Opportunities for Antimicrobial Stewardship Interventions Among Solid Organ Transplant Recipients

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KEYWORDS

- Antimicrobial stewardship • Organ transplant • Diagnostic stewardship
- Antibiotic allergy

KEY POINTS

- Antimicrobial stewardship is needed to address rising rates of antimicrobial resistance, reduce antimicrobial-associated adverse events such as *Clostridioides difficile* infection, and optimize antimicrobial use in solid organ transplantation recipients.
- Over the past decade, diverse and rapidly evolving antimicrobial stewardship interventions have arisen in this field, including those at the patient level and health system level.
- Growing evidence supports delabeling antibiotic allergies in transplant candidates and recipients.
- Treatment of asymptomatic bacteriuria does not prevent progression to urinary tract infection and/or pyelonephritis in kidney recipients who are more than 1-2 months post-transplant.

INTRODUCTION

Antimicrobial stewardship is valuable to transplant programs to reduce the threat of antimicrobial resistance, improve patient outcomes, and attenuate risks of drug toxicities.[1,2] Antimicrobial stewardship interventions are designed to measure and improve appropriate use of antimicrobial agents by promoting the optimal antimicrobial drug regimen including dose, duration of therapy, and route of administration.[3,4] The importance of antimicrobial stewardship was nationally recognized following

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the Centers for Diseases Control and Prevention (CDC)'s 2013 report detailing antibiotic resistance threats, which was since updated in 2019.[5,6] In the years that followed, the US health care facilities were required to implement antimicrobial stewardship programs (ASP), but they are not mandated specifically for transplant centers or programs.[7–9]

The need for transplant-specific antimicrobial stewardship is well recognized, both in United States and internationally.[1,10–24] Many emphasize transplant recipients are among those who would benefit most from ASP. Although transplantation has advanced significantly, complex surgeries, frequent antibiotic exposure, and immunosuppressive regimens place solid organ transplant recipients (SOTr) at disproportionately higher risk of infectious complications and antimicrobial resistance.[6] SOTr are at higher risk for colonization with and infection from multidrug-resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci*, extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*, multidrug-resistant *Pseudomonas aeruginosa* and carbapenemase-producing *Enterobacterales* (CRE).[6,25] SOTr are also subject to increased risk of drug toxicities due to polypharmacy and drug–drug interactions and often require special attention to antimicrobial selection and dosing in the setting of renal or hepatic dysfunction.[2] Utilization of costly prophylactic and therapeutic antimicrobials by transplant patients accounts for the top tier of hospital antimicrobial expenditures.[26] Other factors, such as physician's perceptions of patient complexity, anxiety regarding severity of illness, and variation in host risk factors, such as level of immunosuppression, recency of surgery, and potential for drug–drug interactions, present challenges in the implementation of ASP interventions.[1,25] Limited data inform ASP initiatives in the transplant population, but it is a field ripe with opportunities. There have been several calls to action published over the past decade which highlight the need for multidisciplinary approaches, collaboration with experts in transplantation, the use of early and appropriate diagnostics to guide therapy, and optimized duration.[10–13,17,27–29] We present current practices in ASP and discuss their applicability for use in SOT. We review (1) the metrics that ASP interventions target, (2) opportunities for diagnostic stewardship in transplant, and (3) syndrome- and systems-based targets for ASP interventions.

DEVELOPMENT OF ANTIMICROBIAL STEWARDSHIP PROGRAMS METRICS

Design of Interventions

The foundation for ASP interventions begins by establishing working relationships with transplant providers including medical transplant physicians, surgeons, advanced practice providers, pharmacists, and nursing staff. Such relationships build trust and ensure a mutual goal of improving patient care.[13] Multidisciplinary ASP interventions are supported by the Infectious Diseases Society of America[4,13] Therefore, collaboration with transplant infectious disease providers in ASP efforts is essential for its success as they are well positioned to obtain buy-in from multidisciplinary members of the transplant teams. In addition, it may be beneficial to perform an assessment of transplant providers' knowledge, attitudes, and practices surrounding antibiotic use to gauge what is needed for successful behavior change. This analysis could be formal, using a survey to understand prescribing practices,[30,31] or informal, through open discussion with transplant providers. There are several existing frameworks available to understand what is needed to shape the desired behavior change and may be useful tools when designing interventions.[32–35] One example is *The Behavior Change Wheel*, which offers a step-by-step guide to developing

interventions through the lens of behavior change techniques.[35] Use of these strategies may help ASPs avoid incorrect assumptions about interventions.

Metrics

As ASP initiatives are a means of quality improvement, their development and implementation should use standardized and valid measures. The use of standardized metrics allows for streamlined development of interventions and provides a system to track progress during implementation. Measurements of quality improvement initiatives are typically grouped into outcome measures, process measures, and balancing measures.[1] Outcome measures usually relate to the type of intervention, such as cost analyses, mortality, or other adverse outcomes, but can also be specific to infections, like resistance rates or clearance of an infection. Process measures are used to assess whether an intervention has the desired effect and should be in line with outcome measures. These types of metrics may be more feasible than outcome measures as they can be less labor-intensive to collect. The most common process measures in ASP initiatives are antibiotic use rates, particularly for the use of agents such as intravenous vancomycin or high-risk antimicrobials, and cost analyses. Another process measure to consider is the assessment of guideline-concordant antibiotic prescribing. Balancing measures are those that seek to ensure unintended negative consequences do not occur with implementation of a new intervention. Balancing measures sometimes overlap with outcome measures, for instance, when evaluating mortality, readmission rates, or surgical site infections. Additional examples are provided in **Table 1**.

DIAGNOSTIC STEWARDSHIP OPPORTUNITIES

Diagnostic stewardship is the process of modifying the process of ordering, performing, and reporting diagnostic tests to improve patient care.[36] When used properly, diagnostic stewardship can lead to a reduction in inappropriate antimicrobial use and associated costs. Diagnostic stewardship often requires collaboration with the clinical laboratory and other clinicians to be successful. There are many opportunities for interventions across the spectrum of patient care, which include characterizing when a test is ordered, when a laboratory processes a specimen, or when results are reported (**Table 2**).

Many rapid diagnostic tools are available (**Table 3**), but optimal use in SOTr remains relatively unstudied.[37] Test performance, result interpretation, and costs associated with each test warrant collaboration with ASP with implementation. ASP can develop institutional guidance, inform diagnostic restrictions, and provide audit and feedback with associated antimicrobials. Examples of diagnostic stewardship for diarrheal illnesses and pneumonia are outlined in the syndromic target sections below.

Multiplex blood culture panels have been widely adopted in the past decade with numerous commercial options available. These panels are particularly helpful in the transplant population for their ability to detect resistance genes. In one study that included transplant recipients, a multiplex blood culture panel showed decreased time to appropriate antibiotic therapy, especially in the setting of high rates of resistant gram-negative organisms.[38] Use of multiplex blood culture panels should be employed in conjunction with ASP to aid in interpretation, promote early de-escalation of unnecessary agents, and improve time to effective therapy, length of stay, and mortality.[39,40] Although there are developments in the realm of metagenomic sequencing and broad-range polymerase chain reaction testing, ASP may choose to

Table 1
Measurements of quality improvement initiatives

Metric	Definition	Examples
Outcome measures	Outcome that is specific to the type of intervention	Primary outcomes[1] • Mortality • Length of stay • Appropriate use of antibiotics[119] Adverse events • Toxicity • Graft injury • Drug–drug interactions Infection specific[120–122] • Microbiologic cure • Resistance patterns • Antibiograms Infection prevention • *Clostridioides difficile* rates • Multidrug-resistant organism rates
Process measures	Assess whether intervention has intended effect and is congruent with outcome measures	Antibiotic use • Databases such as NHSN, Vizient, HEDIS[123] • Antibiotic use to Antimicrobial Resistance (AU/AR) ratio[124] Cost analysis
Balancing measures	Outcome to assess for unintended negative impacts • May overlap with outcome measures	• Length of stay • Readmission rates • Mortality • Recurrent or relapsed infection • Patient satisfaction • Surgical site infections (TransQIP)[125,126] • Desirability of outcome ranking[127,128]

restrict these due to the risk of false positive results and unclear utility in transplant recipients.

SYNDROMIC TARGETS FOR ANTIMICROBIAL STEWARDSHIP

Diarrheal Illnesses in Transplant

Antimicrobial stewardship opportunities for diarrheal illness in transplant recipients are largely diagnostic stewardship interventions. Diarrhea is a common complaint among transplant recipients and can cause significant morbidity in this population. The use of multiplex polymerase chain reaction (PCR) panels for the evaluation of diarrhea in transplant recipients increases the probability of identifying an infectious cause of diarrhea compared to ordering individual tests. Among liver transplant recipients, the use of multiplex PCR panels for diarrhea led to a change in antimicrobial therapy, reduction in length of stay, and a trend toward lower rates of colonoscopy and readmission within 30 days.[41] However, these panels offer the most benefit when used early in a hospitalization and may lead to false positive results due to high sensitivity of PCR. Use of diagnostic selection criteria such as reserved for those patients with liquid stool or only within 48 to 72 hours of admission to the hospital may mitigate some of the downsides of using multiplex PCR panels for diarrhea.[42]

Table 2
Diagnostic stewardship opportunities

Diagnostic Stewardship Opportunities	Examples
When a test is ordered	Order sets • Pneumonia bundle with recommended empiric antibiotic choices Clinical decision support tools • Embedded treatment algorithms for common diagnoses Electronic nudges • Timed reminders to reassess need for antimicrobial agent Requirements for ordering a test • Confirmation of > 3 liquid bowel movements for *C difficile* testing
When a specimen is processed	Use of specimen acceptance criteria • Laboratory rejection of formed stool for *C difficile* testing • Laboratory rejection of culture swabs for acid-fast bacilli cultures Reflex testing • Urinalysis with defined quantity of pyuria reflexes to urine culture • Positive hepatitis C antibody reflexes to quantitative PCR
When results are reported	Electronic nudges • Alert if receipt of laxative within 24 hours of *C difficile* testing Framing of results • Masking of antimicrobial susceptibility results to limit use of agents Cascading results • Stepwise unmasking of antimicrobial susceptibility results based on resistance pattern

Transplant recipients are at high risk for *Clostridioides difficile* infections (CDI), largely due to the collection of epidemiologic risk factors such as the need for empiric and prophylactic antibiotics, invasive surgery, intensive care, and immunosuppression.[43] Transplant recipients with CDI have worse outcomes in terms of 30-day readmission and mortality, underscoring the importance of antimicrobial stewardship to prevent CDI.[42,44] SOTr have higher rates of both colonization and disease due to *C. difficile* than the general population, often leading to overtreatment.[45] ASP can implement diagnostic criteria and multi-step laboratory testing for confirmation of toxins in stool. Diagnostic criteria may include documentation of at least three unformed stools, absence of a laxative receipt, and laboratory rejection of formed stool specimens to reduce testing on patients who have transient diarrhea.[46,47] One approach is to use a clinical support tool in the electronic medical record which requires the provider to answer a series of questions to order *C. difficile* testing. Kueht and colleagues implemented this strategy among SOTr and showed a significant decrease of 47% in *C. difficile* testing and a significant reduction in days of therapy (522 days of therapy per 1000 days compared to 300 days of therapy per 1000 patient days). This strategy did not alter the rate of negative tests.[48]

Antimicrobial stewardship teams may be tasked with developing local guidance or performing audit and feedback for CDI treatment of prophylaxis for high-risk patient

Table 3
Commercially available rapid diagnostic tools

Panel	Organism(s)
Whole blood	
T2Biosystems	Bacteria and *Candida* panels
Growth from blood culture	
Accelerate Diagnostics: PhenoTest BC Kit	Gram-positive bacteria, gram-negative bacteria, and *Candida* panels
BioFire: FilmArray	Gram-positive bacteria, gram-negative bacteria, and *Candida* panels
Cepheid: Xpert	*Staphylococcus aureus*
GenMark Diagnostics: ePlex BCID	Gram-positive bacteria, gram-negative bacteria, and fungal panels
Luminex: Verigene	Gram-positive bacteria, gram-negative bacteria, and *Candida* panels
OpGen: AdvanDx	*Staphylococcus aureus* and coagulase-negative *Staphylococci* panel, gram-negative panel, and *Candida*
Respiratory specimens	
ARIES	Influenza A/B and RSV panel; *Bordetella parapertussis* and *pertussis*
BioFire: FilmArray	Upper and lower respiratory pathogens: viruses, bacteria
Cepheid: Xpert	SARS-CoV-2, Influenza A/B, and RSV panel; *Mycobacterium tuberculosis* and rifampin resistance
GenMark Diagnostics: Respiratory Patho	Upper and lower respiratory pathogens: viruses, bacteria
Luminex: Verigene and NxTAG	Viruses and *Bordetella* species or *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*
OpGen: Unyvero System	Lower respiratory tract bacterial pathogens and *Pneumocystis jirovecii*
Stool	
ARIES	*Clostridioides difficile* and Norovirus
BioFire: FilmArray	Bacteria, viruses, and parasites
Cepheid: Xpert	*Clostridioides difficile* and Norovirus
Luminex: Verigene, xTAG, NxTAG	Bacteria, viruses, and parasites

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populations such as SOTr due to their high burden of *C difficile* disease. However, more data are necessary to provide such guidance in SOTr. Although Infectious Disease Society of America (IDSA) guidelines recommend fidaxomicin as the preferred treatment of CDI, there are insufficient data comparing clinical outcomes from fidaxomicin and oral vancomycin therapy in SOTr specifically.[49,50] Therapies to prevent primary or recurrent CDI in SOTr is another area in need of further study. A meta-analysis of oral vancomycin prophylaxis showed a strong protective effect for primary and

secondary *C. difficile* infections in over 900 patients, which included SOTr.[51] However, only 1 of 11 studies were randomized controlled trial (RCT), and dosing and duration strategy were variable. High-quality studies are needed on SOTr to support oral vancomycin prophylaxis. Similarly, the addition of bezlotoxumab to standard of care to prevent recurrent CDI in transplant recipients offers promise but larger studies are needed.[52]

Asymptomatic Bacteriuria in Renal Transplant

Screening and treating asymptomatic bacteriuria (ASB) in kidney transplant recipients is a "low-hanging fruit" for antimicrobial stewards in transplantation. The 2019 Infectious Disease Society of America's Clinical Practice Guidelines of ASB and the 2019 American Society of Transplantation Infectious Disease Community of Practice Guidelines for Urinary Tract Infection in Solid Organ Transplantation recommend against the treatment of ASB after 2 months post-kidney transplant because the risk of inducing drug resistance outweighs the benefit of treating ASB.[53,54] Some challenged these recommendations due to few studies with high-quality study designs.[55]

Gradually, more data emerged. A summary of supporting data among comparative trials is summarized in **Table 4**. Three RCTs demonstrated that ASB treatment does not prevent progression to urinary tract infection (UTI) and/or acute pyelonephritis.[56–58] Insufficient data exist within 2 months of transplant. Meanwhile, studies consistently reflect that ASB treatment is followed by the development of drug-resistant organisms.[56,57,59–61]

CMV Management Opportunities

Post-transplant cytomegalovirus (CMV) infection is common and represents an opportunity for ASP. CMV management can align with stewardship principles of the right drug (valganciclovir vs alternative antivirals for resistant, refractory CMV), dose (when CMV therapeutics require renal dose adjustment), duration (often based on serial CMV serum monitoring using highly sensitive assays), and de-escalation (back to prophylaxis or pre-emptive monitoring for example).

Antimicrobial stewardship-minded transplant providers should approach CMV management with specific targets. Antivirals directed at CMV are subject to overuse and misuse, which can lead to toxicities, CMV resistance, and poor patient outcomes including graft rejection and loss.[62,63] CMV-related stewardship activities can target not only these adverse events but also decrease the incidence of CMV disease, unnecessary testing, duration of therapy, hospital admission, lengths of stays, and associated costs.[62,64] With the availability of maribavir as an oral therapy for resistant and refractory CMV, a future ASP goal may be to limit the development of maribavir-resistant CMV and decrease foscarnet duration and its associated toxicities, hospital admissions, and costs.

Establishing local CMV management guidelines is the first step for transplant-specific ASP, which should be organ-specific and based on donor and recipient CMV risk profiles. The American Society of Transplantation guidance on prevention and management of CMV in solid transplant offers a primer for transplant clinicians,[65] and many transplant centers have adapted these locally. In a survey regarding stewardship strategies in the US transplant centers, 82% and 70% developed center-specific guidelines for CMV prophylaxis and treatment, respectively.[10] Local guidance may depend on the availability of highly sensitive CMV serum assays and could establish assay specific virologic thresholds for treatment of specific populations (eg, R+). Some centers may need to consider and address the appropriate use of CMV-specific T-cell immunity panels.

Table 4
Studies of ASB treatment versus no treatment in renal transplant recipients

Study	Timing of ASB	Clinical Outcomes
Coussement et al,[56] 2021 Multicenter RCT, n = 199	≥2 months post-transplant	No difference in UTI in subsequent 12 months. Antibiotic use 5x higher in treated group. Resistant organisms emerged in treated group.
Sabé et al,[57] 2021 Multicenter RCT, n = 87	≥1 month post-transplant	No difference in acute graft pyelonephritis during 12-month follow-up (primary outcome). No difference in graft rejection or dysfunction, hospitalization, or mortality. Antibiotic resistance developed more commonly in treated group than non-treated group.
Antonio et al,[58] 2022 Single center RCT, n = 80	≤2 months post-transplant	No difference in UTI and pyelonephritis during follow-up (up to 2 months post-transplant). Trend toward more recurrent UTIs in treated group. More hospitalizations in the treated group but no difference in UTI-related hospitalizations. High baseline ESBL *E. coli/ Klebsiella sp* but insufficient data regarding the emergence of resistance.
Origüen et al,[129] 2016 Single center RCT, n = 112	≥2 months post-transplant	No difference in acute graft pyelonephritis during 2-year follow-up (primary outcome). No differences in UTI incidence, graft function or rejection, all-cause mortality, *C diff* infection.
Moradi et al,[130] 2005 Prospective case control, n = 88	>1 year post-transplant	Treatment of ASB did not decrease the rate of UTIs during 1-year follow-up period.
Green et al,[131] 2013 Retrospective cohort; ages ≥16 y, n = 112	1–12 months post-transplant	No differences in hospitalization for UTI (primary outcome). More UTIs following treatment of ASB vs no treatment. More antibiotic resistance developed in treated group.

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Table 4
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Study	Timing of ASB	Clinical Outcomes
El Amari et al,[60] 2011 Retrospective, n = 77	>1 month post-transplant	No differences in progression to UTI and graft function in treated vs untreated ASB patients. Following treatment of *E coli* and *E faecalis* ASB, 78% developed resistant organisms.
Bohn et al,[132] 2019 Retrospective observational, n = 64 with ASB	<12 months post-transplant	Treatment of AB was not associated with progression to UTI.
Bonnéric et al,[133] 2019 Retrospective pediatric, n = 37	2–24 months post-transplant	Acute pyelonephritis and UTIs occurred more commonly in the treated ASB group.
Kotagiri et al,[134] 2017 Retrospective, n = 75 with ASB	<12 months post-transplant	Treatment of ASB reduced the risk of UTI compared to untreated ASB.
Arencibia et al,[61] 2016 Prospective, n = 20 with ASB	Anytime post-transplant	Spontaneous clearance in 70% of untreated ASB. Bacterial clearance in 49% of treated ASB. Emergence of resistance in 48% of treated ASB patients.

Abbreviations: ASB, asymptomatic bacteriuria; ESBL, extended spectrum beta-lactamase producing; RCT, randomized controlled trial; UTI, urinary tract infection.
Studies above were conducted in adult kidney transplant recipients unless otherwise specified.

ASP strategies can be applied to CMV management in SOTr. Prospective audit and feedback and/or pre-authorization may be applied to the use of foscarnet, maribavir, and letermovir. Alternatively, transplant centers may restrict these agents to infectious disease consultation or approval.[62] Institutional ASP should be engaged with the addition of newer antiviral therapeutics as they necessitate formulary review and updates in local management. Some transplant centers have had success with pharmacist-driven antimicrobial stewardship interventions that utilize a combination of stewardship strategies, including local algorithms for serum CMV monitoring and treatment, standardized dosing algorithm for renal dose adjustment and monitoring, and prospective monitoring and feedback to name a few.[62,64]

Respiratory Infections

Bacterial pneumonia

Opportunities for antimicrobial stewardship interventions exist for health care-associated pneumonia in the early post-transplant period (<30 days) and community acquired pneumonia in the late post-transplant period (>6–12 months post-transplant) to direct diagnostic workup and duration of therapy. The national community acquired and health care-associated pneumonia guidelines excluded immunocompromised patients due to their increased risk for opportunistic infections,[66,67] but they represent a large proportion of pneumonia-associated hospitalizations.[68] Bacterial etiologies and clinical presentation in SOTr vary and empiric antibiotics require consideration of the following: individual's level of immunosuppression, time from transplant, history

of microorganisms, and local antibiograms. In SOTr, pneumonia occurs most commonly early post-transplant (<30 days post-transplant) and then >6 to 12 months post-transplant.[69] In the early post-transplant period, donor-derived and recipient airway colonization are important factors informing therapy in lung transplant recipients, whereas in liver transplant recipients, gram-negative bacterial etiologies predominate.[69] To date, there is no consensus for the appropriate duration of therapy, which remains an important target for antimicrobial stewardship.[1]

Determining the microbiologic etiology of pneumonia is important in SOTr to target therapy.[69] Access to rapid diagnostic platforms, such as the Biofire Filmarray Respiratory Panel or multiplex bacterial PCR panels, may allow for rapid identification for prespecified bacterial ± viral targets and subsequently targeted antimicrobial therapy.[70] Although no studies evaluated SOTr exclusively, early studies that included immunocompromised patients found earlier time-to-detection of a respiratory pathogen[71,72] and decreased duration of inappropriate antibiotic therapy.[71,73] One study examined the clinical impact of Biofire Pneumonia Plus (BPP), which includes viral, bacterial, and some resistance targets, in 60 lung transplant recipients with suspected lower respiratory tract infection who underwent bronchoscopy. The median time to result was 2.3 hours using BPP compared to 23.4 hours for viral detection using immune fluorescence testing and 25.2 hours for conventional cultures. Faster clinical decisions resulting in treatment modifications occurred in the BPP group (2.8 hours) compared to viral and traditional microbiologic methods (28.1 and 32.6 hours, respectively), which were statistically significant. There were six treatment modifications based on traditional lab methods missed by BPP, including three fungal pathogens.

Bronchoscopy delay may lead to increased antibiotic exposure. Azadeh and colleagues[74] compared Filmarray Respiratory Panel (17 viral and 3 bacterial targets) results from simultaneously collected bronchoalveolar lavage and nasopharyngeal specimens in immunocompromised patients, 27% of which were SOTr, and found 89% concordance between the samples, driven largely by shared negative results potentially offering more rapid identification of predominately viral pneumonia and antibiotic de-escalation.

Although rapid diagnostics for lower respiratory tract infections is promising, transplant providers and antimicrobial stewards need to consider diagnostic stewardship, limiting repeat testing within a short period as re-detection of targets is common and can result in overtreatment. In SOTr with a high likelihood of opportunistic infection or more than one pathogen, providers need to consider the presence of organisms not present on diagnostic panels, particularly fungal organisms. However, rapid molecular tests with high negative predictive values for methicillin-resistant *Staphylococcus aureus (*MRSA) and *Pseudomonas aeruginosa* can be helpful in ruling out these organisms, allowing discontinuation of vancomycin or de-escalating from anti-Pseudomonal agents.

Respiratory syncytial virus

In the past decade, antimicrobial stewards targeted the use of ribavirin to treat RSV in SOTr. Ribavirin is utilized to treat RSV upper and lower respiratory tract infections in SOTr based on conflicting evidence and is available in aerosolized, oral, and intravenous forms.[75] Aerosolized ribavirin is challenging to administer and costly, nearly 30,000 dollars per day.[2,75,76] Small observational studies offered efficacy with oral ribavirin including lung transplant recipients,[77–80] including in one comparing aerosolized and oral ribavirin with no significant differences in 6-month outcomes.[77] Therefore, due to both financial and administration constraints, many centers have elected to pursue oral ribavirin only, while others may permit inhaled ribavirin in only

rare instances. Centers may offer local guidance for clinical circumstances for which ribavirin is considered or restrict use to certain transplant providers. Updated experience following the implementation of ribavirin guidance and restrictions, including clinical outcomes in lung transplant recipients with RSV, may add to the literature informing future antimicrobial stewardship interventions surrounding the use of ribavirin.

COVID-19

An evolving antimicrobial stewardship need during the COVID-19 pandemic surrounds antibiotic use in SOTr with COVID-19. Antibiotic overuse in hospitalized COVID-19 patients was common early in the pandemic.[81,82] SOTr were more likely to develop severe COVID-19 requiring hospitalization or leading to mortality,[83] which likely heightened pressure to add empiric antibiotics for secondary bacterial infections. A retrospective review found a higher prevalence of bacterial and fungal co-infections in SOTr with COVID-19, which was associated with prior hospitalization and the use of broad-spectrum antibiotics.[84] When clinicians have a high index of suspicion for secondary infections in SOTr with COVID-19, prompt diagnostic workup should be emphasized to allow targeted and/or de-escalation of antibiotic therapies.

Meanwhile, as antiviral guidance evolved during the pandemic, so too have ASP efforts surrounding COVID-19. The initial stewardship priorities included audit and feedback of therapies for appropriateness, managing and prioritizing limited antiviral supply, and ensuring compliance with Food and Drug Administration (FDA) emergency use authorizations.[85] More recent therapeutic advances offered outpatient treatment options for SOTr with mild–moderate COVID-19, including monoclonal antibodies, 3-day remdesivir infusions, and oral nirmatrelvir-ritonavir and molnupiravir.[86] Therefore, COVID-19-related ASP priorities have shifted over time toward updating therapeutic guidance based on newer COVID-19 variants, ordering and administration of outpatient therapeutics, and limiting toxicities and drug–drug interactions, such as oral nirmatrelvir-ritonavir's boosted effects of calcineurin-inhibitors and mTOR inhibitors.[87]

Invasive Fungal Infections

SOTr are at increased risk for invasive fungal infections (IFIs) and the use of antifungals is common. Invasive *Candida* and *Aspergillus* represent the most common IFIs in SOT.[88] The diagnosis of these infections may be difficult, which contributes to antifungal overuse. Prolonged antifungal therapy and prophylaxis account for 42% to 66% of antifungal overuse.[89] De-escalation from empiric therapy remains one of the most challenging aspects of antifungal stewardship.[90]

Use of fungal antigen tests is often employed. However, the performance of assays such as Aspergillus galactomannan (GM) and β-D-glucan (BDG) have variable sensitivity and specificity in solid organ overuse transplant recipients.[42] In this population, sensitivity of the serum GM for diagnosis of invasive Aspergillosis ranges from 22% to 68% across the different organ types.[91–93] Of particular concern is the low sensitivity of the assay to predict *Aspergillus tracheobronchitis* in lung transplant recipients.[42] Sensitivity and specificity for diagnosis of invasive Aspergillosis increase when GM is obtained on bronchoalveolar lavage specimens and when a higher cutoff of 1.0 is used, specificity improves.[94,95] BDG may also be used for diagnosis of invasive fungal infections (with the exception of *Mucorales* and *Cryptococcus*), but sensitivity and specificity in transplant recipients are much lower ranging from 57% to 80% and <50%, respectively,[96] though it is more useful in the diagnosis of *Pneumocystis jirovecii* pneumonia among SOTr.[97] The use of serum GM and BDG for the diagnosis of

invasive fungal infections should be cautiously employed for compatible syndromes, but discouraged when used outside these parameters as it may lead to overdiagnosis and overtreatment. Other antifungal stewardship opportunities include guideline development, post-prescriptive review, and IV-to-oral antifungal conversion.[2,4,89,90]

SYSTEMS-BASED TARGETS FOR ANTIMICROBIAL STEWARDSHIP

Antibiotic Allergies

Antibiotic allergy labels (AAL) are defined as antibiotic allergies that are a part of the patient's medical record. AAL are common among SOTr and prevalence ranges from 16% to 17% in the literature.[98–100] The most common types of AAL are beta-lactams and sulfamethoxazole-trimethoprim (SMX-TMP). Beta-lactam allergies pose significant challenges to SOTr as they may negatively impact surgical prophylaxis, lead to the use of unnecessary broad-spectrum agents, and increase the use of antibiotics in the immediate post-transplant setting.[100,101] SMX-TMP allergies pose a significant risk with the inability to use first-line prophylaxis for *P jirovecii* and *Nocardia* infections. The use of broader spectrum antibiotics in those with beta-lactam allergies may lead to the development of multidrug-resistant organisms[102–105] while the use of second- or third-line prophylaxis agents in those with SMX-TMP allergy may be more costly.[106]

AAL delabeling is the practice of removing AAL from a patient's chart either by testing or medical reconciliation.[107] Delabeling is associated with increased use of narrow spectrum agents, reduced length of hospital stay[107], and improved prescribing with guideline-preferred regimen[101] making it an ideal target for ASP. Delabeling of AAL has been shown to be safe in the pre-transplant setting for those with AAL to vancomycin, SMX-TMP, beta-lactams, and fluoroquinolones and cost-effective in the setting of SMX-TMP delabeling.[106] AAL delabeling begins with an assessment of the severity of the reaction. Those with suspected non-immune reactions, that is, non-allergic symptoms, or those who have documented tolerance to the drug, may have the AAL removed without testing.

Delabeling of penicillin AAL begins with risk stratification (**Table 5**).[108] For penicillin allergy risk stratification at the point of care, consider the use of PEN-FAST, a clinical decision rule which was validated in a diverse population including SOTr.[109] The American Academy of Allergy, Asthma and Immunology (AAAAI) recommends direct oral amoxicillin challenge without preceding skin testing for patients with low-risk penicillin allergy features, while skin testing is reserved for those patients with a history of high-risk features.[110] For those with SMX-TMP allergy, desensitization is no longer recommended by the AAAAI. Instead, direct oral challenge in one or two steps may be considered for most patients.[110] In a recent study, 17 SOTr patients underwent direct oral challenge with SMX-TMP with 16 successfully passing the challenge, which suggests that the AAAAI's recommendation extends to use in SOTr.[111] Direct oral challenge now plays a role in the assessment of AAL for cephalosporins, fluoroquinolones, and macrolides as well.[110]

Perioperative stewardship

Surgical site infections (SSI) in SOTr lead to longer hospitalizations, higher costs, increased graft failure, and mortality.[112,113] Targeting antimicrobial SSI perioperative prophylaxis serves both stewardship and infection prevention goals. Perioperative SSI guidance in SOTr exists,[114,115] but additional antimicrobial stewardship opportunities remain. Institutions may be reluctant to follow guidelines based on local SSI history or established practices. Data based on local data may be reassuring. For example, Allen and colleagues[116] narrowed their left ventricular assist device (LVAD) SSI prophylaxis from a four-drug regimen (vancomycin, rifampin, ciprofloxacin, and

Table 5
Risk stratification of reported antibiotic allergies

Non-Allergic Symptoms	Low-Risk Symptoms	Severe Immediate Symptoms	Severe Delayed Symptoms
Gastrointestinal symptoms	Remote history (>5–10 years ago) of non-severe symptoms	Diffuse hives or urticaria	Oral or eye ulcerations
Family history of allergy	Delayed onset of urticaria	Angioedema	Skin or mucosal sloughing
Fear of allergy	Remote history (>5–10 years ago) of urticaria	Dyspnea, wheezing, cough	Immune mediate kidney or liver injury
		Shock	Stevens-Johnsons syndrome
		Comatose	Toxic epidermal necrolysis
			Drug reaction with eosinophilia and systemic symptoms
			Acute generalized exanthematous pustulosis

Adapted from Stone CA, Trubiano J, Coleman DT, Rukasin CRF, Phillips EJ. The challenge of de-labeling penicillin allergy. Allergy: European Journal of Allergy and Clinical Immunology. 2020;75(2):273-288; with permission.

fluconazole) to anti-*Staphylococcal* coverage only (vancomycin and cefazolin) without changes in 30- or 90-day mortality. Some argue for individualized perioperative antimicrobial use based on organ-specific guidelines, donor and recipient microbial colonization, antibiotic allergies, and PK/PD dosing parameters surrounding SOTr's end-organ failure.[117,118] Antibiotic allergy delabeling could also optimize transplant SSI prophylaxis.[100] Other opportunities in peritransplant prophylaxis include optimizing intra-operative antimicrobial dosing and clarifying post-operative dose duration.[118]

SUMMARY

Transplant recipients benefit from antimicrobial stewardship program interventions. We reviewed ASP metrics and designs upon which current and future interventions can build. Diagnostic stewardship opportunities include *C. difficile* testing and many rapid diagnostic platforms, which should be paired with antimicrobial stewardship guidance for optimal use in transplant recipients. Among syndromic and systems-based antimicrobial stewardship opportunities, growing evidence supports delabeling antibiotic allergies in transplant candidates and recipients and withholding treatment of ASB in patients who received renal transplantation more than 2 months ago. Larger studies are needed to build on observational and retrospective antimicrobial stewardship studies in transplant recipients.

CLINICS CARE POINTS

- Clinicians can target *C. difficile* infections in transplant recipients through diagnostic testing stewardship and comparative trials of therapeutic and prophylactic agents.
- Renal transplant recipients do not benefit from treatment of ASB when greater than 2 months from transplant.
- Solid organ transplant recipients benefit from antibiotic allergy delabeling, allowing receipt of narrowed, targeted antibiotics.

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