cell carcinoma receiving anti-PD-1 immune checkpoint inhibitors. *Eur Urol*. 2020;78:498-502. doi:10.1016/j.eururo.2020.07.011
137. Willems RJ, Top J, van Santen M, et al. Global spread of vancomycin-resistant *Enterococcus faecium* from distinct nosocomial genetic complex. *Emerg Infect Dis*. 2005;11:821-828. doi:10.3201/1106.041204
138. Arcilla MS, van Hattem JM, Haverkate MR, et al. Import and spread of extended-spectrum beta-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. *Lancet Infect Dis*. 2017;17:78-85. doi:10.1016/S1473-3099(16)30319-X
139. Frost I, Van Boeckel TP, Pires J, Craig J, Laxminarayan R. Global geographic trends in antimicrobial resistance: the role of international travel. *J Travel Med*. 2019;26:taz036. doi:10.1093/jtm/taz036
140. Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol*. 2003;24:699-706. doi:10.1086/502278
141. Schentag JJ, Ballow CH, Fritz AL, et al. Changes in antimicrobial agent usage resulting from interactions among clinical pharmacy, the infectious disease division, and the microbiology laboratory. *Diagn Microbiol Infect Dis*. 1993;16:255-264. doi:10.1016/0732-8893(93)90119-r
142. Ansari F, Gray K, Nathwani D, et al. Outcomes of an intervention to improve hospital antibiotic prescribing: interrupted time series with segmented regression analysis. *J Antimicrob Chemother*. 2003;52:842-848. doi:10.1093/jac/dkg459
143. Cole KA, Rivard KR, Dumkowi LE. Antimicrobial stewardship interventions to combat antibiotic resistance: an update on targeted strategies. *Curr Infect Dis Rep*. 2019;21:33. doi:10.1007/s11908-019-0689-2
144. Klepser ME, Adams AJ, Klepser DG. Antimicrobial stewardship in outpatient settings: leveraging innovative physician-pharmacist collaborations to reduce antibiotic resistance. *Health Secur*. 2015;13:166-173. doi:10.1089/hs.2014.0083
145. Zhang ZG, Chen F, Ou Y. Impact of an antimicrobial stewardship programme on antibiotic usage and resistance in a tertiary hospital in China. *J Clin Pharm Ther*. 2017;42:579-584. doi:10.1111/jcpt.12544
146. Petrelli F, Ghidini M, Ghidini A, et al. Use of antibiotics and risk of cancer: a systematic review and meta-analysis of observational studies. *Cancers (Basel)*. 2019;11:1174. doi:10.3390/cancers11081174
147. Peyrony O, Gerlier C, Barla I, et al. Antibiotic prescribing and outcomes in cancer patients with febrile neutropenia in the emergency department. *PLoS One*. 2020;15:e0229828. doi:10.1371/journal.pone.0229828
148. Spellberg B. The new antibiotic mantra—“shorter is better.” *JAMA Intern Med*. 2016;176:1254-1255. doi:10.1001/jamainternmed.2016.3646
149. Koenig C, Schneider C, Morgan JE, Ammann RA, Sung L, Phillips B. Association of time to antibiotics and clinical outcomes in patients with fever and neutropenia during chemotherapy for cancer: a systematic review. *Support Care Cancer*. 2020;28:1369-1383. doi:10.1007/s00520-019-04961-4
150. Kim NH, Koo HL, Choe PG, et al. Inappropriate continued empirical vancomycin use in a hospital with a high prevalence of methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2015;59:811-817. doi:10.1128/AAC.04523-14
151. 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:e56-93. doi:10.1093/cid/cir073
152. Schmidt-Hieber M, Teschner D, Maschmeyer G, Schalk E. Management of febrile neutropenia in the perspective of antimicrobial de-escalation and discontinuation. *Expert Rev Anti Infect Ther*. 2019;17:983-995. doi:10.1080/14787210.2019.1573670
153. Le Clech L, Talarmin JP, Couturier MA, et al. Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study. *Infect Dis (Lond)*. 2018;50:539-549. doi:10.1080/23744235.2018.1438649
154. Heinz WJ, Buchheidt D, Christopheit M, et al. Diagnosis and empirical treatment of fever of unknown origin (FUO) in adult neutropenic patients: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Hematol*. 2017;96:1775-1792. doi:10.1007/s00277-017-3098-3
155. Rearigh L, Stohs E, Freifeld A, Zimmer A. De-escalation of empiric broad spectrum antibiotics in hematopoietic stem cell transplant recipients with febrile neutropenia. *Ann Hematol*. 2020;99:1917-1924. doi:10.1007/s00277-020-04132-0
156. Aguilar-Guisado M, Espigado I, Martin-Pena 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:e573-e583. doi:10.1016/S2352-3026(17)30211-9
157. la Martire G, Robin C, Oubaya N, et al. De-escalation and discontinuation strategies in high-risk neutropenic patients: an interrupted time series analyses of antimicrobial consumption and impact on outcome. *Eur J Clin Microbiol Infect Dis*. 2018;37:1931-1940. doi:10.1007/s10096-018-3328-1
158. Puerta-Alcalde P, Cardozo C, Suarez-Lledo M, et al. Current time-to-positivity of blood cultures in febrile neutropenia: a tool to be used in stewardship de-escalation strategies. *Clin Microbiol Infect*. 2019;25:447-453. doi:10.1016/j.cmi.2018.07.026
159. Byun JM, Jeong DH. Antibiotic prophylaxis for gynecologic cancer surgery. *Taiwan J Obstet Gynecol*. 2020;59:514-519. doi:10.1016/j.tjog.2020.05.008
160. Gerding DN. The search for good antimicrobial stewardship. *Jt Comm J Qual Improv*. 2001;27:403-404. doi:10.1016/s1070-3241(01)27034-5
161. Doron S, Davidson LE. Antimicrobial stewardship. *Mayo Clin Proc*. 2011;86:1113-1123. doi:10.4066/mcp.2011.0358
162. Gudiol C, Carratala J. Antibiotic resistance in cancer patients. *Expert Rev Anti Infect Ther*. 2014;12:1003-1016. doi:10.1586/14787210.2014.920253
163. Wolf J, Margolis E. Effect of antimicrobial stewardship on outcomes in patients with cancer or undergoing hematopoietic stem cell transplantation. *Clin Infect Dis*. 2020;71:968-970. doi:10.1093/cid/ciz903
164. Rosa RG, Goldani LZ, dos Santos RP. Association between adherence to an antimicrobial stewardship program and mortality among hospitalised cancer patients with febrile

- neutropaenia: a prospective cohort study. *BMC Infect Dis.* 2014;14:286. doi:10.1186/1471-2334-14-286
165. Pillinger KE, Bouchard J, Withers ST, et al. Inpatient antibiotic stewardship interventions in the adult oncology and hematopoietic stem cell transplant population: a review of the literature. *Ann Pharmacother.* 2020;54:594-610. doi:10.1177/1060028019890886
 166. Bantar C, Sartori B, Vesco E, et al. A hospitalwide intervention program to optimize the quality of antibiotic use: impact on prescribing practice, antibiotic consumption, cost savings, and bacterial resistance. *Clin Infect Dis.* 2003;37:180-186. doi:10.1086/375818
 167. Rahal JJ, Urban C, Horn D, et al. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial *Klebsiella*. *JAMA.* 1998;280:1233-1237. doi:10.1001/jama.280.14.1233
 168. Cook PP, Catrou P, Gooch M, Holbert D. Effect of reduction in ciprofloxacin use on prevalence of methicillin-resistant *Staphylococcus aureus* rates within individual units of a tertiary care hospital. *J Hosp Infect.* 2006;64:348-351. doi:10.1016/j.jhin.2006.06.033
 169. Raymond DP, Pelletier SJ, Crabtree TD, et al. Impact of a rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. *Crit Care Med.* 2001;29:1101-1108. doi:10.1097/00003246-200106000-00001
 170. Timbrook TT, Hurst JM, Bosso JA. Impact of an antimicrobial stewardship program on antimicrobial utilization, bacterial susceptibilities, and financial expenditures at an academic medical center. *Hosp Pharm.* 2016;51:703-711. doi:10.1310/hpj5109-703
 171. Doernberg SB, Abbo LM, Burdette SD, et al. Essential resources and strategies for antibiotic stewardship programs in the acute care setting. *Clin Infect Dis.* 2018;67:1168-1174. doi:10.1093/cid/ciy255
 172. Centers for Disease Control and Prevention. Core Elements of Outpatient Antibiotic Stewardship. Accessed May 24, 2020. [cdc.gov/antibiotic-use/core-elements/outpatient.html](https://www.cdc.gov/antibiotic-use/core-elements/outpatient.html)
 173. Marcelin JR, Chung P, Van Schooneveld TC. Antimicrobial stewardship in the outpatient setting: a review and proposed framework. *Infect Control Hosp Epidemiol.* 2020;41:833-840. doi:10.1017/ice.2020.94
 174. US Food and Drug Administration. 2019 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. Accessed May 24, 2021. [fda.gov/animal-veterinary/cvm-updates/fda-releases-annual-summary-report-antimicrobials-sold-or-distributed-2019-use-food-producing](https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-annual-summary-report-antimicrobials-sold-or-distributed-2019-use-food-producing)
 175. Martin MJ, Thottathil SE, Newman TB. Antibiotics overuse in animal agriculture: a call to action for health care providers. *Am J Public Health.* 2015;105:2409-2410. doi:10.2105/AJPH.2015.302870
 176. Landers TF, Cohen B, Wittum TE, Larson EL. A review of antibiotic use in food animals: perspective, policy, and potential. *Public Health Rep.* 2012;127:4-22. doi:10.1177/003335491212700103
 177. Angulo FJ, Nargund VN, Chiller TC. Evidence of an association between use of anti-microbial agents in food animals and anti-microbial resistance among bacteria isolated from humans and the human health consequences of such resistance. *J Vet Med B Infect Dis Vet Public Health.* 2004;51:374-379. doi:10.1111/j.1439-0450.2004.00789.x
 178. Centers for Disease Control and Prevention. Food and Food Animals. Accessed May 24, 2021. [cdc.gov/drugresistance/food.html](https://www.cdc.gov/drugresistance/food.html)
 179. Chen Y, Hammer EE, Richards VP. Phylogenetic signature of lateral exchange of genes for antibiotic production and resistance among bacteria highlights a pattern of global transmission of pathogens between humans and livestock. *Mol Phylogenet Evol.* 2018;125:255-264. doi:10.1016/j.ympev.2018.03.034
 180. Thacker SB, Berkelman RL. Public health surveillance in the United States. *Epidemiol Rev.* 1988;10:164-190. doi:10.1093/oxfordjournals.epirev.a036021
 181. Simonsen GS. Antimicrobial resistance surveillance in Europe and beyond. *Euro Surveill.* 2018;23:1800560. doi:10.2807/1560-7917.ES.2018.23.42.1800560
 182. Perez F, Villegas MV. The role of surveillance systems in confronting the global crisis of antibiotic-resistant bacteria. *Curr Opin Infect Dis.* 2015;28:375-383. doi:10.1097/QCO.0000000000000182
 183. Tsutsui A, Suzuki S. Japan Nosocomial Infections Surveillance (JANIS): a model of sustainable national antimicrobial resistance surveillance based on hospital diagnostic microbiology laboratories. *BMC Health Serv Res.* 2018;18:799. doi:10.1186/s12913-018-3604-x
 184. Johnson AP. Surveillance of antibiotic resistance. *Philos Trans R Soc Lond B Biol Sci.* 2015;370:20140080. doi:10.1098/rstb.2014.0080
 185. Kadri SS, Boucher HW. U.S. Efforts to curb antibiotic resistance—are we saving lives? *N Engl J Med.* 2020;383:806-808. doi:10.1056/NEJMp2004743
 186. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. *Infect Control Hosp Epidemiol.* 2008;29:996-1011. doi:10.1086/591861
 187. Lake JG, Weiner LM, Milstone AM, Saiman L, Magill SS, See I. Pathogen distribution and antimicrobial resistance among pediatric healthcare-associated infections reported to the National Healthcare Safety Network, 2011-2014. *Infect Control Hosp Epidemiol.* 2018;39:1-11. doi:10.1017/ice.2017.236
 188. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. *Infect Control Hosp Epidemiol.* 2013;34:1-14. doi:10.1086/668770
 189. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol.* 2016;37:1288-1301. doi:10.1017/ice.2016.174
 190. Alm RA, Gallant K. Innovation in antimicrobial resistance: the CARB-X perspective. *ACS Infect Dis.* 2020;6:1317-1322. doi:10.1021/acscinfecdis.0c00026
 191. Rex JH, Fernandez Lynch H, Cohen IG, Darrow JJ, Outterson K. Designing development programs for non-traditional antibacterial agents. *Nat Commun.* 2019;10:3416. doi:10.1038/s41467-019-11303-9
 192. Rex JH, Outterson K. Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach. *Lancet Infect Dis.* 2016;16:500-505. doi:10.1016/S1473-3099(15)00500-9
 193. Ardal Cm Findlay D, Savic M, et al. Revitalizing the Antibiotic Pipeline: Stimulating Innovation While Driving Sustainable Use and Global Access. Final Report. DRIVE-AB; 2018. Accessed February 21, 2021. drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf
 194. Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB). Recommendations for Incentivizing the Development of Vaccines,

- Diagnostics, and Therapeutics to Combat Antibiotic-Resistance. PACCARB; 2017. Accessed February 21, 2021. [hhs.gov/web/508/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf](https://www.hhs.gov/web/508/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf)
195. O'Neill J. Review on Antimicrobial Resistance. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. Review on Antimicrobial Resistance; 2016. Accessed February 21, 2021. [amr-amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf](https://www.amr-amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf)
 196. Towse A, Hoyle CK, Goodall J, Hirsch M, Mestre-Ferrandiz J, Rex JH. Time for a change in how new antibiotics are reimbursed: development of an insurance framework for funding new antibiotics based on a policy of risk mitigation. *Health Policy*. 2017;121:1025-1030. doi:10.1016/j.healthpol.2017.07.011
 197. Dutescu IA, Hillier SA. Encouraging the development of new antibiotics: are financial incentives the right way forward? A systematic review and case study. *Infect Drug Resist*. 2021;14:415-434. doi:10.2147/IDR.S287792
 198. Spaulding CN, Klein RD, Schreiber HLT, Janetka JW, Hultgren SJ. Precision antimicrobial therapeutics: the path of least resistance? *NPJ Biofilms Microbiomes*. 2018;4:4. doi:10.1038/s41522-018-0048-3
 199. Karam G, Chastre J, Wilcox MH, Vincent JL. Antibiotic strategies in the era of multidrug resistance. *Crit Care*. 2016;20:136. doi:10.1186/s13054-016-1320-7
 200. Boucher HW, Ambrose PG, Chambers HF, et al. White paper: developing antimicrobial drugs for resistant pathogens, narrow-spectrum indications, and unmet needs. *J Infect Dis*. 2017;216:228-236. doi:10.1093/infdis/jix211
 201. Melander RJ, Zurawski DV, Melander C. Narrow-spectrum antibacterial agents. *Medchemcomm*. 2018;9:12-21. doi:10.1039/C7MD00528H
 202. Schooley RT, Biswas B, Gill JJ, et al. Development and use of personalized bacteriophage-based therapeutic cocktails to treat a patient with a disseminated resistant *Acinetobacter baumannii* infection. *Antimicrob Agents Chemother*. 2017;61:e00954-17. doi:10.1128/AAC.00954-17
 203. Regeimbal JM, Jacobs AC, Corey BW, et al. Personalized therapeutic cocktail of wild environmental phages rescues mice from *Acinetobacter baumannii* wound infections. *Antimicrob Agents Chemother*. 2016;60:5806-5816. doi:10.1128/AAC.02877-15
 204. Nielsen TB, Pantapalangkoor P, Luna BM, et al. Monoclonal antibody protects against *Acinetobacter baumannii* infection by enhancing bacterial clearance and evading sepsis. *J Infect Dis*. 2017;216:489-501. doi:10.1093/infdis/jix315
 205. Cotter PD, Ross RP, Hill C. Bacteriocins—a viable alternative to antibiotics? *Nat Rev Microbiol*. 2013;11:95-105. doi:10.1038/nrmicro2937
 206. Ghequire MG, Dingemans J, Pirnay JP, De Vos D, Cornelis P, De Mot R. O serotype-independent susceptibility of *Pseudomonas aeruginosa* to lectin-like pyocins. *Microbiologyopen*. 2014;3:875-884. doi:10.1002/mbo3.210
 207. Howard JJ, Sturge CR, Moustafa DA, et al. Inhibition of *Pseudomonas aeruginosa* by peptide-conjugated phosphorodiamidate morpholino oligomers. *Antimicrob Agents Chemother*. 2017;61:e01938-16. doi:10.1128/AAC.01938-16
 208. Moustafa DA, Wu AW, Zamora D, et al. Peptide-conjugated phosphorodiamidate morpholino oligomers retain activity against multidrug-resistant *Pseudomonas aeruginosa* in vitro and in vivo. *mBio*. 2021;12:e02411-20. doi:10.1128/mBio.02411-20
 209. Geller BL, Li L, Martinez F, et al. Morpholino oligomers tested in vitro, in biofilm and in vivo against multidrug-resistant *Klebsiella pneumoniae*. *J Antimicrob Chemother*. 2018;73:1611-1619. doi:10.1093/jac/dky058
 210. Sulakvelidze A, Alavidze Z, Morris JG Jr. Bacteriophage therapy. *Antimicrob Agents Chemother*. 2001;45:649-659. doi:10.1128/AAC.45.3.649-659.2001
 211. Drulis-Kawa Z, Majkowska-Skrobeck G, Maciejewska B, Delattre AS, Lavigne R. Learning from bacteriophages—advantages and limitations of phage and phage-encoded protein applications. *Curr Protein Pept Sci*. 2012;13:699-722. doi:10.2174/138920312804871193
 212. Zurawski DV, McLendon MK. Monoclonal antibodies as an antibacterial approach against bacterial pathogens. *Antibiotics (Basel)*. 2020;9:155. doi:10.3390/antibiotics9040155
 213. Motley MP, Banerjee K, Fries BC. Monoclonal antibody-based therapies for bacterial infections. *Curr Opin Infect Dis*. 2019;32:210-216. doi:10.1097/QCO.0000000000000539
 214. Joerger RD. Alternatives to antibiotics: bacteriocins, antimicrobial peptides and bacteriophages. *Poult Sci*. 2003;82:640-647. doi:10.1093/ps/82.4.640
 215. Yang SC, Lin CH, Sung CT, Fang JY. Antibacterial activities of bacteriocins: application in foods and pharmaceuticals. *Front Microbiol*. 2014;5:241. doi:10.3389/fmicb.2014.00241
 216. Shelburne SA, Kim J, Munita JM, et al. Whole-genome sequencing accurately identifies resistance to extended-spectrum beta-lactams for major Gram-negative bacterial pathogens. *Clin Infect Dis*. 2017;65:738-745. doi:10.1093/cid/cix417
 217. Li X, Lin J, Hu Y, Zhou J. PARMAP: a pan-genome-based computational framework for predicting antimicrobial resistance. *Front Microbiol*. 2020;11:578795. doi:10.3389/fmicb.2020.578795
 218. Hubbard ATM, Mason J, Roberts P, et al. Piperacillin/tazobactam resistance in a clinical isolate of *Escherichia coli* due to IS26-mediated amplification of blaTEM-1B. *Nat Commun*. 2020;11:4915. doi:10.1038/s41467-020-18668-2
 219. Maurer FP, Christner M, Hentschke M, Rohde H. Advances in rapid identification and susceptibility testing of bacteria in the clinical microbiology laboratory: implications for patient care and antimicrobial stewardship programs. *Infect Dis Rep*. 2017;9:6839. doi:10.4081/idr.2017.6839
 220. Maxson T, Mitchell DA. Targeted treatment for bacterial infections: prospects for pathogen-specific antibiotics coupled with rapid diagnostics. *Tetrahedron*. 2016;72:3609-3624. doi:10.1016/j.tet.2015.09.069
 221. Trevas D, Caliendo AM, Hanson K, Levy J, Ginocchio CC. Diagnostic tests can stem the threat of antimicrobial resistance: infectious disease professionals can help. *Clin Infect Dis*. 2021;72:e893-e900. doi:10.1093/cid/ciaa1527
 222. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the treatment of extended-spectrum beta-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-P. *aeruginosa*). *Clin Infect Dis*. 2021;72:e169-e183. doi:10.1093/cid/ciaa1478
 223. Baselga J, Bhardwaj N, Cantley LC, et al. AACR Cancer Progress Report 2015. *Clin Cancer Res*. 2015;21(19 suppl):S1-S128. doi:10.1158/1078-0432.CCR-15-1846