Antibiotic resistance in the patient with cancer: Escalating challenges and paths forward

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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.

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Bacterial resistance to penicillin was encountered in patients *(1)* 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 Administration *(16)* 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

Table 1: **Antibiotic-resistance mechanisms in ESKAPE bacteria**[a]

Resistance t ype (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	β-Lactamases	Penicillins	**ESBL-producing** *K. pneumoniae* (Zhang 2016[31])[b]
	Aminoglycoside-modifying enzymes	Aminoglycosides	**ESBL-producing** *E. coli* (Cornejo-Juarez 2015[32]) **CRE** *K. pneumoniae* (Satlin 2027[33])c **Carbapenem-resistant** *A. baumannii* (Bodro 2014[34]) **Methicillin-resistant** *S. aureus (MRSA)* (Bodro 201434) **Metallo β-lactamase–producing** *P. aeruginosa* (Toleman 2004[35])
Antibiotic target modification et al. 2017[65])	Alteration of the peptidogly can synthesis pathway	Glycopeptides	**Vancomycin-resistant** *E. faecium* (Alatorre-Fernandez et al. 2017[65])
	Mutations in DNA gyrase	Fluoroquinolones	**Fluoroquinolone-resistant clinical isolates of** *E. coli* (Conrad 1996[37])
	Ribosomal mutations	Tetracyclines	
Antibiotic efflux	Overexpression of multidrug-resistant	Tetracyclines and Fluoroquinolones	**Efflux pump-overexpressing** *K. pneumoniae* and *E. coli* (Hamed 2018[38])
Reduced permeability of antibiotic	Downregulation or mutations in porin proteins	Penicillins	*K. pneumoniae* with porin deletions (Satlin 2013[39])
		Cephalosporins	

Abbreviations: CRE, carbapenem-resistant Enterobacterales-like; ESBL, extended-spectrum β-lactamase.
[a]ESKAPE indicates Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.
[b]ESBLs break down and destroy some commonly used antibiotics, including penicillins and cephalosporins (Centers for Disease Control and Prevention 2019[40]).
[c]CRE-like E. coli and K. pneumoniae develop resistance to the group of antibiotics called carbapenems (Centers for Disease Control and Prevention 2019[41]).

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 tumours *(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

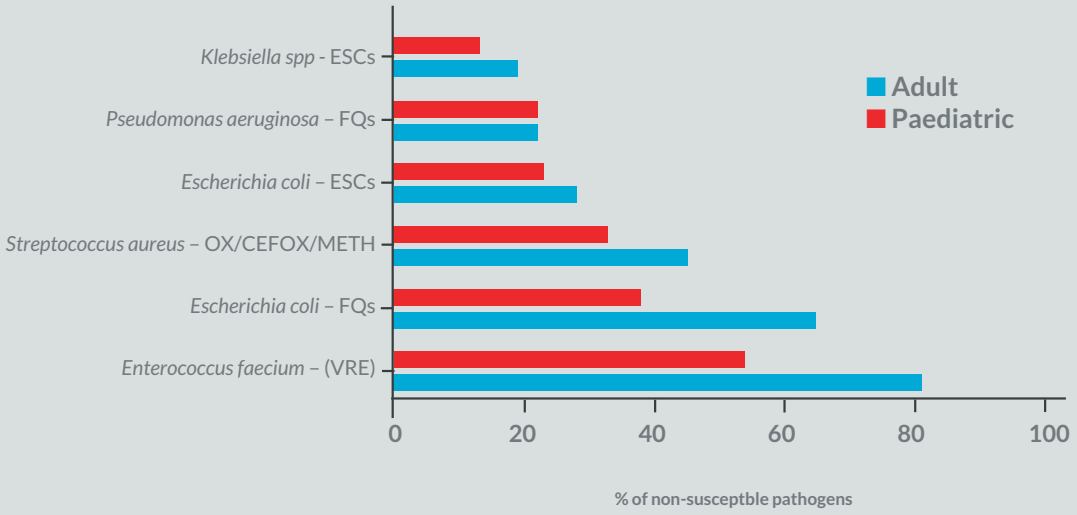
Table 2: Antibiotic resistance in patients with cancer: highlights from the last 5 years

POPULATION STUDIED	RESISTANT MICROORGANISMS	RISK FACTORS FOR DEVELOPMENT OF ANTIBIOTIC RESISTANCE	INTERPRETATIONS	REFERENCE
BSI episodes in patients with cancer (January 1995 to May 2015)	*Enterococcus faecium* (EF)	• Prolonged antibiotic exposure	• 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)	*Enterococcus faecium*	• Previous hospitalization • Levofloxacin extended prophylaxis	• Ampicillin-resistant EF (AREfm) colonization was detected in 32 of 52 patients (61.4%) • Multidrug-resistant (MDR) clones of AREfm in intestine of patients with cancer increase the development of bacteremia	Sanchez-Diaz 2016 [64]
BSIs in patients with hematologic malignancies (January 2008 to December 2012)	*Enterococcus faecium*	• Prophylactic antibiotics • Vancomycin therapy during the previous 3 mo	• 58 Episodes of EF BSI episodes from a total of 15,095 blood cultures • Higher mortality was associated with vancomycin-resistant isolates	Alatorre-Fernandez 2017 [65]
BSIs in malignant hematology and oncology patients (2008-2014)	*Enterococcus faecium*	• Prior antibiotic exposure	• 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)	*Pseudomonas* aeruginosa (PA)	• Previous hospitalization • Prior use of fluoroquinolones	• 64 Patients with PA BSIs were studied • 37.5% Isolates were MDR • PA is an important pathogen in patients who have hematologic malignancies associated with high mortality	Tofas 2020 [61]
BSIs in patients with hematologic malignancies and hematopoietic cell transplant recipients (January 2012 to March 2018)	*Pseudomonas aeruginosa*	• Fluoroquinolone prophylaxis	• 55 Episodes of PA bacteremia among 51 patients • Fluoroquinolone prophylaxis was associated with nonsusceptibility 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)	*Pseudomonas aeruginosa*	• Prior therapy with piperacillin-tazobactam • Prior anti-pseudomonal carbapenem use • Fluoroquinolone prophylaxis	• 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)	*Klebsiella pneumoniae* (KP)	• HAIs	• 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)	*Klebsiella pneumoniae*	• History of systemic steroid • Combination antimicrobial therapy	• In total, 230 consecutive cases of KP infection were studied • 12.6% of hypervirulent KP isolates produced extended-spectrum β–lactamase	Zhang 2016 [31]
BSIs in malignant hematology and oncology patients (January 2014 to September 2018)	*Klebsiella pneumoniae*	• Carbapenem exposure within 30 d before the onset of BSIs	• 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)	*Methicillin-resistant Staphylococcus aureus (MRSA)*	• HAIs	• 21.1% of MRSA was documented from 450 patients reported with *S. aureus* infection • Protective factors for mortality included catheter removal and initiation of adequate treatment for *S. aureus* <48 h after positive blood cultures	Bello-Chavolla 2018 [70]
Patients with erythrodermic cutaneous T-cell lymphoma (CTCL) (2012-2016)	*Staphylococcus aureus*		• Of 50 events, 17 (34%) were due to MRSA • The MRSA prevalence was high in patients with erythrodermic CTC	Emge 2020 [71]
Patients with cancer (June 2014 to March 2016)	Methicillin-resistant *Staphylococcus aureus*		• 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)	*cinetobacter baumanni (AB)i*		• 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)	*Acinetobacter baumannii*	• HAIs	• 66 AB strains (62.3%) were considered infection, and 40 (37.7%) were considered colonization • Highlighted the threat that represents the transfer of colo nized patients with MDR strains between institutions	Cornejo-Juarez 2020 [62]
Patients with malignant hematology (January 2014 to June 2015)	*Acinetobacter baumannii*	• Previous carbapenem exposure • Previous hospitalization	• 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: BLIs, bloodstream infections; HAIs, hospital-acquired infections.

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

Figure 1: Antibiotic resistance is common in patients with cancer. This bar graph displays the percentage of pathogens reported from adult and paediatric 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, cefoxitin, or methicillin; VRE, vancomycin- resistant Enterococcus.*

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 unfavourable outcomes in patients with cancer

Antibiotic resistance leads to detrimental effects in patients with cancer, who rely on antibiotics to prevent and treat 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 4,000 to 10,000 additional infections and 500 to 1,000 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 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 unfavourable outcomes in patients with both hematological malignancies and solid tumours *(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 tumours than in those with hematological malignancies *(90)*. This could be because of a lower incidence of BSIs reported in solid tumours 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 tumours, whereas endogenous sources and catheter-related BSIs were frequent in patients with hematological malignancies *(91)*. The risk of infection in patients with solid tumours 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 tumours, resulting in postobstructive pneumonia, lung abscess, or urinary tract infections. Common sites of infection in patients with solid tumours 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 tumours had more frequent infections because of MDR organisms compared with patients younger than 70 years *(87)*. Another study demonstrated that patients with solid tumours 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 tumours. 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 biopsies *(98)*; 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 colour 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 US$ 20 billion in health care and US$ 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 US$ 24,770 per stay for adults and US$ 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 US$ 50,000 to US$ 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 US$ 2,470 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 1,847 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 patients with febrile neutropenia, specifically, mortality in those with hematological malignancies and solid tumours. 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 programmes 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 programmes 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 *(173)*. 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, multi-faceted 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 centres 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 effective- ness of antibiotic stewardship programmes *(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 (5,626 adult centers and 2,545 paediatric centres) *(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$ 1,581 million, whereas the average annual revenue from an antibiotic's sales is roughly US$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. ■

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