Antimicrobial Stewardship in Immunocompromised Hosts

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Abstract Although an antimicrobial stewardship program (ASP) as a primary tool to combat global development of antimicrobial resistance has been widely accepted in the last decade, the key principles of ASP have not always been adopted in patients with significant immune defects. Multiple barriers exist for implementing ASP in this population: physician's perceptions regarding the immunocompromised as sicker patients and fear of poor outcomes, a wide range of possible infectious etiologies with diagnostic uncertainty, complexity in making early diagnosis, impaired inflammatory responses, and difficulty in controlling the source of infections due to thrombocytopenia, and limited surgical interventions. However, ASP in the immunocompromised hosts is an important patient safety measure as development of multidrug-resistant (MDR) pathogens is an emerging problem. This chapter discusses strategies and the need for ASP in the immunocompromised host with cancer.

Keywords Antimicrobial stewardship program (ASP) · Formulary Management · Drug Interactions · Early de-escalation in febrile neutropenic patients · Antimicrobial Restriction · Prospective audit and feedback · Microbiological data · Duration of therapy · Antifungal stewardship · Biomarkers · Rapid Diagnostics · Intravenous to oral

Goals and Opportunities of ASP in Immunocompromised Hosts

ASP aims to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use such as toxicity, collateral damage and development of resistance as well as to reduce cost without compromising outcome [1]. The same goals apply to the patients with immune deficiency. Furthermore, opportunities for

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ASP exist for both prophylaxis and treatment in the immunocompromised host by optimizing drug selection, dose, route and duration.

ASP Modalities in Immunocompromised Hosts

Formulary Management

ASP plays a crucial role in formulary decisions of antimicrobials. Formulary choices must balance the accessibility of key treatment options for immunocompromised hosts and adverse effects including drug costs. For example, ASP streamlines the hospital formulary based on potential drug interactions between antimicrobials and chemotherapy/immunosuppressants (e.g., nafcillin-tacrolimus interaction via CYP3A4 v. no interaction between oxacillin-tacrolimus for treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) infections), cost (e.g. cost effectiveness analysis between ceftaroline and other anti-methicillin-resistant *S. aureus* (MRSA) agents) and spectrum of coverage (e.g., limitation of the use of ceftolozane/tazobactam or ceftazidime/avibactam v. a narrower spectrum agent when broad spectrum coverage is not necessary). ASP should also assess drug supply and usage (e.g., drug shortages in cefepime, piperacillin-tazobactam), changes in price (e.g., increase in price of flucytosine, IV erythromycin), and availability of newer agents with similar usage (e.g., isavuconazole v. posaconazole) to modify hospital-wide guidelines without compromising patient care. Once a drug is added to the formulary, ASP provides oversights on the implementation of restricted use via staff education, ordering requirements in the computer software program, and preauthorization (antimicrobial restriction) and prospective audit and feedback.

Antimicrobial Prophylaxis During Neutropenia

While there are guidelines available for antimicrobial prophylaxis in cancer patients including a recent review of biologicals and targeted therapies [2], collaboration between infectious diseases specialists and hematologists is essential to risk stratify who would need antimicrobial prophylaxis and to formulate the prophylaxis regimen due to complex immune dysfunctions in these hosts and unique infectious risks associated with certain stage of diseases or chemotherapeutic agents. For example, a review of infectious complications of patients who received blinatumomab, an anti-CD19 immunotherapy for relapsed/refractory B-cell acute lymphoblastic leukemia (ALL), noted a high rate (15%) of nodular, possible mold pneumonia [3]. While NCCN guidelines recommend fluconazole or micafungin as an antifungal prophylaxis for most ALL patients [4], more potent anti-mold prophylaxis was advocated when blinatumomab recipients presented with baseline neutropenia (i.e. ANC < 500 cells/μL) due to relapsed or refractory disease.

Fluoroquinolone prophylaxis has been recommended by the guidelines for high-risk patients who are going to be profoundly neutropenic for >7 days [4]. Despite the rising concern over fluoroquinolone resistance, a recent Cochrane review confirmed the reduction in mortality and infection rates still outweighs the risk of resistance, costs and adverse events associated with fluoroquinolone prophylaxis [5]. In the meantime, there are studies showing different classes of antibiotics such as third-generation cephalosporins or sulfamethoxazole-trimethoprim provided similar outcomes as fluoroquinolone prophylaxis [5, 6]. ASP should play a role in antimicrobial prophylaxis by closely monitoring local patterns of resistance, recommending alterative prophylaxis if needed based on prior infectious history or other clinical characteristics, and recommending antibacterial prophylaxis only in selected high-risk patients, but not in all neutropenic patients.

Choice of Agents for Neutropenic Fever

While many clinicians prefer IV antibiotics in the setting of neutropenic fever, oral antibiotics such as a combination of fluoroquinolone (i.e., ciprofloxacin or levofloxacin) plus amoxicillin/clavulanate (or clindamycin for those with a penicillin allergy) have been recommended for outpatient empirical therapy [7]. Adherence to the guidelines and adoption of the established tools for risk assessment provide ASP opportunities. There are several tools such as MASCC (Multinational Association for Supportive Care in Cancer) scoring and clinical criteria that may be used to differentiate who can be treated as an outpatient versus inpatient. The joint guideline by ASCO (American Society of Clinical Oncology) and IDSA (Infectious Diseases Society of America) endorses the use of a more recently validated tool, CISNE (the Clinical Index of Stable Febrile Neutropenia) score, which is more sensitive and specific in solid tumors for this purpose [7].

Regarding the inpatient management of neutropenic fever, IDSA guidelines recommend a variety of anti-pseudomonal beta-lactam antibiotics in the absence of complications (e.g., hypotension, pneumonia, and colonization of resistant organisms) [8]. While comparative studies did not find differences in clinical or safety outcomes amongst various agents either as monotherapy or in combination [9], institutions can streamline their preferred agents for febrile neutropenia from an ASP perspective. Colonization with resistant organisms poses a substantial risk for infection and a high mortality in immunocompromised hosts [10]. ASP should prescreen patients at highest risk for infections with MDR organisms to tailor individualized empiric antibiotic recommendations. For example, empiric use of carbapenems should be advocated if there is a history of MDR *Pseudomonas* aeruginosa or extended-spectrum β-lactamase (ESBL) producing *Enterobacteriaceae*. Otherwise, it should be reserved when narrower spectrum anti-pseudomonal agents can be utilized.

Also, ASP should limit antibiotics with Gram-positive coverage such as MRSA in accordance with current guidelines. For example, vancomycin is not

recommended as initial empiric therapy for neutropenic fever in the absence of a catheter-related infection, skin or soft-tissue infection, pneumonia or hemodynamic instability [8]. The use of empiric antibiotics with anti- vancomycin-resistant *Enterococcus* (VRE) activity once febrile neutropenia develops for those with VRE colonization is under debate. Recent studies showed no difference in mortality between the empiric linezolid group and the control group [11] and no impact on mortality from delayed VRE bloodstream infection treatment [12].

Early De-escalation After Neutropenic Fever

IDSA guidelines for neutropenic fever published in 2011 recommend the initial regimen be continued until clear signs of marrow recovery (i.e., an increasing absolute neutrophils count (ANC) that exceeds 500 cells/μL) in patients with unexplained fever [8]. There have been several recent studies that evaluated early de-escalation of antibiotics. Le Clech *et al* compared the outcomes of early antibiotic de-escalation in two phases for patients with hematologic malignancy with fever of unknown origin (FUO) [13]; in the first phase all antibiotics were stopped 48 h after resolution of fever as recommended by the ECIL-4 guidelines [14], and in the second phase antibiotics were stopped on day 5 whether febrile or afebrile. The composite endpoint defined as in-hospital mortality, intensive care unit (ICU) admission, relapse of febrile neutropenia ≤48 h after discontinuation of antibiotics in afebrile patients or a new documented infection in patients with persistent fever were not different between the two groups and the duration of antibiotics was shorter in the second group (7 v. 5 days, $p = 0.002$). While having limitations inherent to a nonrandomized trial, such as, a longer duration of neutropenia in the first group (20 v. 12 days, $p = 0.01$) and different types of chemotherapy and stem cell transplant between the groups, the study demonstrated the feasibility of early de-escalation in febrile neutropenic patients with a hematologic malignancy. In another study by Aguilar-Guisado *et al*, early de-escalation of antibiotics after 72 h of apyrexia and clinical recovery irrespective of neutrophil count recovery was evaluated [15]. This was a superiority, open-label, randomized, controlled phase 4 trial from six hospitals in Spain which included 156 high-risk febrile neutropenic patients with hematological malignancies but without microbiologically or clinically documented infection. When compared to the control group (i.e., anti-pseudomonal antibiotics were continued until ANC > 500 cells/μL), the experimental group showed significantly shorter days of empirical antimicrobials (16.1 v. 13.6 days, $p = 0.026$) with similar rates of adverse events. One out of 78 and three out of 79 patients died from the experimental and control group, respectively.

Two recent studies specifically assessed early de-escalation in hematopoietic stem cell transplantation recipients (HSCT). The first study by Snyder *et al* compared the rates of recurrent fever, *Clostridium difficile*-associated infection, length of stay, intensive care unit (ICU) admission, in-hospital mortality, need for re-escalation of therapy, rate of positive blood cultures and pharmacoeconomic impact

between the early de-escalation group (i.e., empiric antibiotics were de-escalated to prophylaxis after 5 days if defervesced) and control group [16]. They found no difference in the rate of recurrent fever (15% in early de-escalation group v. 19% in control group, 90% CI, −0.088 to 0.163) and in other clinical outcomes, but showed a significant decrease in antimicrobial use in the early de-escalation group which resulted in an estimated antimicrobial cost reduction per 1000 transplant days of approximately $10,000 ($22,300 v. $32,760, p = 0.012).

The second study in HSCT patients by Gustinetti *et al* is a single center study from Italy and compared clinical and economical outcomes between early de-escalation (i.e., de-escalation to a narrower spectrum β-lactam or switching to fluoroquinolone prophylaxis or discontinuation within 96 h in afebrile patients) and late de-escalation (i.e., de-escalation after 96 h) [17]. Failure of de-escalation/discontinuation was defined as escalating or restarting antibiotic therapy, having a blood stream infection or fever recurrence within 96 h from de-escalation/discontinuation. In the early de-escalation group (n = 26), the failure of de-escalation occurred in 4 patients (15.4%, 4/26) including a fever recurrence (n = 1), bartholinitis (n = 1), and bacteremia (n = 2). Of note, these bacteremias were not recurrences of previous infections and all failures were successfully treated with escalation of antibiotic therapy. In the late de-escalation group, the failure of de-escalation occurred in 6 patients (19%, 6/31) which included 2 bacteremia (one *Pseudomonas putida*, and one *Enterococcus faecium*) and fever recurrence. None of these cases resulted in septic shock or death. In multivariate analyses, the presence of blood stream infection was associated with early de-escalation, which reflects their antimicrobial de-escalation practice driven by microbiologic culture regardless of count recovery.

In summary, early de-escalation and discontinuation of broad spectrum anti-pseudomonal antibiotics in febrile neutropenic patients is feasible while the timing for early de-escalation varies amongst studies. Until newer international guidelines address these aforementioned studies, ASP should be mindful of these results and may consider early de-escalation in selected patients in consultation with infectious diseases clinicians and the hematologist/oncologist.

Clinical Pathway

The 2016 Infectious Diseases Society of America (IDSA) guideline for implementing an ASP endorses the use of facility-specific clinical practice guidelines [18]. Studies have shown that an interdisciplinary development of such guidelines improved awareness and uptake of clinical pathways via multifaceted dissemination and an implementation strategy [18]. Highly employed clinical guidelines for cancer, HSCT and solid organ transplant patients included febrile neutropenia, antifungal prophylaxis, treatment of invasive fungal infections and cytomegalovirus prophylaxis [19]. An institutional antimicrobial use clinical pathway should be based on consensus guidelines, local susceptibility data and cost [9]. For example, Metan

et al replaced a carbapenem with piperacillin/tazobactam ± amikacin as a first-line empiric antibacterial regimen except in high risk patients after experiencing a high incidence of carbapenem-resistant Gram-negative bacilli in patients with neutropenic fever [20]. High risk patients were defined as known colonizers with ESBL-producing Enterobacteriaceae who presented with severe sepsis, septic shock, nosocomial pneumonia, or recently transferred from the ICU with a high prevalence of MDR Gram-negative bacilli. This led to a significant reduction in carbapenem use without affecting mortality.

Antimicrobial Restriction

Not only restricting certain antimicrobials that require infectious diseases consultation or an indication for use when prescribing, but also optimizing the duration of antimicrobial use is an important ASP strategy. For example, a simple reminder of daily carbapenem use to prescribers or an automatic email to reassess the duration of certain targeted broad spectrum antibiotics can be used to limit the duration.

Prospective Audit and Feedback

If resources and manpower are available, a prospective audit and feedback (PAF) based on a review of empiric therapy, de-escalation or escalation based on clinical and microbiological data, and duration of therapy should be implemented by the ASP. PAF can be very labor intensive, and identification of appropriate patients for intervention can be challenging if not supported by a computerized surveillance system. The key is allocation of necessary resources, a persistent effort by dedicated, well-trained personnel, and ongoing communication with clinicians [18].

Antifungal Stewardship

While many ASPs have focused initial efforts on reducing inappropriate antibiotic use in awareness of the perils of resistant bacteria, antifungal stewardship should be in place given the evidence of poor use of antifungals which has showed low adherence to guidelines or labeling [21–24] and emergence of resistant organisms, namely azole-resistant *Aspergillus fumigatus* [25], echinocandin-resistant *Candida glabrata* [26], and MDR *Candida auris* [27]. Similar to antibacterial prophylaxis, antifungal prophylaxis is recommended for high-risk patients but not for low-risk patients with anticipated neutropenia less than 7 days. Institutions caring for large

numbers of high-risk patients should have local guidelines for antifungal prophylaxis directed against *Candida, Aspergillus, Mucormycosis, Pneumocystis jiroveci* and a surveillance program for early diagnosis of invasive fungal infections. For example, use of early chest CT [28] or quantitative polymerase chain reaction (PCR) assays targeting *Rhizomucor, Lichtheimia, Mucor/Rhizopus* has been advocated for early diagnosis of mucormycosis [29]. The *Aspergillus* galactomannan (GM) test is relatively specific for *Aspergillus*, but β-1,3-D-glucan (BDG) is a component of the cell wall of most fungi and thus has low specificity. Due to the reduced sensitivities and specificities of BDG or *Aspergillus* GM tests, use of these tests are limited and results should be interpreted in conjunction with other clinical, microbiological and radiological findings. For example, the sensitivity of the *Aspergillus* GM test decreases if a patient has already been on an antifungal; a persistently positive GM is associated with higher mortality; and persistent BDG can occur despite resolution of fungal infection [30]. As more biomarkers become available, the ASP should evaluate if each test alone or in combination is valuable in antifungal stewardship and if so, then develop a pathway utilizing these tools for de-escalation or early escalation of antifungals.

Use of Biomarkers

Procalcitonin has been extensively studied as an ASP tool, but its role in neutropenic patients is less clear. For example, complicating factors of routine post-transplant physiology and the effect of transplant-specific therapies such as anti-thymocyte globulin caused an elevated procalcitonin level which was not associated with infection [31]. Despite concerns about potentially limited procalcitonin production in neutropenic patients, a review of 30 articles on the use of procalcitonin in this population concluded procalcitonin may be able to discriminate fever due to systemic infections from non-infectious etiologies [32]. Based on the reported procalcitonin levels in febrile neutropenic patients, the authors reported that values less than 0.5 ng/mL are less likely to occur in patients with infection and a delayed peak may be possible with fungal infections [32]. Similar to non-neutropenic patients, serial measurement of procalcitonin may be useful in determining the duration of therapy. On the other hand, in a recent study in febrile neutropenic patients undergoing HSCT, procalcitonin showed a limited sensitivity of 66% and a specificity of 75% with a cut-off of 0.5 ng/mL [33]. Furthermore, the procalcitonin-guided protocol did not reduce the use of antibiotics in febrile neutropenia in a randomized controlled trial by Lima et al. [34] In summary, procalcitonin needs to be considered as a supplemental tool for diagnosis, but not as a tool to replace proper clinical and microbiological diagnosis or to withhold initiating antibiotics.

There are other biomarkers such as adrenomedullin or TREM 1 (triggering receptor expressed on myeloid cells-1); adrenomedullin was used in community-acquired pneumonia to predict prognosis and TREM-1, to distinguish bacterial

pneumonia from nonbacterial pulmonary disease [35]. Similarly to procalcitonin, the complexity of immunology and the influence of concurrent immunosuppressive medications in the immunocompromised hosts need to be considered when attempting to use these biomarkers.

Rapid Diagnostics

Early identification of bacterial, viral and fungal pathogens and their antimicrobial susceptibility is critical in managing infectious diseases. ASP should assess rapid diagnostics for test accuracy, turn-around time and the extent to which they can prevent the unnecessary initiation or continuation of antimicrobials [36]. ASP should also provide education to providers on the appropriate test population, adequate interpretation of results, limitations of the test, and optimal selection of antimicrobials based on the results [37]. Notably, the benefits of rapid diagnostics will be lost in the absence of real-time ASP interventions [38].

Novel Approaches to Rapid Phenotypic Antimicrobial Susceptibility Testing

Rapid identification of carbapenemase producing Enterobacteriaceaes (CPE) is critical for medical management of this MDR infection as well as for infection control. Rapid Carb Blue Kit (Rosco Diagnostica, Taastrup, Denmark) and Rapidec Carba NP test (bioMerieux, Marcy L'Etoile, France) both detect carbapenemases distinctively from other beta-lactam hydrolyzing enzymes such as ESBL or AmpC (chromosomally encoded or plasmid-mediated) within 2 h. These tests measure color changes caused by carbapenemases-induced imipenem hydrolysis and subsequent acidification of the indicator solution. Both tests have high sensitivity (94–96%) and specificity (96–100%) for carbapenemases including KPC, NDM, VIM and OXA-48 with decreased sensitivity to OXA-48 (94%) [39–41].

Commercially available systems to report identification and susceptibility for the entire antibiogram include the Accelerate PhenoTest BC (Accelerate Diagnostics, Tucson, USA). It uses fluorescence in situ hybridization (FISH) for species identification (1.4 h) and automated time-lapse imaging for susceptibility (6.6 h) directly from positive blood culture [42]. Sensitivity and specificity are 97.5% and 99.3% for identification and 96.3% and 96.4% for susceptibility, respectively. While it provides faster results by approximately 24 h for identification and 42 h for susceptibility with high sensitivity and specificity as compared to standard methods, clinical evidence for patient outcome is lacking. ASP should develop an action plan per test results taking into account the test limitations (eg., false negative identification, major error in susceptibility) to reduce adverse outcomes.

Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS)

MALDI-TOF MS fingerprinting enables clinical microbiology laboratories to rapidly identify cultured microorganisms. Compared to other biochemical conventional techniques, turnaround times are typically reduced by at least a working day to several days for slower growing species [43]. Vitek MS (BioMerieux, St. Louis, MO, USA) uses MALDI-TOF MS technology to rapidly identify bacteria, viruses and fungi including *Mycobacteria, Nocardia* and molds from different sample origins (e.g., blood, tissue, etc.). Perez *et al*, in their study to include Gram-negative rod bacteremia with ESBL or MDR, found a significant reduction in time to optimal antibiotic therapy (80.9 h v. 23.3 h, $p < 0.001$) and reduced mortality in the intervention group when they adopted MALDI-TOF MS directly from positive blood culture and simultaneously set up for rapid antimicrobial susceptibility testing [44]. Use of MALDI-TOF MS was a significant predictor of survival as well (OR 0.3, 95% confidence interval 0.12–0.79).

Direct Pathogen Identification Using Nucleic Acid Amplification

One example of singleplex PCR as an ASP tool is to adopt nasal MRSA screening to rule out MRSA pneumonia [45]. In a recent meta-analysis by Parente *et al*, nasal MRSA screening showed a high specificity and a negative predictive value (NPV) in ruling out MRSA pneumonia; the NPV was 98.1% for community-acquired MRSA pneumonia and 94.8% for ventilator-associated pneumonia. While current IDSA guidelines for HAP/VAP advocates for empiric MRSA coverage in the presence of a risk factor for MRSA infection [46], many patients can avoid MRSA coverage based on the negative nasal MRSA screening result. Another example is singleplex *C. difficile* PCR. Since *C. difficile* represents the most common cause of infectious diarrhea, *C. difficile* PCR testing should be done prior to ordering the multiplex gastrointestinal panel. One caveat is that the sole use of *C. difficile* PCR is no longer recommended to diagnose *C. difficile* infection due to the extremely high sensitivity of this test and is now to be combined with stool toxin tests [47].

Examples of multiplex PCR include respiratory or meningitis/encephalitis panels from direct respiratory or CSF samples. Interestingly, when using multiplex respiratory virus panels, Semret *et al* found antibiotic management was most significantly associated with radiographic suspicion of pneumonia and less with the RVP results [48]. In other words, other than influenza virus, positivity for viruses was not associated with de-escalation or discontinuation of antibiotics. As highlighted by the authors, when introducing a tool such as a respiratory viral panel, the ability to interpret positive results in the context of the clinical illness and the legitimate concerns of bacterial coinfections need to be addressed.

There are platforms that use nucleic acid amplification for rapid pathogen characterization from positive blood cultures. Examples include Verigene BC

(Luminex, Austin, TX, USA) and FrilmArray BCID (BioMerieux, St. Louis, MO, USA). Some resistant markers are included in the kit and aid in escalation/de-escalation of antibiotics as well.

T2 Candida or T2 Bacteria

Distinguished from other platforms, T2 Candida (T2 Biosystems, Lexington, MA, USA) or T2 Bacteria (T2 Biosystems, Lexington, MA, USA) uses whole blood without the need for culture or nucleic acid extraction [49]. It utilizes PCR amplification from whole blood followed by nanoparticle T2 magnetic resonance detection directly from whole blood allowing detection of candidemia or bacteremia within hours. The rapid turnaround time (i.e., 3–5 h) and high sensitivity- specificity (e.g., 91.1% and 99.4% for T2 Candida) present opportunities for decreased mortality [50]. These tests not only showed enhanced sensitivity as compared to blood cultures, but also offered opportunities for antifungal streamlining based on an excellent specificity. There are clinical data showing decreased time to initiation of antifungals in candidemic patients after adopting the T2 Candida system [51]. Of note, accounting for the imperfect sensitivity of 91.1%, their ASP guideline advocated for empiric antifungal therapy with suspected candidemia in both the pre- and post-T2 candida system [51]. Also, another study by Patch ME *et al* emphasized the importance of paired blood cultures and T2 Candida testing to overcome the imperfect sensitivity of the system. This study showed a decreased time to initiation of antifungal therapy as well as a decreased length of hospital stay by 8 days [52]. ASP should help develop clinical decision support in adopting and interpreting these test results in the appropriate clinical context.

Intravenous to Oral Antibiotics

IV-to-oral conversion is a strategy strongly recommended by the 2016 IDSA guideline [18], and can be safely applied to immunocompromised hosts unless patients cannot tolerate oral therapy or have issues with oral absorption (e.g., significant gastrointestinal (GI) graft-versus-host disease (GVHD), severe mucositis, GI obstruction from tumor). Examples of highly bioavailable antimicrobials that can be switched from IV-to-oral in 1:1 ratio include fluoroquinolones, clindamycin, linezolid, sulfamethoxazole-trimethoprim, metronidazole, and azoles (voriconazole, isavuconazole, fluconazole). When an oral equivalent is not available, infectious diseases consultation can assess and recommend an oral regimen to avoid IV catheters and outpatient parenteral therapy [18].

Antimicrobial Pharmacokinetic and Pharmacodynamics (PK/ PD)

Dose optimization through adequate understanding of antimicrobial PK/PD parameters is another vital stewardship tool. Especially when dealing with MDR organisms leaving limited viable options, maximizing the PK/PD driven dosing for a chosen agent becomes essential. For example, ceftolozane-tazobactam is a broad spectrum anti-pseudomonal cephalosporin whose efficacy is driven by free drug concentration remaining above the minimum inhibitory concentration for a defined proportion of the dosing interval (%*f*T > MIC). It currently has FDA dosing recommendations of 1.5 g q8h given over 1 h for intra-abdominal or urinary tract infection while the clinical trial for hospital-acquired bacterial pneumonia uses a 3 g q8h dosing regimen. In a retrospective review of 35 patients treated with ceftolozane-tazobactam against carbapenem-resistant *P. aeruginosa*, all three patients with a ceftolozane-tazobactam MIC ≥8 mg/L failed therapy and doses used varied between 1.5 and 3 g q8h [53]. On the other hand, when PK/PD was analyzed from a 14 year-old child with cystic fibrosis, %*f*T > MIC for ceftolozane-tazobactam at a MIC of 8 mg/L were 56.3% for 1.5 g q8h (over 1 h) and 93.8% for 3 g q8h (over 3 h), respectively [54]. Furthermore, the human simulated dose of ceftolozane-tazobactam 3 g q8h given over 3 h when combined with amikacin or colistin has shown a synergistic killing effect for *P. aeruginosa* isolates with MICs ≥4 mg/L in an *in vitro* pharmacodynamics model [55]. These findings highlight not only the opportunities for success by maximizing the dose evidenced by PK/PD parameters but also the importance of understanding pharmacodynamic synergy effects between antimicrobials. In the immunocompromised hosts, maximizing PK/PD driven efficacy becomes even more important given the reduced host immune function and the risk of developing resistance due to increased exposure to antimicrobials in this population.

Antimicrobial Allergy Assessment

In the 2016 IDSA and SHEA guidelines for antibiotic stewardship, it is recommended that ASPs promote allergy assessment and penicillin skin testing (PST) when appropriate [18]. Approximately 10% of patients carry a penicillin allergy label [56], and it often impedes the appropriate selection of antibiotics. Antibiotic selection in these patients is associated with inferior microbiological and clinical outcomes (e.g., the less effective use of vancomycin in place of the more effective use of a semisynthetic penicillin for invasive MSSA infection) [57], adverse events (e.g., replacement of penicillin with clindamycin leading to increased *C. difficile* infection), use of more expensive and broader spectrum antibiotics [58], and increased readmissions [59] as well as excess mortality [60]. There are many ASP

Table 1 Antimicrobial stewardship modalities in the immunocompromised hosts

Modalities	Key points
Formulary management	Streamline hospital formulary based on drug interactions, cost, spectrum of coverage, drug supply and usage, dosing, efficacy and safety
Prophylaxis during neutropenia	Provide institutional guidelines for antimicrobial prophylaxis along with international guidelines depending on local patterns of resistance, prior infectious histories, and infectious risks of certain chemotherapy/biologics and cancer diagnosis/ stage
Choice of agents for neutropenic fever	Provide guidelines for the empiric use of anti-MRSA, anti-VRE coverage as well as anti-pseudomonal coverage upon NPF
	Monitor adherence to the guidelines
	Prescreen patients at highest risk for MDR organisms to tailor individualized empiric antibiotics
Early de-escalation after NPF	There are newer data suggesting the feasibility of early de-escalation of anti-pseudomonal beta lactams after NPF
	Until international guidelines are updated reflecting these data, early de-escalation may be attempted in selected patients in consultation with infectious diseases specialists and hematologist/oncologist
Clinical pathway	Interdisciplinary development of local clinical practice guideline is a proven tool to improve implementation
Antimicrobial restriction	Have certain antimicrobials be restricted
	Assess the duration of restricted antimicrobials
Prospective audit and feedback	Allocate necessary resources to identify and prioritize the issues
	Provide persistent effort by dedicated and well-trained personnel
Antifungal stewardship	Antifungal stewardship needs to be in place
	Utilize CT screening, or biomarkers such as Aspergillus galactomannan test for early detection of invasive fungal infection
Use of biomarkers	Kinetics/dynamics of biomarkers can be altered in the immunocompromised hosts, thus requiring careful interpretation when adopted in this population
Rapid diagnostics	Continually evaluate evolving technologies to enhance organism detection, susceptibility and resistance reporting
	Provide clinical decision support involving rapid diagnostics
Intravenous to oral conversion	It can be safely implemented in the immunocompromised hosts unless there are issues with oral absorption such as GI GVHD, GI obstruction from tumor, and severe mucositis
Dose optimization using PK/PD	Maximize antimicrobial efficacy by PK/PD driven dosing when dealing with MDR organisms in the setting of immune deficiency
Allergy assessment	Assess antimicrobial allergy history and record in detail
	Utilize penicillin skin testing if available
	Focus on rashes to differentiate antimicrobial-related rash from other etiologies

NPF neutropenic fever, *CISNE* the clinical index of stable febrile neutropenia, *MRSA* Methicillin-resistant *Staphylococcus aureus, VRE* vancomycin-resistant enterococcus, *GI* gastrointestinal, *GVHD* graft-versus-host disease, *PK/PD* pharmacokinetic/dynamic, *MDR* multidrug-resistant

initiatives addressing delabeling of penicillin allergy either combined with PST or not. For example, detailed clinical history by itself has shown to increase delabeling of penicillin allergy [61]. PST driven by Infectious Diseases fellows [62] or pharmacists [63] and resultant delabeling of penicillin allergy have shown significantly increased use of penicillins or cephalosporins in place of broader spectrum, suboptimal or more costly alternative agents. Before concluding a rash was from an antimicrobial, other factors that can cause skin rashes should be considered: namely chemotherapy, GVHD, vasculitis, leukemia cutis, pyoderma gangrenosum, and Sweet's syndrome *et cetera*. In summary, allergy assessment focusing on a detailed characterization of the rash needs to be highlighted in this population along with other basic information such as onset and timing of the reaction, severity, and type of reactions.

Key Points

In the era of antimicrobial resistance, a strong ASP in immunocompromised hosts is of utmost importance for patient safety. There have been many successful practice models embracing ASP strategies in this population (Table 1). There are unique opportunities for ASP in this population including optimal antimicrobial prophylaxis, management of neutropenic fever and early de-escalation after neutropenic fever resolves. Since this population is more vulnerable to opportunistic infections including rare organisms, evolving technologies in rapid diagnostics to enhance sensitivity and the speed of organism detection and susceptibility testing should continually be evaluated and combined with real time ASP interventions when adopted.

References

1. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. Clin Infect Dis. 2007;44:159–77.
2. Winthrop KL, Mariette X, Silva JT, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (soluble immune effector molecules [II]: agents targeting interleukins,immunoglobulins and complement factors). Clin Microbiol Infect. 2018;24:S21–40. https://doi.org/10.1016/j.cmi.2018.02.002.
3. So W, Pandya S, Quilitz R, et al. Infectious risks and complications in adult leukemic patients receiving blinatumomab. Mediterr J Hematol Infect Dis. 2018;10(1):e2018029. https://doi.org/10.4084/MJHID.2018.029.

4. National comprehensive cancer network. Prevention and treatment of cancer-related infections version I. 2018. Accessed online on Apr 2018. https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy.
5. Gafter-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev. 2012;(4):CD004386.
6. Yemm KE, Barreto JN, Mara KC, et al. A comparison of levofloxacin and oral third-generation cephalosporins as antibacterial prophylaxis in acute leukaemia patients during chemotherapy-induced neutropenia. J Antimicrob Chemother. 2018;73:204–11.
7. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol. 2018:JCO2017776211. https://doi.org/10.1200/JCO.2017.77.6211.
8. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with Cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52:e56–93.
9. Tverdek FP, Rolston KV, Chemaly RF. Antimicrobial stewardship in patients with cancer. Pharmacotherapy. 2012;32:722.
10. Giannella M, Bartoletti M, Morelli MC, et al. Risk factors for infection with carbapenem-resistant klebsiella pneumoniae after liver transplantation: the importance of pre and posttransplant colonization. Am J Transplant. 2015;15:1708–15.
11. Lisboa LF, Miranda BG, Vieira MB, et al. Empiric use of linezolid in febrile hematology and hematopoietic stem cell transplantation patients colonized with vancomycin-resistant Enterococcus spp. Int J Infect Dis. 2015;33:171–6.
12. Cho SY, Lee DG, Sm C, et al. Impact of vancomycin resistance on mortality in neutropenic patients with enterococcal bloodstream infection: a retrospective study. BMC Infect Dis. 2013;13:504.
13. Le Clech L, Talarmin JP, Couturier MA, et al. Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study. Infect Dis (Lond). 2018;50(7):539–49. https://doi.org/10.1080/23744235.
14. Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European conference on infections in leukemia. Haematologica. 2013;98:1826–35.
15. Aguilar-Guisado M, Espigado I, Martin-Pena A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (how long study): an open-label, randomized, controlled phase 4 trial. Lancet Haematol. 2017;4:e573–83.
16. Snyder M, Pasikhova Y, Baluch A. Early antimicrobial de-escalation and stewardship in adult hematopoietic stem cell transplantation recipients: retrospective review. Open Forum Infect Dis. 2017;11(4):ofx226. https://doi.org/10.1093/ofid/ofx226.
17. Gustinetti G, Raiola AM, Varaldo R et al. De-escalation and discontinuation of empirical antibiotic treatment in a cohort of allogeneic hematopoietic stem cell transplantation recipients during the pre-engraftment period. Biol Blood Marrow Transplant 2018; pii:S1083-8791(18)30131-9. doi: https://doi.org/10.1016/j.bbmt
18. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. Clin Infect Dis. 2016;62:e51.
19. Seo SK, Lo K, Aboo L. Current state of antimicrobial stewardship at solid organ and hematopoietic cell transplant centers in the US. Infect Control Hosp Epidemiol. 2016;37:1195.
20. Metan G, Kaynar L, Yozgat N, et al. A change for the antibacterial treatment policy to decrease carbapenem consumption at a haematopoietic stem cell transplantation centre. Infez Med. 2017;25:33.

21. Nivoix Y, Launoy A, Moulin JC, et al. Adherence to recommendations for the use of antifungal agents in a tertiary care hospital. J Antimicrob Chemother. 2012;67:2506–13.
22. Sutepvarnon A, Apisarnthanarak A, Camins B, et al. Inappropriate use of antifungal medications in a tertiary care center in Thailand: a prospective study. Infect Control Hosp Epidemiol. 2008;29:370–3.
23. Singh N, Wagener MM, Cacciarelli TV, et al. Antifungal management practices in liver transplant recipients. Am J Transplant. 2008;8:426–31.
24. Munoz P, Rojas L, Cervera C, et al. Poor compliance with antifungal drug use guideline by transplant physicians: a framework for educational guidelines and an international consensus on patient safety. Clin Transpl. 2012;26:87–96.
25. Lelievre L, Groh M, Angebault C, et al. Azole resistant Aspergillus fumigates: an emerging problem. Med Mal Infect. 2013;43:139–45.
26. Vallabhaneni S, Cleveland AA, Farley MM, et al. Epidemiology and risk factors for echinocandin nonsusceptible Candida glabrata bloodstream infections: data from a large multisite population-based Candidemia Surveillance Program, 2008-2014. Open Forum Infect Dis. 2015;2:ofv163.
27. Clancy CJ, Nguyen MH. Emergence of Candida auris: an international call to arms. Clin Infect Dis. 2017;64:141–3.
28. Legouge C, Caillot D, Chretien ML, et al. The reversed halo sign: pathognomonic pattern of pulmonary mucormycosis in leukemic patients with neutropenia? Clin Infect Dis. 2014;58:672–8.
29. Millon L, Herbrecht R, Grenouillet F, et al. Early diagnosis and monitoring of mucormycosis by detection of circulating DNA in serum: retrospective analysis of 44 cases collected through the French Surveillance Network of Invasive Fungal Infections (RESSIF). Clin Microbiol Infect. 2016 Sep;22(9):810.e1–8. https://doi.org/10.1016/j.cmi.2015.12.006.
30. Maertens JA, Blennow O, Duarte RF, et al. The current management landscape: aspergillosis. J Antimicrob Chemother. 2016;71(Suppl 2):ii23–9.
31. Brodska H, Drabek T, Malickova K, et al. Marked increase of procalcitonin after the administration of antithymocyte globulin in patients before hematopoietic stem cell transplantation does not indicate sepsis: a prospective study. Crit Care. 2009;13:R37.
32. Sakr Y, Sponholz C, Tuche F, et al. The role of procalcitonin in febrile neutropenic patients: review of the literature. Infection. 2008;36:396–407.
33. Sanchez-Yepes M, Aznar-Oroval E, Lorente-Alegre P, et al. Use of procalcitonin and C-reactive protein in infection markers in febrile neutropenic patients undergoing haematopoietic stem cell transplant. Enferm Infecc Microbiol Clin. 2014;32:418–23.
34. Lima SS, Nobre V, de Castro Romanelli RM et al. Procalcitonin-guided protocol is not useful to manage antibiotic therapy in febrile neutropenia: a randomized controlled trial. Ann Hematol. 2016;95(7):1169–76. https://doi.org/10.1007/s00277-016-2639-5.
35. Stover KR, Kenney RM, King ST, et al. Evaluation of the use of novel biomarkers to augment antimicrobial stewardship program activities. Pharmacotherapy. 2018;38:271–83.
36. Robilotti E, Holubar M, Seo SK, et al. Feasibility and applicability of antimicrobial stewardship in immunocompromised patients. Curr Opin Infect Dis. 2017;30:346–53.
37. Minejima E, Wong-Beringer A. Implementation of rapid diagnostics with antimicrobial stewardship. Expert Rev Anti-Infect Ther. 2016;14:1065–75.
38. Messacar K, Paker SK, Todd JK, et al. Implementation of rapid molecular infectious disease diagnostics: the role of diagnostic and antimicrobial stewardship. J Clin Microbiol. 2017;55:715–23.
39. Novais A, Brilhante M, Pres J, et al. Evaluation of the recently launched rapid carb blue kit for detection of carbapenemase-producing Gram-negative bacteria. J Clin Microbiol. 2015;53:3105–7.
40. Poirel L, Nordmann P. Rapidec carba NP test for rapid detection of carbapenemase producers. J Clin Microbiol. 2015;53:3003–8.

41. Garcia-Fernandez S, Morosini MI, Gijon D, et al. Detection of carbapenemase production in a collection of Enterobacteriaceae with characterized resistance mechanisms from clinical and environmental origins by use of both Carba NP and Blue-Carba tests. J Clin Microbiol. 2016;54:464–6.
42. Lutgring JD, Bittencourt C, TeKippe EM, et al. Evaluation of the accelerate pheno system: result from two academic medical centers. J Clin Microbiol. 2018;56:e01672–17.
43. Cassagne C, Normand AC, L'Ollivier C, et al. Performance of MALDI-TOF MS platforms for fungal identification. Mycoses. 2016;59:678–90.
44. Perez KK, Olsen RJ, Musick WL, et al. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. J Infect. 2014;69:216–25.
45. Parente DM, Cunha CB, Mylonakis E, et al. The clinical utility of methicillin resistant Staphylococcus aureus (MRSA) nasal screening to rule out MRSA pneumonia: a diagnostic meta-analysis with antimicrobial stewardship implications. Clin Infect Dis. 2018;67:1–7. https://doi.org/10.1093/cid/ciy024.
46. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63:e61–111.
47. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;xx(00):1–48.
48. Semret M, Schiller I, Jardin BA, et al. Multiplex respiratory virus testing for antimicrobial stewardship: a prospective assessment of antimicrobial use and clinical outcomes among hospitalized adults. J Infect Dis. 2017;216:936–44.
49. Pfaller MA, Wolk DM, Lowery TJ. T2MR and T2Candida: novel technology for the rapid diagnosis of candidemia and invasive candidiasis. Future Micoribiol. 2016;11:103–17.
50. Mylonakis E, Clancy CJ, Ostrosky-Zeichner L, et al. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clin Infect Dis. 2015;60:892–9.
51. Wilson JM, Alangaden G, Tibbetts RJ, et al. T2 magnetic resonance assay improves timely management of candidemia. J Antimicrob Stewardship. 2017;1:12–8.
52. Patch ME, Weisz E, Cubillos A, et al. Impact of rapid, culture-independent diagnosis of candidaemia and invasive candidiasis in a community health system. J Antimicrob Chemother. 2018;73:iv27–30.
53. Munita JM, Aitken SL, Miller WR, et al. Multicenter evaluation of ceftolozane/tazobactam for serious infections caused by carbapenem-resistant Pseudomonas aeruginosa. Clin Infect Dis. 2017;65:158–61.
54. Ang JY, Abdel-Haq N, Zhu F, et al. Multidrug-resistant Pseudomonas aeruginosa infection in a child with cystic fibrosis. Antimicrob Agents Chemother. 2016;60:5627–30.
55. Rico-Caballero V, Abuhussain SA, Kuti JL et al. Efficacy of human-simulated exposures of ceftolozane/tazobactam alone and in combination with amikacin or colistin against multidrug-resistant Pseudomonas aeruginosa in an in vitro pharmacodynamics model. Antimicrob Agents Chemother 2018. pii: AAC.02384-17. doi: https://doi.org/10.1128/AAC.02384-17.
56. Trubiano JA, Pai Mangalore R, Baey YW, et al. Old but not forgotten: antibiotic allergies in general medicine (the AGM study). Med J Aust. 2016;204:273.
57. Gonzalez C, Rubio M, Romero-Vivas J, et al. Bacteremic pneumonia due to Staphylococcus aureus: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. Clin Infect Dis. 1999;29:1171.
58. Li M, Krishna MT, Razag S, et al. A real-time prospective evaluation of clinical pharmaco-economic impact of diagnostic label of 'penicillin allergy' in a UK teaching hospital. J Clin Pathol. 2014;67:1088–92.

59. Blumenthal KG, Shenov ES, Varughese CA, et al. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. Ann Allergy Asthma Immunol. 2015;115:294–300.
60. Charneski L, Deshpande G, Smith SW, et al. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. Pharmacotherapy. 2011;31:742–7.
61. Sigona NS, Steele JM, Miller CD. Impact of a pharmacist-driven beta-lactam allergy interview on inpatient antimicrobial therapy: a pilot project. J Am pharm Assoc (2003). 2016;56:665.
62. Heil EL, Bork JT, Schmalzle SA, et al. Implementation of an infectious disease fellow-managed penicillin allergy skin testing service. Open Forum Infect Dis. 2016;3:ofw155.
63. Chen JR, Tarver SA, Alvarez KS, et al. A proactive approach to penicillin allergy testing in hospitalized patients. J Allergy Clin Immunol Pract. 2017;5:686–93.