The Role of the Antimicrobial Stewardship Pharmacist in the Care of the Oncology Patient

MLS Oncology Pharmacotherapy Conference

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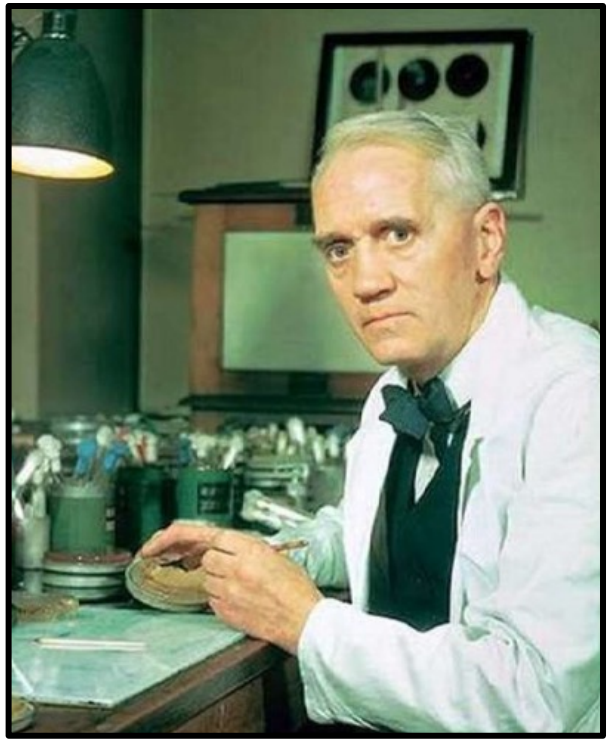
A Quote from Alexander Fleming, 1945



“The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism”

Objectives

- Define antimicrobial stewardship (AMS) and describe an antimicrobial stewardship program's (ASP) impact on patient outcomes
- Outline ASP interventions specific to oncology patients aligned with CDC Core Elements
- Recognize the importance of a multidisciplinary approach to implement an ASP in the immunocompromised patient population

What is Antimicrobial Stewardship?

Antimicrobial Stewardship (AMS)

- The coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal drug, dose, and duration of therapy

Antimicrobial Stewardship Program (ASP)

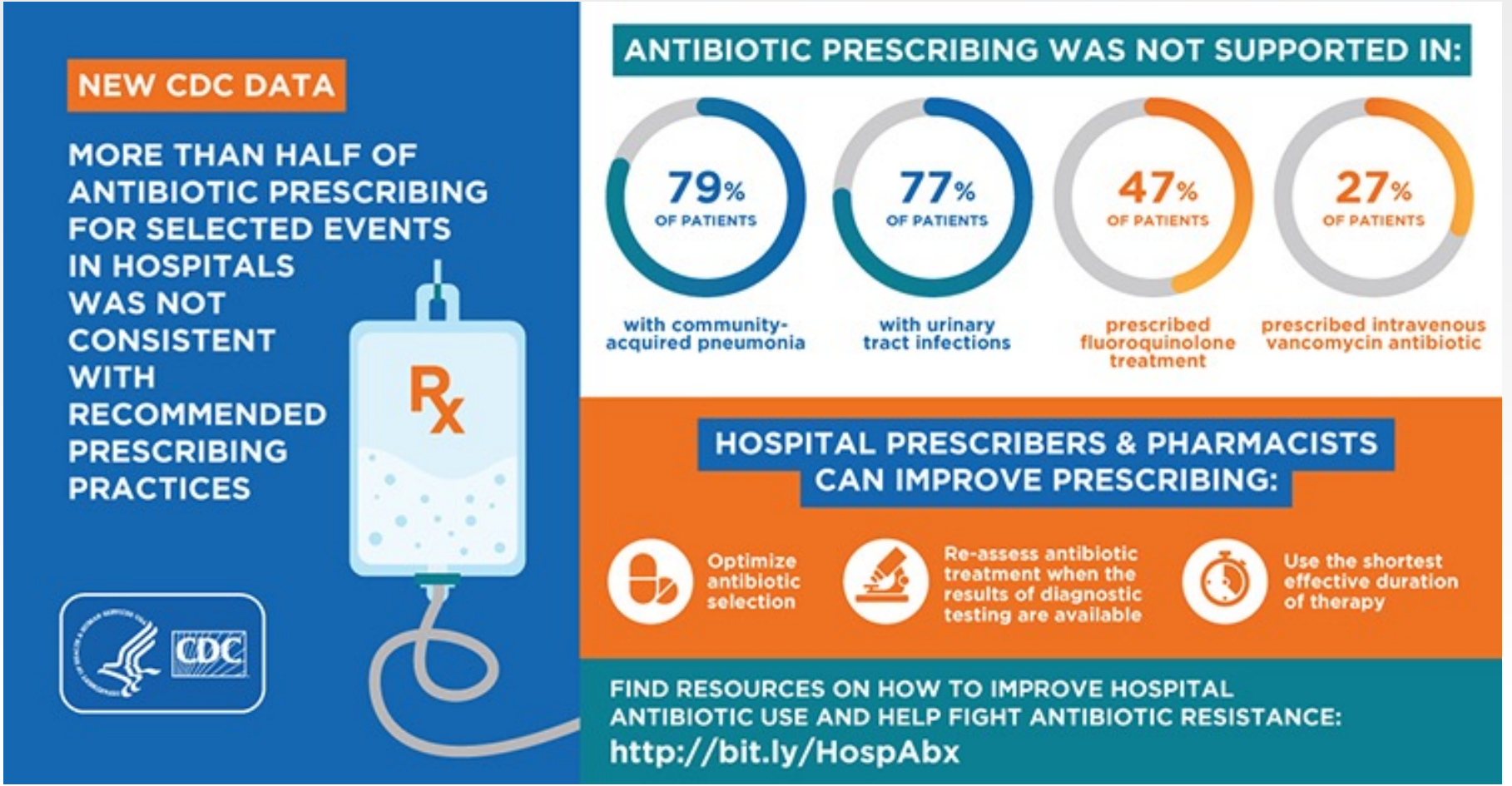
- A hospital-based program that seeks to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use

Dyar OJ, et al. *Clin Microbiol Infect*. 2017;23(11):793-798.

Why is Antimicrobial Stewardship Important?

- Antimicrobial stewardship programs increase cure rates while reducing harm of antimicrobials such as:
  - Emergence of antimicrobial resistance
  - Increased risk for *Clostridioides difficile* infection (CDI)
  - Increased adverse events
  - Increased hospital costs
  - Increased hospital length of stay

CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at https://www.cdc.gov/antibiotic-use/core-elements/hospital.html.



CDC. Core Elements of Hospital Antibiotic Stewardship Programs 2019.

Regulation of Antimicrobial Stewardship Programs

2014	• CDC recommended US hospitals have ASPs to address the rise in antibiotic-resistant pathogens and guide appropriate antibiotic use
2016	• IDSA/SHEA published guidelines to evaluate interventions that can be implemented by ASPs in emergency department, acute inpatient, and long-term care settings
2017	• TJC published a new Medication Management standard addressing ASP for hospitals, critical access hospitals, and nursing care centers
2019	• CMS issued a rule to implement ASPs as a condition of participation for hospitals, critical access hospitals, and dialysis facilities
2020	• TJC published new antimicrobial stewardship requirements for ambulatory health care organizations
2022	• CMS published infection prevention and control (IPC) and antibiotic stewardship program guidance updates
2023	• TJC's new and revised antibiotic stewardship requirements will apply to all TJC - accredited hospitals and critical access hospitals

Barlam TF, et al. *Clin Infect Dis*. 2016;62(10):e51-e77.
CDC - Centers for Disease Control and Prevention. Core Elements of Antibiotic Stewardship.
TJC - The Joint Commission. New and Revised Requirements Addressing Antibiotic Stewardship for the Hospital and Critical Access Hospital Programs.
CMS - The Centers for Medicare and Medicaid Services. Infection Prevention and Control and Antibiotic Stewardship Program Interpretive Guidance Update.

IDSA: Infectious Diseases Society of America
SHEA: Society for healthcare Epidemiology of America

CDC Core Elements of Hospital Antimicrobial Stewardship Programs

Accountability

Leadership Commitment

Pharmacy Expertise

Tracking

Action

Reporting

Education

CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at https://www.cdc.gov/antibiotic-use/core-elements/hospital.html.


Antibiotic Stewardship
Effective Infection Prevention & Control
Controlling the Source of Infection
Prescribing Antibiotics Only When Truly Needed
Prescribing Appropriate Antibiotic Dosages
Using the Shortest Duration of Antibiotics According to Evidence
Reassessing Treatment Based on Culture Results
Supporting Surveillance of AMR and HAIs and Monitoring of Antibiotic Consumption
Educating Staff
Supporting an Interdisciplinary Approach

The Value of an Antimicrobial Stewardship Pharmacist

- CDC 2019 Core Elements and IDSA 2007 ASP guidelines strongly recommend a clinical pharmacist with infectious diseases training over a general clinical pharmacist where available to serve as co-leader for the ASP team
- Bessesen et al. compared non-ID trained pharmacists to ID trained pharmacists and found ID trained pharmacists were more likely to:
  - Adhere to local treatment guidelines (96.8% vs 87%; $p<0.002$)
  - Modify therapy within 24 hours based on availability of laboratory data (86.7% vs 72.6%; $p<0.03$)
  - Discontinue antibiotics for non-bacterial causes (78% vs 33.3%; $p<0.0002$)

Bessesen MT, et al. *Hosp Pharm.* 2015;50(6):477-483.
Dellit TH, et al. *CID.* 2007;44(2):159-177.

Every Extra Day Counts!

Risk of Harm Increases Each Day of Antibiotic Treatment

↑9%	↑5%	↑4%	↑4%
***Clostridioides difficile* infection**	**Antibiotic-associated adverse effects**	**Penicillin-resistant *Streptococcus pneumoniae***	**Anti-pseudomonal resistance**
Retrospective study of 1883 patients receiving antibiotics for community acquired pneumonia (CAP)	Retrospective study of 6481 patients receiving antibiotics for CAP or health care-associated pneumonia (HCAP)	Prospective study of 461 children <4 years of age who received a penicillin or cephalosporin antibiotic in past 2 months	Retrospective study of 7118 patients with sepsis receiving meropenem, cefepime, or piperacillin-tazobactam

Chalmers JD, et al. J Infect. 2016;73(1):45-53; Vaughn VM, et al. Ann Intern Med. 2019;171(3):153-163.
Nasrin D, et al. BMJ. 2002;324(7328):28-30; Teshome BF, et al. Pharmacotherapy. 2019;39(3):261-270.

Shorter vs. Longer Durations

Indication	Short Duration (days)	Long Duration (days)	Result
Community-acquired Pneumonia	3 or 5	7, 8, or 10	No difference
Hospital-acquired or Ventilator-associated Pneumonia	7 or 8	14 or 15	No difference
Acute Exacerbation of Chronic Bronchitis/ Chronic Obstructive Pulmonary Disease	≤ 5	≥ 7	No difference
Complicated Urinary Tract Infections or Pyelonephritis	5 or 7	10 or 14	No difference
Complicated/ Post-Op Intra-Abdominal Infection (with source control)	4 or 8	10 or 15	No difference
Acute Bacterial Skin and Skin Structure Infection (Cellulitis or Major Abscess)	5 or 6	10	No difference
Empiric Neutropenic Fever	Afebrile and stable × 72 h	Afebrile and stable × 72 h and with ANC > 500 cells/mcL	No difference

Adapted from: Wald-Dickler N, et al. *CID.* 2019;69(9):1476-1479.

Antimicrobial Stewardship in Patients With Cancer

- Patients with cancer are vulnerable to infections because of:
  - Prolonged or recurrent episodes of neutropenia
  - Repeated courses of immunosuppressive agents
- Antimicrobial stewardship efforts in immunocompromised patients are challenging
  - Complexity of cases
  - Difficulty with accurate and timely diagnoses
  - High mortality related to invasive infections

- The current literature is limited by **underrepresentation of cancer patients or exclusion of this population completely**

Aitken SL, et al. Journal of the National Comprehensive Cancer Network. 2019;17(7):772-5.
Pillinger KE, et al. Annals of Pharmacotherapy. 2020;54(6):594-610.

Unmet Needs and Opportunities for Antimicrobial Stewardship

- Fever and Neutropenia
- Antibacterial Prophylaxis
- Antifungal Use and Prophylaxis
- Antiviral Use and Prophylaxis
- Adverse Effects of Antimicrobials
- Expansion of Diagnostic and Susceptibility Testing Methods
- Lack of Dedicated ASP Guidelines and the Need for Multidisciplinary Implementation

Majumdar A, et al. Antibiotics. 2023;12(3):592.

Febrile Neutropenia Epidemiology

Oncologic emergency

Major dose-limiting toxicity of chemotherapy

Occurs in >80% of patients with hematologic malignancies

- Documented infection occurs in only 20-30% of episodes

Occurs in 5-30% of patients with solid tumors

Associated with substantial morbidity, mortality, and cost

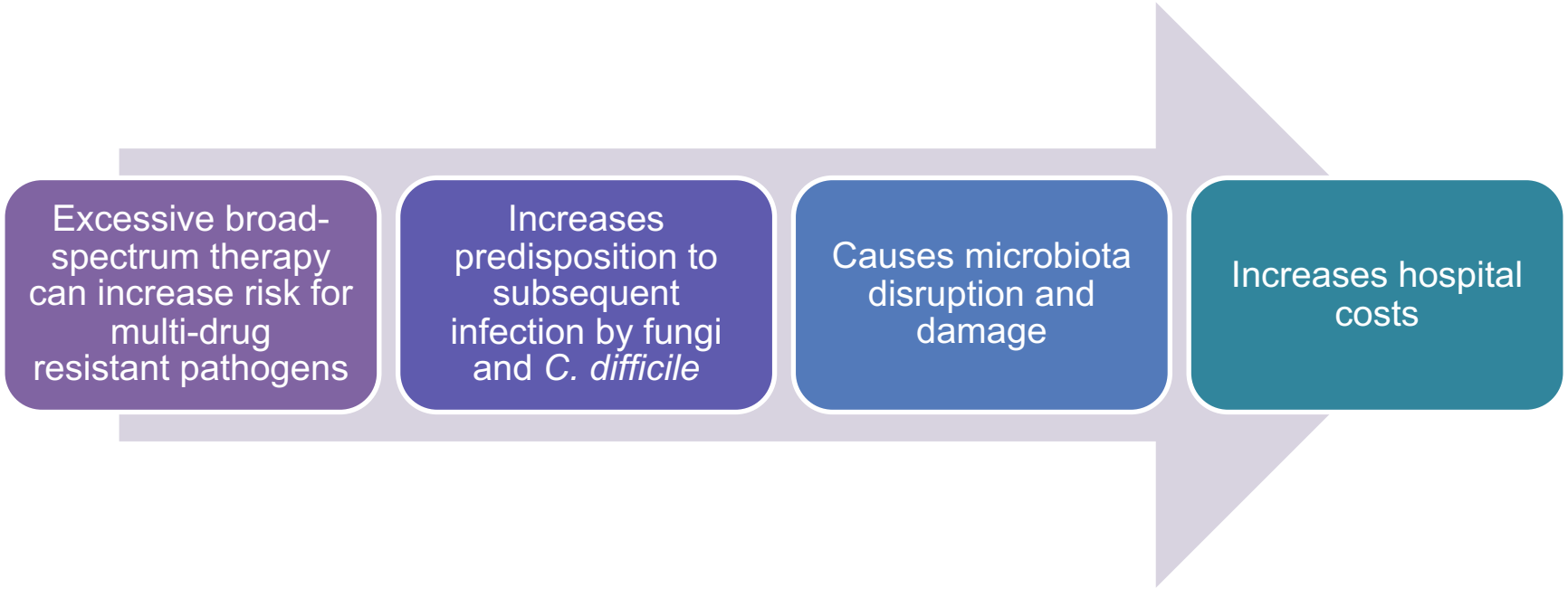
- Mortality rates 8-14%

Gustinetti. *Virology.* 2016;7(3):280-297.
Freifeld AG, et al. *Clinical Infectious Diseases* 2011;52(4):e56-93.

Febrile Neutropenia in Hematologic Malignancies and Hematopoietic Stem Cell Transplantation (HSCT)

Mortality

Issues with Long-Term Antibiotics



Majumdar A, et al. Antibiotics. 2023;12(3):592.

Antimicrobial Impact on Microbiota

- Long-term antimicrobial use has also been linked to the disruption of the microbiota
  - AML patients with lower stool Shannon diversity index undergoing induction of chemotherapy with resulting neutropenia experienced an **increased infection incidence**
  - Lack of microbiome diversity during the peri-transplant period has been associated with **poor overall survival post-HSCT and increased graft-versus-host disease (GVHD) incidence**

Majumdar A, et al. Antibiotics. 2023;12(3):592.

Financial Burden of Febrile Neutropenia

A study of hospitalizations for cancer-related neutropenia in the United States in 2012 including 108,000 patients

- Total costs per year
  - Adult: $2.3 billion
  - Pediatric: $439 million
- Approximately 8% of all cancer-related hospital costs
  - Admission extended 3 days
  - Emergency room admissions
- $5,700 more than adults admitted for other indications

Tai E, et al. J Oncol Pract. 2017;13(6):552-561.

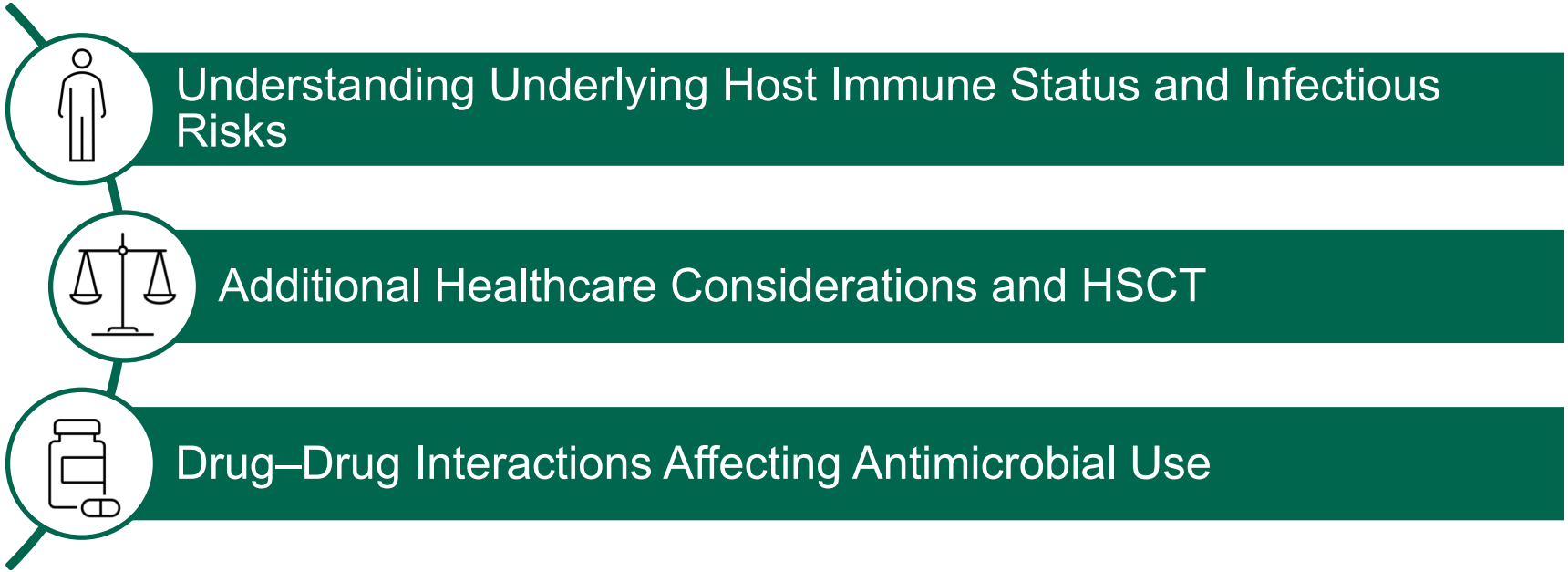
Comparison of Guideline Recommended Duration of Empiric Therapy for Febrile Neutropenia

NCCN Guidelines (2022)	ESMO Guidelines (2016)	IDSA Guidelines (2011)	ECIL-4 (2011)
• Clinical or Microbiological Documented Infection: Suggested minimum duration based on type of infection • FUO: ANC ⩾ 500 cells/mcL and recovering OR • Can consider these options if ANC < 500 cells/mcL: ○ Discontinue therapy ○ De-escalate to prophylaxis ○ Continue current regimen until neutropenia resolves	Clinical or Microbiological Documented Infection and FUO: ANC ⩾ 500 cells/mcL and recovering AND afebrile and asymptomatic for ⩾ 48 h OR If ANC < 500 cells/mcL but afebrile for 5-7 days, consider discontinuation	Clinical or Microbiological Documented Infection and FUO: • ANC ⩾ 500 cells/mcL and recovering AND afebrile and asymptomatic for ⩾ 48 h	Clinical or Microbiological Documented Infection: • Continue for at least 7 days until infection is microbiologically eradiated and patient is afebrile for at least 4 days FUO • Consider discontinuation if patient stable for 72–96 h and afebrile for ⩾ 48 h, regardless of ANC

Adapted from: Keck JM, et al. Therapeutic Advances in Infectious Disease. 2022;9:20499361221138346.

FUO: fever of unknown origin
ANC: absolute neutrophil count

Unique Challenges to Antimicrobial Stewardship in Oncology Patients



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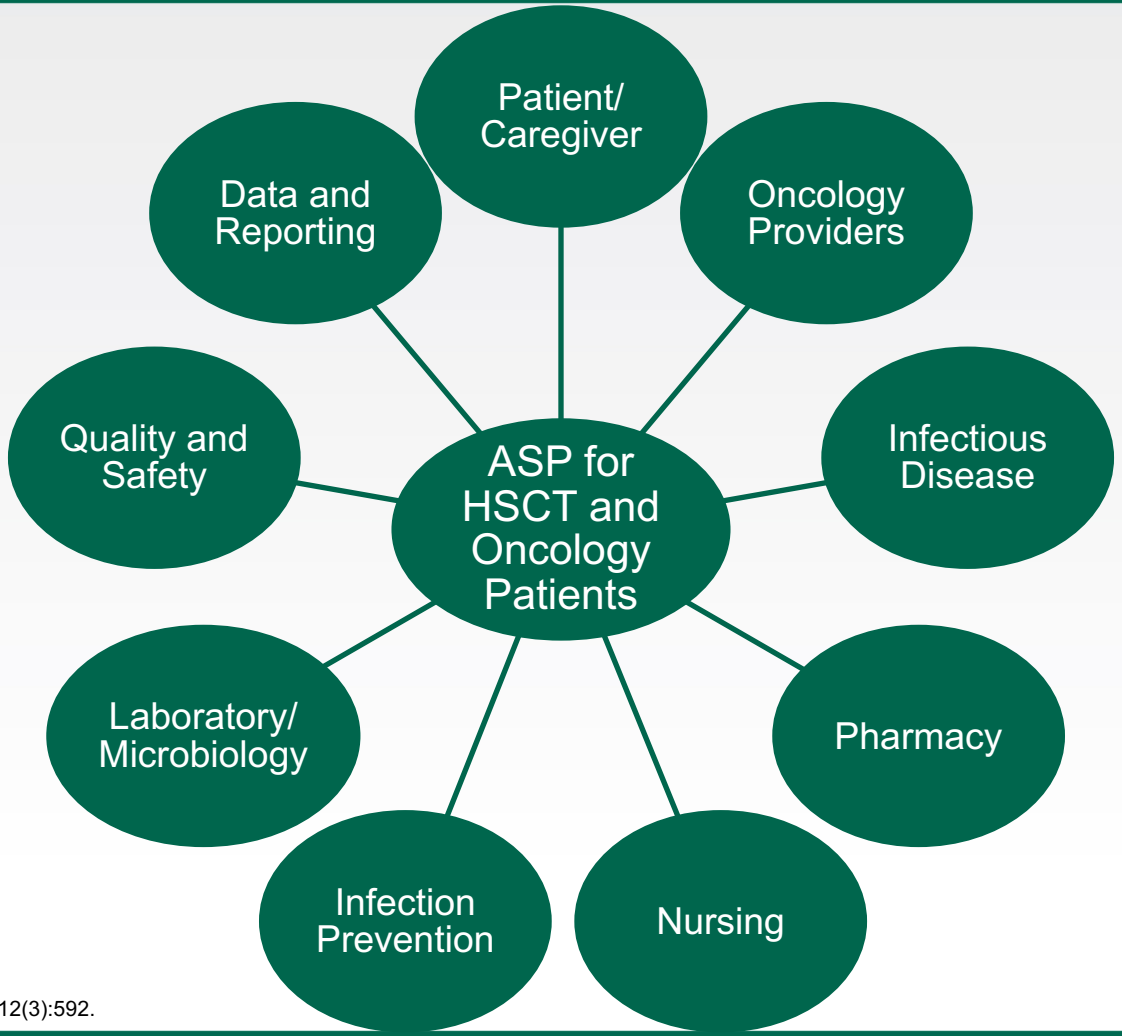

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Febrile Neutropenia Management

Antibiotic Strategy	Pros	Cons
Continuing antibiotics until count recovery	• Safest option to prevent sepsis and transfer to ICU • Current guideline recommendations	• ↑ Development of MDROs • ↑ Length of stay • ↓ Quality of life for patients
De-escalating in afebrile hemodynamically stable patients	• ↓ Exposure to antibiotics • ↓ Length of stay • ↓ Development of MDROs • ↑ Quality of life for patients	• Not endorsed by national guidelines • No currently defined criteria for safest practice • Could increase resistance to fluoroquinolones • Risks associated with fluoroquinolones

Activities That Promote Appropriate Antimicrobial Prescribing

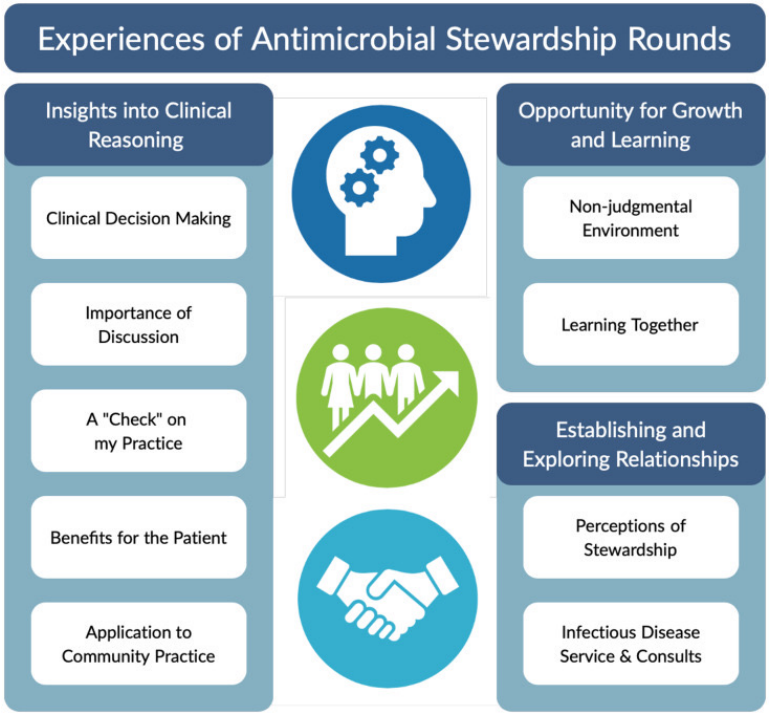
- Implement daily prospective audit and feedback
- Develop tools that help prescribe appropriate antimicrobial therapy
- Establish and monitor stewardship-related metrics
  - Antibiotic use
  - Cancer-specific antibiogram
  - *C. difficile* infections
  - Multidrug-resistant organisms
- Develop a structure and culture that promotes appropriate antimicrobial prescribing
- Use microbiology and laboratory results to improve antimicrobial prescribing
- Provide periodic feedback to key stakeholders; share predefined metrics, identify areas for improvement, and share successes and challenges

Aitken SL, et al. Journal of the National Comprehensive Cancer Network. 2019;17(7):772-5.

CDC Core Element	Example of ASP Interventions Focused on HSCT/Oncology Patients
Hospital Leadership Commitment	• Accessible information systems (e.g., electronic medical record, surveillance data) • Dedicated staff for antimicrobial stewardship
Accountability	Multidisciplinary approach among hematology/oncology, infectious disease, and pharmacy (“handshake stewardship”)
Pharmacy Expertise	• Antibacterial, antifungal, and antiviral prophylaxis • Dose optimization (e.g., extended infusion of beta-lactams) • Duration of empiric antimicrobials for febrile neutropenia • IV to PO conversion
Action	• Development of population specific guidelines • Febrile neutropenia • Antifungal prophylaxis and treatment • Cytomegalovirus prophylaxis • Use of microbiology methods to assist with prescribing
Tracking	• Population- and/or unit-specific antibiograms • Prevalence of MDRO • Prospective audit and formulary restriction
Reporting	• Tracking and shared reporting of outcomes specific to HSCT/oncology • *C. difficile* • Catheter-related infections • Prevalence of MDRO
Education	• Population-specific antibiograms • Microbiome diversity

Majumdar A, et al. Antibiotics. 2023;12(3):592.

Clinical Integration With A Handshake



- Better understanding of the culture of antibiotic prescribing
- Reinforces shared, team goal of positive patient outcomes

McCreary ML, et al. Antimicrob Steward Healthc Epidemiol. 2021;1(1):e11.

Take Home Points

Adoption and operation of ASPs in medical facilities is essential for the management of appropriate amicrobial use

Immunocompromised patients are ideal candidates for direct ASP involvement

- ASPs should consider incorporating targeted interventions, particularly for the treatment of febrile neutropenia

Downstream consequences of different antimicrobial agents in immunocompromised patients are poorly described

A multidisciplinary approach is imperative in order to successfully implement ASP in immunocompromised patients

Thank you!