Curr Treat Options Infect Dis (2019) 11:161–176
DOI 10.1007/s40506-019-00189-2

Antimicrobial Stewardship (M Stevens, Section Editor)

Antimicrobial Stewardship in Patients with Hematological Malignancies: Key Considerations

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Published online: 7 May 2019

This article is part of the Topical Collection on *Antimicrobial Stewardship*

Keywords Antimicrobial · Antifungal · Stewardship · Malignant · Hematology · Quality

Abstract

Purpose of review This review establishes current evidence supporting antimicrobial stewardship programs for malignant hematology and hematopoietic stem cell transplant patients. It describes best practices and identifies opportunities for research. It examines metrics relevant to the patient population, and new approaches to the management of high-risk febrile neutropenia.
Recent findings There is an urgent need for antimicrobial stewardship programs to optimize antimicrobial use in malignant hematology and stem cell transplant patients. Audit and feedback is effective and safe. Febrile neutropenia is a key area to optimize antimicrobial use. Shortening duration of antimicrobial therapy in fever of unknown origin appears to be feasible. Routine antimicrobial prophylaxis has been reexamined. Locally developed guideline for high-risk febrile neutropenia is a major intervention. Antifungal stewardship and rapid diagnostic technologies reduce unnecessary antifungal use. Metrics for antimicrobial stewardship programs in malignant hematology and stem cell transplant are multifaceted.
Summary Antimicrobial stewardship in the malignant hematology and stem cell transplant population is feasible, effective, and safe. Current gaps in knowledge include the optimal duration of antimicrobial use in fever of unknown origin, and the safety of targeted therapy despite neutropenia. The ideal human resources requirement is unclear. Cost-effectiveness of antimicrobial stewardship interventions remains to be determined.

Introduction

Antimicrobial stewardship (AMS), defined 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, has been advocated to improve patient outcomes and quality of care [1••]. Increasingly, antimicrobial stewardship programs are mandated by accrediting bodies such as The US Joint Commission and Accreditation Canada for acute care hospitals, skilled-nursing care facilities, and other complex continuing care settings to mitigate infections caused by multidrug resistant organisms (MDRO), adverse effects of antimicrobials including *Clostridioides difficile* infections, and to optimize resource utilization [1••, 2, 3]. While encouraging, published literature related to the safety and efficacy of AMS interventions in patients with hematological malignancies remains scarce, and data on appropriate performance indicators or metrics for AMS programs in this population are lacking [4••].

The empiric nature of antimicrobial use in high-risk febrile neutropenia (defined as "profound" with nadir absolute neutrophil count ≤ 500 cells/μL (0.5×10^9/L), "prolonged" with duration ≥ 7 days, and fever ≥ 38.5 °C or 38.3 °C sustained for at least 1 h) presents a unique challenge [5••, 6••, 7]. In patients with leukemia and hematopoietic stem cell transplant (HSCT), prolonged and profound neutropenia increases their vulnerability to severe or atypical infections, yet the focus of infection may not be easily identified [8]. The conventional approach to treat fever of unknown origin with empiric broad-spectrum antibiotics until neutrophil recovery creates selective pressure that contributes to antimicrobial resistance, adverse effects, and invasive fungal infections [6••, 9••]. However, literature guiding management of neutropenic fever in the era of antimicrobial resistance and stewardship is limited.

This review aims to highlight current evidence supporting AMS interventions specific for leukemia/malignant hematology (MH) patients, describe best practices, and identify key opportunities. It examines AMS metrics relevant to MH and HSCT populations, and new approaches to the management of high-risk febrile neutropenia.

The why: making the case for antimicrobial stewardship

Burden of antimicrobial resistance

Patients with hematological malignancies need effective antibiotics to treat infectious complications associated with immune defects and chemotherapy; therefore, antimicrobial resistance (AMR) significantly impacts their outcomes [10••, 11]. An international study of 65 HSCT centers from 25 countries reported that among 704 Gram-negative rod isolates, of which 73% were *Enterobacteriaceae*, 50% were fluoroquinolone-resistant, and 18.5% were carbapenem-resistant [12••]. A modeling study using published data estimated that 26.8% of pathogens causing infections after chemotherapy in US patients with hematological malignancies are resistant to standard antibiotic prophylaxis, primarily fluoroquinolones [13••]. A 30% reduction in efficacy of fluoroquinolones translates into 683 additional infection-related deaths annually [13••]. Extended-spectrum beta-lactamase-producing (ESBL) *E. coli* is of particular concern, as they account for 17–37% of all bloodstream infections caused by *Enterobacteriaceae*, with associated mortality rates reported as 13 to 45% [14]. In a multicenter prospective study, 21-day mortality in leukemia patients was higher at 42% in patients with bloodstream infections caused by multidrug-resistant *Pseudomonas aeruginosa*, compared with those infected with susceptible strains at 13% [15••]. Lastly, vancomycin-resistant enterococcus (VRE) bloodstream infections have emerged as a cause of morbidity and

mortality in leukemia and HSCT patients [16••]. In a registry study with 7128 patients (adults and pediatrics) with acute leukemia, 3.2% had VRE bloodstream infections within 100 days of post-HSCT, which was associated with a 2.9-fold increase in mortality compared with patients without VRE infections [17••].

Adverse effects of antimicrobials including *Clostridioides difficile* infection

MDRO are associated with worse mortality partly because of inadequate activity in empiric antibiotics, which may prompt clinicians to select second- or third-line alternatives with higher susceptibility rates, despite toxicity or efficacy concerns [12••, 14, 16••]. Polymyxins, colistin, and tigecycline have been re-introduced into the antibiotic armamentarium to treat extensively antibiotic-resistant *Enterobacteriaceae*, *P. aeruginosa*, and *Acinetobacter spp.* [14, 18]. Clinicians may routinely use combination therapy to ensure adequate empiric activity or to prevent treatment-emergent resistance, but such practices predispose patients to adverse events, and may not be effective [19]. Lastly, hematological malignancies and HSCT double *C. difficile* infection risks due to exposure to healthcare facilities, disruption of microbiome from broad-spectrum antimicrobials and chemotherapy, and are associated with higher mortality [20, 21••, 22••].

Antimicrobial shortage and limited development of new antibiotics

Antimicrobial shortage is a major chronic problem in healthcare [23••, 24••, 25]. Many broad-spectrum antibiotics affected are needed in patients with hematological malignancies and HSCT for their antipseudomonal activity, e.g., piperacillin-tazobactam, meropenem, aminoglycosides, and cefepime [23••, 24••, 25]. Interventions to manage the shortages have led to unintended consequences, including higher *C. difficile* rates, increased usage of alternatives with worse adverse effects, and modifications of local febrile neutropenia guidelines to accommodate the shortages [23••, 24••]. Despite the World Health Organization's call for new antibiotics in the Global Action Plan on Antimicrobial Resistance and the Priority List Pathogens, new compounds against resistant Gram-negative bacteria remain under-represented and are urgently needed [26]. Efficacy and toxicity data of new antibiotics in leukemia or HSCT are limited, yet treatment failure and emergent resistance have been reported, for example, in the new antipseudomonal cephalosporin ceftolozane-tazobactam [27••, 28].

Resource stewardship

A retrospective cohort study of pediatric leukemia patients undergoing HSCT involving 27 transplant centers in US children's hospitals found that antipseudomonal antibiotic use ranged from 436 to 1121 days of therapy (DOT) per 1000 neutropenic days, with variability in choice of agents [29••]. Broad-spectrum Gram-positive antibiotic use ranged from 153 to 728 DOT/1000 neutropenic days, driven by vancomycin use [29••]. Antibiotic use was not strongly associated with days of significant illness or mortality, and the authors recommended that AMS is needed to optimize antibiotics in pediatric HSCT patients [29••]. Antimicrobials are life-saving resources for patients with hematological malignancies and HSCT, while AMR and antimicrobial-

associated adverse effects are detrimental to patients. To accomplish system-level improvements, a programmatic approach is needed.

The how: implementing an antimicrobial stewardship program in malignant hematology and hematopoietic stem cell transplant

The who: human resources

Currently, AMS teams are recommended to be interdisciplinary, led/co-led by physicians and pharmacists with infectious disease and AMS training, and ideally include nurses and infection prevention practitioners [30, 31••]. Dedicated funding with adequate resource allocation and clear accountability structure with senior leadership is required [30, 32••].

Explicit endorsement from administrators and local clinical leaders in hematology-oncology to champion the AMS cause (Fig. 1) is essential for successful implementation [5••, 33••]. Their engagement validates the AMS team's interventions and helps overcome real and potential challenges [33••, 34]. Particularly, their advocacy helps the AMS team to address misconceptions among prescribers, which may be beliefs and attitudes that their patients need more antibiotics because they are "sicker" than a normal host, or due to diagnostic uncertainty, atypical symptom presentation, and limited data on treating infections in immunocompromised hosts [5••, 33••]. A strong liaison with an infectious disease team promotes a standardized approach and minimizes

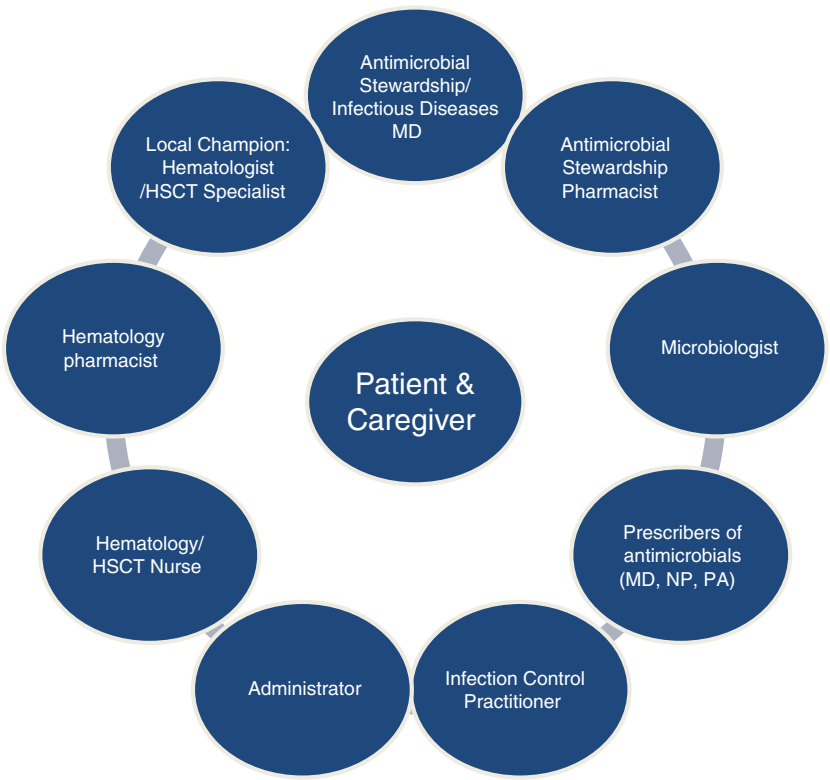

Fig. 1. Antimicrobial stewardship team and partners for hematological malignancies and hematopoietic stem cell transplant

professional conflicts, as their expertise is often sought in complex cases such as patients with invasive fungal infections or MDRO [35]. Yeo et al. compared infectious disease specialists' recommendations with those from the AMS team in a hospital-wide review, where 33.6% (48/143) patients had hematological malignancies [35]. Although 18.9% of recommendations were discordant between AMS and infectious diseases, the review improved communications among the primary, infectious disease, and stewardship teams [35].

The what: antimicrobial stewardship interventions

A systematic review and meta-analysis found AMS interventions to be more effective in hematology-oncology than in other settings, with MDRO infections and colonization reduced by 59% (incidence ratio 0.41, 95% CI 0.20–0.85; $p = 0.02$) [4••]. This finding should be interpreted with caution as that it was based on only 3 studies, highlighting the gaps in knowledge with AMS in this setting [4••].

Audit and feedback

AMS aims to produce sustained changes in prescribing behavior; therefore, interventions associated with behavioral sciences have been examined for their effectiveness [36••, 37••]. The strategy of "nudging", often delivered as audit and feedback or post-prescription review, is effective in reducing antimicrobial consumption in patients with hematological malignancies [1••, 38••, 39••]. A cancer institute in Singapore reported decreased use of audited antibiotics (regression analysis coefficient – 2.509, p value of trend = 0.001) in hematology-oncology patients, driven by significant reduction in carbapenems and cephalosporins use [40]. In Canada, a retrospective observational time-series study with audit and feedback as the AMS intervention found significant reduction in antimicrobial consumption (278 vs. 247 defined daily dose/100 patient-days; $p < 0.01$) and cost (C$154.59 vs. C$128.93/patient day, $p = 0.03$) in the intervention group (leukemia unit), without negatively impacting mortality or length of stay [33••]. Consumption and cost were stable in the internal control (allogeneic HSCT unit as same cancer center), but increased in the external control (leukemia-HSCT unit at another hospital) [33••]. However, audit and feedback requires significant human resources. Yeo et al. found substituting infectious disease specialists with infectious disease trainees rotating through AMS rotations correlated with decreased acceptance of AMS recommendations and increased use of broad-spectrum antibiotics at the hematology-oncology unit in Singapore [41]. In the Canadian study, the AMS team for leukemia was an AMS pharmacist and an infectious disease specialist with expertise in immunocompromised hosts; they committed 10 h/week to prepare and conduct audit and feedback at an annual salary cost of C$45,000 [33••].

Formulary restriction or pre-authorization policy

Restriction policy, usually implemented through a pre-approval system maintained by AMS and/or infectious disease clinicians, is associated with reduction in antimicrobial use [1••]. Restriction policy prompts review of clinical data and prior cultures at the time of initiation of therapy [1••]. Selection of targeted drugs is generally based on cost and clinical criteria such as spectrum of activity and toxicity; therefore, this strategy can optimize empiric choices and influences

downstream use [1••]. Disadvantages of restriction policy are the perceived loss of prescriber's autonomy, and lack of empowerment or knowledge transfer to the primary team [1••]. In the MH and HSCT patient population, given their acuity and vulnerability to severe infections, the impact of restriction policy is less clear because they are usually exempted, and infectious disease specialist are often involved.

Revisiting the conventional antimicrobial approach to managing febrile neutropenia

Concerns for MDRO have prompted re-examination of the management of high-risk febrile neutropenia (FN) with ongoing broad-spectrum antimicrobial therapy until ANC $> 0.5 \times 10^9$ cells/L. The 4th European Conference of Infections in Leukemia guideline (ECIL-4) was the first to propose a diagnostic-driven, escalation and de-escalation approach, with timely reassessment at 72 h after initial empiric antibiotic therapy [6••]. It suggests tailoring antibiotic based on the focus of infection and/or causative pathogen(s) identified, and shortening duration of antibiotic following resolution of fever, irrespective of neutropenia, with prompt reassessment of patient as needed [6••]. However, the guideline was based on limited data.

An open-label, randomized, controlled study in six academic hospitals in Spain compared the conventional approach of continuing antibiotics until ANC $> 0.5 \times 10^9$ cells/L with stopping antibiotics if patient was afebrile for 72 h and met pre-defined criteria for clinical recovery [42••]. The intervention group (78 patients) had significantly longer antibiotic-free days than the control group (79 patients), 16.1 vs. 13.6 (95% CI – 4.6 to – 0.3) [42••]. Forty percent of the febrile episodes were of unknown origin, and adverse events rates were not significantly different between the two arms [42••]. This study provided evidence to support an AMS-driven approach to high-risk febrile neutropenia, but its applicability to leukemia or allogeneic HSCT patients was limited by the heterogeneity of the study population. Patients with acute leukemia undergoing induction or reinduction chemotherapy accounted for 31% and 23% of patients in intervention and control group, respectively. Other disease states were autologous HSCT, lymphoma, multiple myeloma, myelodysplastic syndrome, and aplastic anemia, which do not have the same extent of myelosuppression. G-CSF was given to 37% of patients in both arms, which may not be standard practice in leukemia and HSCT patients beyond the study centers [42••].

A tertiary hospital in France implemented the ECIL-4 high-risk FN guideline as an AMS intervention in hematology ward with audit and feedback [43••]. Flow diagrams with clear "stopping rules" for common clinical scenarios were provided to prescribers [43••]. With pre-intervention period of a year, and post-intervention period of 6 months, the authors reported significant reduction in carbapenem consumption of – 135.28 ± 59.49 DDD/bed-day ($p = 0.04$), but no change in overall antibiotic consumption [43••]. There were no significant differences in mortality, intensive care admission, or incidence of bacteremia. The study was limited by a short intervention period; as such, long term safety and efficacy impact are unknown.

Primary prophylaxis with fluoroquinolone is common in MH and HSCT patients, but this practice is also being challenged [44, 45, 46••, 47]. A meta-analysis of 2 randomized controlled trials and 12 observational studies in MH and HSCT patients found fluoroquinolone prophylaxis to have no effect on

mortality (pooled odds ratio [OR] 1.01, 95%CI 0.73–1.41), but was associated with lower rate of bloodstream infections (pooled OR 0.57, 95%CI 0.43–0.74) and episodes of fever during neutropenia (pooled OR 0.32, 95%CI 0.20–0.50) [44]. In few studies, fluoroquinolone prophylaxis resulted in increased colonization or infection with MDRO [44]. Clinical decision on primary prophylaxis should balance the benefit of reduction in fever and bacteremia with risks of fluoroquinolone-associated adverse events at the patient level, and the epidemiology of pathogens at the ward or institution level [45]. To ensure patient safety, the decision should be considered in context of timely reassessment in case of neutropenic sepsis [46••].

Developing local guidelines for infections in patients with hematological malignancies

Although comprehensive, antimicrobial recommendations from published clinical practice guidelines by specialists organizations do not account for local characteristics like susceptibility patterns, healthcare resources, or patient-centered factors [48, 49]. Creating these guidelines can be time and resource-intensive. in addition, it remains a challenge to incorporate new literature in a timely manner [48]. To avoid these pitfalls, locally developed, facility-specific guidelines have been recommended for high-risk febrile neutropenia in MH patients to reduce unnecessary antibiotic use and improve outcomes [1••]. Benefits of facility-specific FN guideline for cancer patients (solid tumor and MH) include optimization of antimicrobial selection and timing of administration [50]. In a minority of studies, clinical outcomes including decreased length of stay and reduction in mortality have been described [50].

To optimize the process to create local high-risk FN best practices guideline, time and resources investment, as well as support from end-user clinicians, it is helpful to follow a healthcare change management framework [51]. The Canada Health Infoway was designed to support change management leaders, managers, and frontline clinicians who are implementing healthcare solutions in their workflow and practice, particularly solutions related to information and communication technology, therefore applicable to the development and implementation of facility-specific guidelines [51]. The framework contains 6 steps: (1) determine governance and leadership to sponsor the initiative; (2) stakeholder engagement with clinician end-users and local champions; (3) workflow analysis and integration of guideline in day-to-day patient care; (4) communications to clinician end-users to raise awareness and dissemination; (5) training and education to empower clinician end-users to adopt the guideline; and (6) ongoing monitoring and evaluation on the utility and impact of the guideline [51]. Steps 1–3 are applicable to the design process, and steps 4–6 to the implementation and dissemination phase. Engaging front-line end-users early in the process is beneficial in promoting collaboration between the AMS and MH teams, and facilitates consensus on contentious issues such as standardization vs. patient-specific practice in the context of quality improvement, particularly in highly vulnerable patient population such as patients with leukemia [52]. Metrics to study the impact of local best practices guidelines are described "Evaluating Antimicrobial Stewardship Through Metrics and Performance Indicators" below. An example of a high-risk FN guideline created using this framework: https://www.antimicrobialstewardship.com/highriskfn.

De-labelling patients with self-reported penicillin or beta-lactam allergy

Approximately 10% of the US population self-report to have a penicillin allergy, and up to 20% in hospitalized patients [53••, 54••]. However, patients who experience IgE-mediated type I hypersensitivity (anaphylaxis) reaction remain uncommon (< 5%) [53••]. Self-reported beta-lactam allergy is associated with worse outcome in non-immunocompromised patients [55]. In patients with hematological malignancies and HSCT requiring antibiotics, a retrospective study with 660 patients from two tertiary centers found 14.1% to be allergic to beta-lactam (9.3% penicillin only and 3.3% cephalosporin only) [54••]. Those patients had worse outcomes than those without beta-lactam allergy: longer hospital stay (11.3 vs. 7.6 days; $p < 0.001$); higher 30-day mortality (7.6% vs. 5.3%; $p = 0.17$); higher 30-day readmission rate (19.2% vs. 15.1%; $p = 0.008$); higher *C. difficile* rate (17.7% vs. 11.6%; $p < 0.001$); and higher hospital costs ($223,046 vs. $173,256; $p < 0.001$) [54••]. A possible explanation was the use of alternative antibiotics such as quinolones for febrile neutropenia, even though beta-lactams such as penicillins would have been safer or more efficacious [54••]. Recently, interventions have been introduced to empower patients and clinicians to de-label self-reported penicillin allergy via structured interviews, oral challenge, and skin testing to identify patients who can safely receive penicillin (or beta-lactam) antibiotics [53••, 56]. While the optimal way to implement this intervention in MH and HSCT patients remains to be determined, one cancer center reported that it is feasible to conduct skin testing to rule out Type I hypersensitivity reactions in cancer patients, including leukemia patients [57]. Among 100 patients who underwent testing, 95% were negative, and more than half went on to receive penicillin-based antibiotics safely [57].

Rapid diagnostic technologies

Recent proliferation of rapid diagnostic technologies (RDT) have changed prescribing practices [58••, 59]. For management of invasive fungal infections, non-culture based testing include galactomannan (GM) and beta-D-glucan (BDG) [60, 61]. Molecular techniques such as PCR testing, alone or in combination with GM or BDG, have been explored in MH patients. In an open-label, parallel-group, randomized controlled trial, 240 adult patients undergoing allogeneic HSCT or chemotherapy for acute leukemia from 6 Australian centers were assigned to either the standard diagnostic strategy based on culture and histology (122 patients), or a GM and PCR strategy (118 patients) [62]. Primary outcome was receipt of empiric antifungal [62]. At 26-week follow-up, 39 patients (32%) in the standard diagnosis group and 18 (15%) in the biomarker diagnosis group received empirical antifungal treatment (difference 17%, 95% CI 4–26; $p = 0 \cdot 002$) [62]. There was no difference in mortality between the two groups, but a significantly higher proportion of patients in the GM-PCR group was diagnosed with probable or possible invasive aspergillosis [62].

Another open-label, controlled, parallel-group randomized trial in 219 adult patients with acute myeloid leukemia and myelodysplastic syndrome on induction therapy, or HSCT from 13 Spanish centers compared weekly GM plus PCR (105 patients) with GM only (114 patients) surveillance screening [63]. Follow-up was 30 days after resolution neutropenia for leukemia and

myelodysplastic syndrome; 210 or 130 days for allogeneic HSCT patients with or without graft-vs.-host disease, respectively [63]. The GM-PCR group had lower cumulative incidence of proven or probable invasive aspergillosis (4.2% vs 13.1%; odds ratio, 0.29 [95% CI, .09–.91]), and less use of empiric antifungal (16.7% vs 29.0%; $p = 0.038$) [63]. All-cause mortality was not different between the two groups [63]. Despite the technological advances in diagnostics, data on cost-effectiveness in the context of reduction in antifungal use and outcomes remain scarce.

Antifungal stewardship

Patients with hematological malignancies and HSCT are vulnerable to invasive fungal infections due to prolonged and profound neutropenia [7, 60, 64]. Antifungals are essential to their care, and commonly prescribed as primary prophylaxis and treatment of invasive fungal infections (IFI) [64, 65]. Antifungal stewardship (AFS) interventions have gained considerable interests for several reasons [66, 67]. First, the burden of infection and associated mortality is high: a systematic review and meta-analysis of 49 studies found that among patients with hematological malignancies, 6.3% (1056/16,815) developed invasive aspergillosis, with a pooled case fatality rate of 29% (95% CI, 20–38%) within 100 days [68]. Second, antifungal treatment options are limited to three main classes, azoles, echinocandins, and polyenes, despite some advances within each class [60, 61]. First-line agents such as voriconazole and amphotericin B deoxycholate (irrespective of formulation) have high propensities for drug-drug interactions, genetic polymorphism, or toxicities requiring close monitoring [69]. Third, IFIs are costly. A study by the Centers for Disease Control and Prevention (CDC) reported hospitalizations in 2005–2014 for *Candida* and *Aspergillus* accounted for the highest total hospitalization costs of any fungal disease, totaling 41,555 hospitalizations and $US 2.6 billion [70]. Furthermore, hospitalizations of invasive mucormycosis in patients with underlying hematological malignancies increased significantly between 2000 and 2013 [71]. Lastly, the changing epidemiology of IFI, including MDR *Candida* spp., voriconazole-resistant *Aspergillus spp*. has strengthened the call for judicious use of available antifungals [72–74].

Interventions of AFS described in the literature are aligned broadly with those of AMS programs: locally developed facility-specific guidelines, audit-feedback process, restriction policy, and education for prescribers [75–77]. Impetus of earlier literature was limited to cost reduction rather than improving appropriateness of use [75, 76]. A tertiary hospital in the UK reported a savings of £180,000 after 1 year intervention, primarily audit and feedback, and over 50% of patients had hematological malignancies [75]. In Spain, a tertiary hospital audited baseline usage data and created a bundled approach with locally developed guidelines, audit and feedback, and education interventions [67, 76]. The AFS interventions were associated with a reduction in total antifungal expenditure from US$3.8 million to US$2.9 million over the first 2 years, generating net savings of US$407,663 and US$824,458 per year after considering the cost of additional staff required [76]. A 5-year follow-up by the authors reported significant decrease in empirical use (from 62 to 30%, $p < 0.001$), with significant increase in targeted therapy and prophylaxis [78].

With improved IFI diagnostic criteria and support from antifungal RDT, recent efforts are directed at reducing empiric antifungal use with a diagnostic-driven approach [79, 80]. An interdisciplinary AFS team with an infectious disease specialist and an AMS pharmacist performed weekly audit-feedback review of antifungal prescriptions in a teaching hospital in London, UK, where 51% of antifungal recipients were high-risk patients with hematological malignancies or in the intensive care unit [81••]. The AFS team applied European Organization for the Research and Treatment of Cancer/Mycosis Study Group (EORTC-MSG) criteria and RDT such as serum galactomannan, PCR, beta-D-glucan, and fungal serology to aid their recommendations [81••]. The team assessed appropriateness of 512 antifungal prescriptions in 432 patients in 6 years, most commonly liposomal amphotericin (35%) and intravenous fluconazole (29%) [81••]. Empiric therapy was found to be unnecessary in 82% (150/183) with patients having no evidence of IFI [81••]. Although antifungal expenditure was reduced by 30% (> £300,000) in the first 3 years, it increased by 20% in the following years, albeit still lower than the national rate [81••].

Evaluating antimicrobial stewardship through metrics and performance indicators

An essential component of a quality improvement programmatic approach is continuous and transparent reporting of metrics and performance indicators, and AMS programs specific to hematological malignancies and HSCT are no exception [30]. Aggregate measures such as expenditure (cost) and consumption metric normalized to patient volume (patient-days), such as defined daily dose (DDD), days of therapy (DOT), and length of therapy (LOT) are commonly used in AMS and AFS programs [82, 83••]. As patients with hematological malignancies and HSCT are commonly profoundly immunocompromised, it is expected that antimicrobial consumption will be higher than in a general population. For a comprehensive understanding of usage patterns, it is more appropriate to benchmark within the institution (year-on-year), or with comparable patient population in similar institutions. Established tools such as the National Healthcare Safety Network Antimicrobial Use Module are useful for like-to-like comparison [84].

In addition to aggregate measures, indicators of impact specific to the intervention should be determined a priori, and tailored to local resources [85, 86••]. Syndrome-specific indicators, such as those related to benchmarks within a locally developed febrile neutropenia guideline, are possible appropriate options. Process outcomes such as adherence to guidelines are useful as ongoing evaluation. To generate a comprehensive assessment of this syndromic approach to AMS, it is beneficial to combine guideline adherence with clinical outcomes, purpose of antimicrobial prescription (prophylaxis, empiric, targeted or pre-emptive) with AMS consumption metrics. For efficient, real-time point prevalence auditing, Australia's National Antimicrobial Prescribing Survey is a general online tool with well-defined criteria to assess appropriateness of antimicrobial use and guideline adherence, irrespective of patient population [87]. However, publications regarding its utility have been limited to emergency department and hospital-wide audits, but not specific to MH and HSCT [88, 89].

Measures such as mortality, length of stay, and *C. difficile* infection rates are commonly reported in the literature as clinical outcomes, or as balancing measures to demonstrate that AMS or AFS interventions did not lead to unintended consequences impacting patient care [4••, 82, 83••].

Conclusion: gaps in knowledge and research opportunities

A key gap in knowledge is the optimal duration of antimicrobial treatment required in a high-risk neutropenic patient following resolution of fever, but still experiencing mucositis. Although data exist on shortening the duration of antimicrobial therapy during neutropenia, clinical trial conditions offer prompt and accessible healthcare services, or ongoing hospitalization. In the real-world setting, this may not be feasible, and clinical practice-based data are needed. Another gap is whether it is safe to target antimicrobial treatment on the identified focus of infection or pathogen, despite ongoing neutropenia and mucositis. As data continue to accumulate on the benefits of de-labelling self-reported beta-lactam allergy, it will be necessary to determine the best timing, safest, and optimal ways to implement this intervention. Evaluation on the partnership between microbiology laboratory and AMS team on maximizing the cost-effectiveness of diagnostic technologies and antimicrobial use is needed. The role of nursing in AMS for MH and HSCT patients remain to be explored. Nursing collaboration has shown to be beneficial in the acute care setting. The ideal make-up of the AMS team for MH and HSCT patients is unclear, including the level of specialty training. Long-term data with appropriate outcome measures beyond consumption and cost of antimicrobials will strengthen AMS programs for this highly vulnerable population. In turn, such data will facilitate the incorporation of AMS programs in health systems that care for MH and HSCT patients.

Compliance with ethical standards

Conflict of interest
The authors declare that they have no conflicts of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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