Antibiotic Stewardship in Onco-Critical Patient

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16.1 Introduction

Antimicrobials are among one of the most crucial advances in the field of healthcare. These drugs are the mainstay of therapy in the management of infections and prompt initiation provides survival advantages in patients with sepsis and septic shock [1, 2]. Hence early and appropriate use has been promoted vigorously in recent times as a standard of care in sepsis management [2]. However many studies report that majority of hospitalized patients were exposed to broad-spectrum antimicrobials and this exposure is often unnecessary, suboptimal, and inadequate [3, 4]. these observations have also pointed out a significant scope of improvement in antimicrobial prescriptions and an urgent need for antimicrobial stewardship.

It is largely noticed that special patient populations (E.g. Cancer patients, immunocompromised patients, anti-cancer therapy patients) were excluded from antimicrobial stewardship program (ASP) research. On the contrary, this special population should have been the most important groups for ASP. The last updated guidelines make ASP mandatory across the spectrum of health care. However, no specific recommendations were made for this subset of patients [4].

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Although basic stewardship tenets (pre-authorization, prospective audit and feedback) are applicable, there are novel aspects in caring for oncology patients. In the present chapter, we make an attempt to evaluate that aspect of care of cancer patients.

16.2 Evolution of the Concept of Antimicrobial Stewardship

As with any other medication, antimicrobials also have serious adverse reactions, and the development of antimicrobial resistance(AMR) is one such emerging and disturbing public health issue [5, 6]. This concern was first raised by Sir Alexander Flemming when he pointed out that 'inappropriate use of Penicillin may lead to adaptation of bacteria against it'. [7] This was a reality soon after the discovery of penicillin when the first methicillin-resistant *Staphylococcus Aureus* (MRSA) isolate was discovered and reported in 1964 [8, 9]. During the following decades, several reports of antimicrobial discoveries and emerging infectious microbes were published in the medical literature. The first time in a futuristic article in the year 1996 it was finally identified that there is a causal relation between antimicrobial use and developing resistance and a robust large-scale method is urgently needed to address this problem [10]. "Stewardship" term was also coined in this context for the first time. This fight with microbes was a global crisis and the discovery of antimicrobials was not able to keep pace with new and emerging resistance [11, 12]. Resistant infection in patients causes a high risk of mortality and at least two times higher cost implications in comparison to susceptible isolates infections [13]. In fact, inappropriate use of antimicrobials can have an adverse effect on the health of patients who were not even exposed to antimicrobials, because of the emergence of resistant infections at the community and institutional level and pose a significant threat to lives [4, 5]. Citing these emerging concerns the Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) released guidelines for the prevention of antimicrobial resistance in hospitals [14]. Ten years later SHEA and IDSA formally adopted the "Antimicrobial Stewardship" term and released guidelines to develop Antimicrobial Stewardship programs (ASP) [15].

ASP formally described by IDSA, SHEA, and Pediatric infectious disease society (PIDS) as "Coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration." [16] These societies strongly recommend the need for ASP at the institutional level and even advocate the need for a legislature for implementing ASP effectively. Last updated guidelines issued jointly by these societies for implementation of ASPs [4]. Similarly, ASP is strongly recommended in Joint Commission International (JCI) publication [17]. This document mandates ASP across all spectrum of healthcare, including cancer and transplant patients.

16.3 Focus of Antimicrobial Stewardship in Oncology Patients

ASP interventions are challenging in immunocompromised, complex oncology context, because of difficulty in accurate diagnosis and higher than usual rates of invasive infections [18]. And for the same obvious reasons, patients with cancer have higher frequency of infection, and antibiotics exposure than the general population. This leads to unusually high antimicrobial pressure on the patient's own normal microbial flora and surrounding environment. In past several years this immense antimicrobial pressure have grown up and led to emergence of resistant MDR microbes and high prevalence of CDI [19–22]. Antimicrobial resistance warrants empirical higher antimicrobials which further increases selection pressure. This vicious cycle is ultimately responsible for higher length of stay in Intensive care units and poor outcomes [23].

There are several opportunities to reduce unnecessary antimicrobial use and hence universal goals of providing timely, efficacious and safe antimicrobials to treat infection and limiting ecological impact of antimicrobials is applicable to oncology patient's population also [4, 23].

One interventional study demonstrated that antibiotics use, emergence of MDR organisms and *clostridium difficile* infections (CDI) emergence was reduced in cancer patients by adapting to ASP interventions with significant harm, and this ultimately can boost patient's health, and reduce medical cost and long term defects [24].

16.4 Summary of Core Elements of Antimicrobial Stewardship

CDC and IDSA have prescribed core elements that should be incorporated in institutional ASPs, a summary of these elements is provided in (Tables 16.1 and 16.2) [4, 25].

Apart from usual stewardship elements and interventions we could identify some specific elements related to stewardship in oncology patients. We shall elaborate on unique factors and interventions in practice of ASP for oncology patients.

16.5 Leadership Commitments

CDC guidelines for ASP suggest a crucial leadership commitment for implementation of the program. Extending the benefits of ASP to oncology patients is urgently needed [18]. The concept of ASP has been woven around the key role of Infectious disease expert and pharmacist; however integration of intensive care in leadership is vital in critical oncology patients for success of ASP.

Table 16.1 Core elements of antibiotic stewardship [4, 25]

Core element	Summary
Leadership commitment	To establish ASP, ensure close collaboration and adequate resource allocation for ASP, formulate strategy, and ensure feedback regulation
Accountability	ASP leader and co-leaders responsibilities to ensure activities and functioning
Pharmacy expertise	ASP trained physician and/or pharmacist to monitor the whole program
Action implementation	Interventions to promote appropriate antibiotics use (Table 2)
Tracking	Regular interval audits of interventions and outcome measures **Antibiotics use** measures: Maintaining and auditing pharmacy record systems data with benchmarks Outcome measures: CDI rates, antibiotics resistance patterns Process/quality measures: Compliance measures, preauthorization audits, adherence to local treatment guides
Reporting	Provide key stewardship updates and antibiograms to physicians, pharmacists, nurses, other key stakeholders and administrations
Education	One of the key components but not effective as an independent measure for stewardship Implement robust infection control and preventive strategy

Table 16.2 Action implementation

Elements	Summary
Priority interventions:	• **Pre-authorization**, • **Prospective audit and feedback** to limit the use, duration of restricted antibiotics, promote a prompt de-escalation • **Facility specific treatment guidelines**
Clinical pathways:	Mandatory selection of case definition and logical selection of antimicrobial, based on microbiology lab provided local antibiograms guidance
Provider-based interventions	• Antibiotics time outs • Assessing drug allergy
Pharmacy-based interventions	• Documentation of indications for antibiotics • Automatic changes from intravenous to oral antibiotic therapy • Dose adjustments: When needed, such as in cases of organ dysfunction, especially renal, or based on therapeutic drug monitoring • Dose optimization • Duplicative therapy alerts • Time-sensitive automatic stop orders • Detection and prevention of antibiotic-related drug-drug interactions
Microbiology based interventions	• Selective reporting of antimicrobial susceptibility testing results • Comments in microbiology reports • Rapid diagnostics and testing for galactomannan and 1–3-beta-D-glucan for rapid bacterial and fungal diagnosis aids
Nursing based interventions	• Optimizing microbiology cultures: a proper technique to reduce culture contaminations • Intravenous to oral transitions • Prompting antibiotic reviews (“timeouts”)

16.6 Clinical Guidelines

ASP stakeholders and oncology clinicians should jointly develop clinical case definition based guidelines for a judicious approach towards an oncologic patient. Treatment pathways for febrile neutropenia, antifungal prophylaxis in neutropenia, cytomegalovirus treatment and prophylaxis guidance are few important clinical pathways.

Till date, data to support the above notion is not available and not studied in trials, but some studies suggest that implementing such integrative antifungal stewardship programs for selection of appropriate therapy in accordance with existing guidelines, improved efficacy, impact, and reduce toxicity and cost [26–28]. One study showed significant cost saving when an internal protocol to switch from Echinocandin to Fluconazole was followed in 70.3% patients based on clinical and susceptibility criteria [29]. Complete adherence to guideline is rarely possible, but even partial adherence can give improve outcomes [30, 31]. A closed integrated group approach (between various specialties E.g. infectious disease, Intensive care leadership, clinical microbiology, oncology, stem cell transplant teams and pharmacy) based guidance should be adopted for such a diverse group of patients who may have many mechanisms of immune paresis.

16.7 Antimicrobial Restriction

Antimicrobial restriction [pre authorization, prospective audit and feedback (PAF)] is one of the key components in ASP, and hence strongly recommended in IDSA guidelines [4]. Limited research data is available in this context as oncology patients are generally considered to be at high risk of resistant infections.

In a study ASP recommendations were able to reduce antimicrobial prescription (coefficient: −3.221; P = 0.039) during the intervention period, however consumption for same increased (pre-intervention: 84.58 defined daily doses [DDDs]/100 patient-days [PDs]; intervention: 102.52 DDDs/100 PDs) authors concluded that PAF implementation was based on culture reports and occurred at 72 h only [32]. Another study revealed decreased antimicrobial use (278 vs. 247 DDDs per 100 PDs; P < 0.01). They didn't noticed any differences in length of stay (LOS), in hospital mortality, or CDI rates [33]. One study using multimodal approach with antibiotics restriction at 48 h for febrile neutropenia, found that vancomycin discontinuation was increased from 31% (31/100) pre-intervention to 70% (70/100) post-intervention (P < 0.0001) [34]. One study focusing on carbapenem restriction based on extensive education, consultation and computerized clinical decision support found decreased carbapenem use post interventions (78.43 vs. 67.43 days of therapy [DOTs]; P = 0.018) demonstrating no differences in all-cause mortality (6.54 and 6.57 deaths per 1000 PDs; P = 0.926). However, reduction in resistance pattern was not observed during the study period [35].

Paucity of data, for the role of preauthorization in oncology patients has probably resulted from a likely increased risk of delaying antibiotics and high risk of resistant infection in this subset of patients. Similarly data for PAF was also not evaluated in large studies, hence not rendered reliable and should be adopted with due cautions as more research in the subject matter is needed. However antimicrobial restriction post administration can be adopted and considered for future research [36].

16.8 Antimicrobial Cycling

This strategy involves deliberate change of antimicrobial strategy to other effective regimens and form a part of formulary management in ASP. However IDSA and SHEA guidelines couldn't recommend it as an effective measure of Antimicrobial Stewardship due to conflicting data. A few studies demonstrated no change in mortality and resistance patterns, however raised concerns regarding gram positive resistance [37, 38]. Another study demonstrated that cycling preserved antibiotics susceptibility of gram negative bacteria but had increased resistance in *Enterococcus spp*.Vancomycin and Ampicillin resistance among Enterococci [39]. hence with the lack of sufficient evidence this aspect of intervention will require further research.

16.9 Intravenous to Oral Conversion (IV to Oral)

Many transplant centers use Intravenous-to-oral antimicrobial strategy, helping reduce cost, hospital length-of-stays, and the need for intravenous catheters [40]. Hence now it is strongly recommended in clinical practice guidelines [4].

Reducing the burden of invasive access in oncology patients is certainly one of the most crucial steps toward infection control and hence it should be considered even more strongly in oncology patients.

16.10 Biologic Markers as Stewardship Tool

Procalcitonin is a biomarker used to determine risk of sepsis and used as a tool for de-escalation of antibiotics. A review which included at least 30 publications concluded that due to limited production ability, delayed peak levels, and lower sensitivity, procalcitonin is unlikely to benefit in management of empirical therapy in neutropenic fever patients [41]. However serial measurements can be of help in reducing duration of therapy, as in non neutropenic patients [42, 43].

16.11 Stewardship of Antifungal Agents

Oncology patients, specifically neutropenic patients, are treated with prophylactic antifungal drugs during the high risk period, as they harbor a higher risk for developing invasive fungal infections(IFI) [44]. Many a times this prophylactic therapy is continued way beyond the high risk period and poses a significant threat for development of resistant fungal infections and toxicity from drugs.

Rapid diagnostic modalities like biomarkers (E.g Galactomannan, (1–3)-b-D-glucan levels), rapid candida detection panel (T2 Biosystems Inc), and imaging modality may enhance ability to diagnose IFIs early [44].

Systematic and standardized implementation of these diagnostics modalities along with antifungal therapies can contribute to successful implementation of antifungal stewardship. Some small studies indicated that ASP interventions can lead improvement in patient care and minimization of antifungal therapy use [45, 46].

16.12 Scope of Future Research

Literature search shows that most of the studies for stewardship in oncology patients are focused on institution specific clinical guidelines and further on de-escalation of antimicrobials. Hence even after there is enough proven benefits of stewardship interventions, there is still fair amount of scope exists for future research. Few specific recommendations have been enumerated in (Table 16.3). Key identified areas are diagnostic stewardship, pharmacological optimizations strategies and lastly audits feedbacks and application interventions.

Table 16.3 Scope of future research for antimicrobial stewardship in oncology patients

Diagnostic stewardship	– Development of oncology specific antibiograms [47] – Procalcitonin based differentiation of bacterial sepsis and de-escalation in oncology subset of patients – Rapid microbiological diagnostics and its impact
Pharmacological optimization	– Role for therapeutic drug monitoring of β-lactams – Safety of intravenous to oral switch of antibiotics in setting of bloodstream infections [48]
Prospective Audit, feedback, and application interventions	– Differences between syndrome-specific and drug-targeted intervention [49]. – Safety of preauthorization strategy [50] – Implementing clinical guidelines of non neutropenic infectious diseases – Antimicrobial Prophylaxis [51] – Oral Vancomycin prophylaxis for *Clostridioides difficile* infection [52, 53]

16.13 Conclusions

- Early and appropriate antimicrobial therapy can be life saving for the oncology patients. However non judicious use of antimicrobials leads to serious individual, institutional and ecological consequences.
- Oncology patients provide us with many novel opportunities for antimicrobial stewardship practice.
- Even in this high risk subset of patients, Antimicrobial stewardship program (ASP) interventions applied with due cautions can yield reasonably successful outcomes.
- Before embarking upon stewardship interventions one must ensure contemporary guidance for antimicrobial use in this subset of patients and also consider local pathogen flora and antibiograms.
- ASP in oncology patients requires a close interaction of infectious disease physicians, pharmacist, oncologist, hematologist and other practitioners.
- Adequate research data is still lacking for ASP in this subset of patients.
- ASP along with a robust infection control program can render sustained positive effect in this subset of patients.
- Even after proven benefits to ASP in oncology patients, there is scope of significant research and practice improvements.

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