Antimicrobial Stewardship in Cancer Consortium

The Antimicrobial Stewardship in Cancer Consortium (ASCC) is a national organization of infectious diseases pharmacists, physicians, and other healthcare professionals dedicated to advancing the practice and science of antimicrobial stewardship in patients with cancer.

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Antimicrobial Stewardship in Patients With Cancer: The Time Is Now

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Although the widespread use of antimicrobials has made modern cancer care possible, the increase in number of infections due to multidrug-resistant organisms and the dearth of effective agents to combat them has created a serious and pressing issue facing healthcare providers who care for patients with cancer.

In 2017, The Joint Commission mandated that every hospital establish an antimicrobial stewardship program (ASP) to optimize anti-infective use and improve patient care.¹ This standard applies not only to general patient populations but also to immunocompromised patients, including those with cancer and undergoing transplantation. This commentary describes the rationale for antimicrobial stewardship in patients with cancer, the current state of antimicrobial stewardship in hematology/oncology, and how healthcare providers caring for patients with cancer can collectively improve antimicrobial use.

Benefits of Antibiotics and Adverse Consequences

The history of cancer therapy is closely entwined with antimicrobial use. Patients with cancer receive prolonged and varied courses of antimicrobial agents to either prevent or treat infection, but such exposure increases the likelihood of bacterial resistance emergence. Infections caused by antibiotic-resistant pathogens, such as fluoroquinolone-resistant streptococci, vancomycin-resistant *Enterococcus*, and multidrug-resistant gram-negative bacteria (including extended-spectrum β -lactamase-producing and carbapenem-resistant strains), in patients with cancer are increasingly common. This is of particular importance in patients with cancer because delays in adequate therapy are associated with significantly increased mortality.² The problem of antimicrobial overuse extends beyond antibiotic resistance and encompasses fungal and viral resistance as well as *Clostridioides difficile* (formerly *Clostridium difficile*) infections.

The role of the microbiome is just beginning to be understood as it relates to clinical outcomes for patients with cancer. A loss of microbiome diversity is linked to increased infections in patients with hematologic malignancy, increased risk of gastrointestinal graft-versus-host disease, and poor response to immune checkpoint inhibitors.³ Although there is still much to learn about the human microbiome and its interplay with antibiotics in patients with cancer, mounting evidence suggests that how we use antimicrobials may have effects that extend far beyond the immediate problems of infections, antimicrobial resistance, and directly observable toxicities.

Current State of Antimicrobial Stewardship in Patients With Cancer

The Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS) advocate for formalizing antimicrobial stewardship in all patient populations.⁴ A practical way to approach this is through the creation of a formal institutional ASP that is led by an infectious disease-trained physician or a clinical pharmacist who works with and educates staff involved in antimicrobial ordering,

dispensing, administering, and monitoring.^{1,5} The goals of an ASP are to optimize clinical outcomes, minimize adverse consequences of antimicrobial use, and reduce antimicrobial overuse.⁵

Antimicrobial stewardship efforts in immunocompromised patients are challenging because of the complexity of cases, difficulty with accurate and timely diagnoses, and high mortality related to invasive infections.⁶ Although more data on patients with cancer are needed, available studies indicate that the benefits of ASPs seen in general populations are applicable to them. In several studies that have included patients with cancer and/or those undergoing hematopoietic stem cell transplantation (HSCT), antibiotic approvals and/or review and feedback to prescribers on existing antibiotic orders (ie, prospective audit and feedback) have been associated with decreased antimicrobial use and cost reduction without resulting in harm.⁶

How Antimicrobial Stewardship Can Be Implemented in Patients With Cancer

The CDC has outlined core elements for ASPs, which describe essential components for their structure and day-to-day function (Table 1). All hospitals accredited by the Centers for Medicare and Medicaid Services (CMS) are now required to adhere to these core elements.¹ The updated 2016 IDSA/SHEA guideline also provides evidence-based recommendations for implementation and measurement of antimicrobial stewardship interventions in inpatient populations, including hematology/oncology patients (Table 2).⁵ We highlight several stewardship strategies that have been successfully applied to patients with cancer.

Clinical Guidelines

Collaboration between the ASP and hematology/oncology or HSCT teams to develop institution-specific, evidence-based guidelines and clinical pathways to standardize prescribing is not only feasible but necessary. Examples of highly used pathways in patients with cancer include the management of fever and neutropenia, antifungal prophylaxis and treatment, and cytomegalovirus prophylaxis and treatment. Combining infectious diseases, hematology/oncology, transplant, and pharmacy expertise is crucial to address the unique aspects of cancer care, such as diverse patient subgroups (eg, solid tumor vs hematologic malignancy), novel cancer therapies, immune dysfunction related to cancer therapies, types of infections (common and opportunistic), and emerging antibiotic resistance. Such efforts should be coupled with an implementation plan and education to ensure uptake of the guidelines.⁵

Table 1. CDC Stewardship Core Elements

Stewardship Core Element	Overview
Leadership commitment	Establish stewardship within the hospital's reporting structure and provide appropriate resources
Accountability	Appoint physician or pharmacist leader responsible for implementing stewardship activities
Drug expertise	Physician or pharmacist should have adequate training in antimicrobial stewardship
Action	Implement processes to promote appropriate antibiotic use
Tracking	Identify and regularly track key stewardship process and outcomes measure
Reporting	Provide key stewardship metrics to physicians, pharmacists, nurses, administrators, and other key stakeholders
Education	Deliver education to healthcare providers that promotes appropriate antibiotic prescribing

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Table 2. Recommended Activities That Promote Appropriate Antimicrobial Prescribing

Implement daily review that promotes appropriate antibiotic prescribing, including drug selection, dose, route, frequency, and duration
Develop tools that help prescribe appropriate antibiotic therapy, including guidelines, order sets, alerts, and educational material
Establish and monitor stewardship-related metrics, including measuring antibiotic use, cancer-specific antibiogram, and tracking <i>C difficile</i> and multidrug-resistant organisms
Develop a structure and culture that promotes appropriate antimicrobial prescribing, including establish multidisciplinary team of key stakeholders interested in antimicrobial stewardship
Use microbiology and laboratory results to improve antimicrobial prescribing; rapid bacterial diagnostic tests can quickly identify an organism and resistance mechanisms, and galactomanin and 1-3-beta-D-glucan can aid in diagnosis of fungal infections
Provide periodic feedback to key stakeholders; share predefined metrics, identify areas for improvement, and share successes and challenges

To date, few published studies have assessed the impact of stewardship-focused clinical guidelines on antibiotic use in patients with cancer, but existing data suggest that these guidelines can optimize antimicrobial use. For example, improved survival in adult and pediatric patients with neutropenia has been shown after implementation of local fever and neutropenia practice protocols, and higher response rates have been shown for invasive aspergillosis when first-line antifungal treatment was prescribed in accordance with consensus guidelines.⁶ Although deviations from guideline-based recommendations do occur, improved patient outcomes have been shown even with partial adherence.⁶ In this rapidly changing field, ASPs must also be prepared to organize efforts to modify clinical guidelines to address drug shortages, new diagnostics, shifting resistance patterns, and novel treatment approaches for patients with cancer (eg, CAR T-cell therapy, immunotherapy).

Safety of Antimicrobial De-Escalation in Patients With Febrile Neutropenia

Retrospective studies suggest that antibiotic de-escalation to fluoroquinolone prophylaxis in patients with febrile neutropenia who have defervesced and remain clinically stable is feasible without adverse consequences, specifically in regard to the requirement to reinitiate broad-spectrum antibiotics.⁷ Previous studies are limited by small sample sizes and their single-center nature; however, they set the stage for prospective evaluations of early antibiotic de-escalation in high-risk patients with cancer. An alternative approach to de-escalation is to simply stop antibiotics after 72 hours of defervescence and clinical recovery, regardless of neutrophil recovery. This strategy was evaluated in a recent open-label, randomized, controlled, multicenter study conducted in Spain.⁷ Short-course antibiotic therapy was associated with less overall antibiotic exposure. The overall incidence of adverse effects was higher in the experimental (ie, short-course) group, but most were considered nonsevere. Conversely, the incidence of severe adverse effects was higher in the control (ie, prolonged therapy) group, with most being secondary infections and safety events related to antimicrobial toxicity. The results of this and other studies suggest that shorter courses of antimicrobial therapy are not only safe but also may be preferred to prolonged therapy, and should encourage further investigation.

Antifungal Stewardship

Although antibiotics and the optimization of care for bacterial infections are the cornerstone of most ASPs, patients with cancer and who have undergone HSCT are at uniquely high risk for invasive fungal infections (IFIs). Given the high frequency and devastating consequences of IFIs, antifungal prophylaxis is nearly universal among the highest-risk patients with cancer.⁸ However, antifungal prophylaxis is frequently continued beyond the high-risk period for these patients and may increase the risk of

toxicities or predispose them to resistant fungal infections during subsequent courses of chemotherapy. Additionally, therapeutic endpoints for patients receiving antifungal therapy for proven or suspected fungal infections remain unclear, and practice is largely heterogeneous.

Rapid diagnostics (eg, T2Candida Panel; T2 Biosystems, Inc), biomarkers (eg, galactomannan, (1–3)- β -D-glucan), and improved imaging may increase the ability to rapidly diagnose and treat true fungal infections, provide targeted therapy while minimizing empirical therapy, and stop therapy in patients without infection.⁸ ASPs are a key component in the systematic standardized implementation of these diagnostic techniques and corresponding antifungal use guidelines. Single-center studies have shown that ASPs can establish subsequent improvements in patient care and appropriate minimization of antifungal use when possible.^{9,10}

Conclusions

Although antimicrobials can be life-saving in patients with cancer, their inappropriate use has shown adverse consequences,

including increasing rates of multidrug-resistant organisms, *C difficile* infections, and disruptions of the healthy microbiome. Although these complications are not unique to oncology, patients with cancer may have the most to gain from the continued effectiveness of anti-infective agents. Nearly all aspects of modern cancer therapy, including high-dose combination chemotherapy, HSCT, complex surgical procedures, and implanted devices, are made possible in part by these drugs; without them, further advances in cancer care may not be possible. Although infectious disease physicians and pharmacists have traditionally been the leaders of antimicrobial stewardship efforts, hematologists, oncologists, and all other practitioners caring for patients with cancer are important partners. Additional data are needed to help this diverse group of clinicians better understand the risk/benefit profile of antimicrobial stewardship at the individual patient level, but successful collaborations between cancer clinicians and the institutional ASP can ensure the long-term success of antimicrobial stewardship in patients with cancer and lead to significant improvements in cancer care.

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