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ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (KC CLAEYS AND J SMITH, SECTION EDITORS)

Challenges of Antimicrobial Resistance and Stewardship in Solid Organ Transplant Patients

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Abstract

Purpose of Review Without effective antimicrobials, patients cannot undergo transplant surgery safely or sustain immunosuppressive therapy. This review examines the burden of antimicrobial resistance in solid organ transplant recipients and identifies opportunities for antimicrobial stewardship.

Recent Findings Antimicrobial resistance has been identified to be the leading cause of death globally. Multidrug-resistant pathogens are associated with significant morbidity and mortality in transplant recipients. Methicillin-resistant *S. aureus* affects liver and lung recipients, causing bacteremia, pneumonia, and surgical site infections. Vancomycin-resistant enterococci is a nosocomial pathogen primarily causing bacteremia in liver recipients. Multidrug-resistant Gram-negative pathogens present urgent and serious threats to transplant recipients. Extended-spectrum beta-lactamase-producing *E. coli* and *K. pneumoniae* commonly cause bacteremia and intra-abdominal infections in liver and kidney recipients. Carbapenemase-producing Enterobacterales, mainly *K. pneumoniae*, are responsible for infections early-post transplant in liver, lung, kidney, and heart recipients. *P. aeruginosa* and *A. baumannii* continue to be critical threats. While there are new antimicrobial agents targeting resistant pathogens, judicious prescribing is crucial to minimize emerging resistance. The full implications of the COVID-19 global pandemic on antimicrobial resistance in transplant recipients remain to be understood. Currently, there are no established standards on the implementation of antimicrobial stewardship interventions, but strategies that leverage existing antimicrobial stewardship program structure while tailoring to the needs of transplant recipients may help to optimize antimicrobial use.

Summary Clinicians caring for transplant recipients face unique challenges tackling emerging antimcirobial resistance. Coordinated antimicrobial stewardship interventions in collaboration with appropriate expertise in transplant and infectious diseases may mitigate against such threats.

Introduction

Antimicrobials are life-saving medications that are essential to modern medicine. Antimicrobial resistance (AMR) is a global health threat that requires urgent multisectoral, multinational, and interdisciplinary action to address—the so-called One Health approach [1, 2]. AMR has been described as the "silent pandemic," further exacerbated by antibiotics used to treat bacterial coinfections and secondary infections associated with the COVID-19 global pandemic [3–6]. AMR disproportionately affects those who are most vulnerable, including immunocompromised patients and solid organ transplant (SOT) recipients [7]. Without effective antimicrobials, transplant surgery cannot be conducted safely, and antirejection immunosuppressants cannot be implemented, as untreatable infections will negate the life-saving purpose of organ transplantation [7]. This review briefly describes the epidemiology of AMR (among bacterial pathogens) from a global perspective, examines the burden of AMR in SOT recipients, and discusses the challenges in the wider context of the COVID-19 pandemic. It

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also highlights opportunities for antimicrobial stewardship initiatives in SOT patients to mitigate against the threats of AMR.

Epidemiology of Antimicrobial Resistance: A Global Perspective

This review follows the international consensus published in 2012 for definitions of acquired resistance [8]. Multidrug resistance (MDR) is defined as nonsusceptibility to at least one agent in three or more antibiotic classes [8]. Extensively drug resistance (XDR) is defined as nonsusceptibility to at least one agent in all but two or fewer antibiotic classes (i.e., bacterial isolates remain susceptible to only one or two classes) [8]. Pandrug resistance (PDR) is defined as nonsusceptibility to all licensed, routinely available antibiotics [8]. Although these definitions have some limitations, they have been applied to the SOT population [9].

Globally, AMR has been identified as a leading cause of death, with the highest burden in low-resource countries [10•]. There are notable regional differences in AMR rates and epidemiology, potentially associated with antibiotic use [7, 10•, 11, 12]. With concerted efforts, AMR rates for some pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) have stabilized, though primarily in high-income countries only, and not in low-resource settings [10•, 13, 14]. Globally, MRSA have shifted from healthcare settings to the community, whereas VRE remain primarily a nosocomial pathogen [15–18, 19••]. Furthermore, VRE with daptomycin- and linezolid-non-susceptibility have been described [20]. Vulnerable patients, such as those with frequent healthcare exposure due to immunocompromised state, are most at risk for contracting infections caused by MDR organisms [19••, 21, 22, 23••]. In contrast to MRSA and VRE, prevalence of MDR Gram-negative bacilli continues to rise and causes significant morbidity and mortality [24••]. Enterobacterales, mainly *Escherichia coli* and *Klebsiella pneumoniae*, are producers of betalactamases, such as cephalosporinases and cabapenemases, whereas non-fermenters such as *Pseudomonas aeruginosa* carry multiple mechanisms of resistance, and *Acinetobacter baumannii* resistance is conferred through carbapenemase (CRAB) [24••]. New antibiotics targeting MDR Gram-negative pathogens, such as ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, meropenem-vaborbactam, among others, have become available in recent years [24••, 25••]. However, none of these agents provides universal and predictable activity, and treatment-emergent resistance has been observed [24••, 25••]. Antimicrobials with suboptimal pharmacokinetics, potential efficacy concerns, and toxicity issues such as polymixins, aminoglycosides, and tigecycline are still being used to treat infections by MDR pathogens based on their expected spectrum of activity, despite their undesirable profiles [24••, 25••].

Epidemiology and Risk Factors of Antimicrobial Resistance in Solid Organ Transplant Patients

Gram-Positive Bacteria

Despite a decrease in MRSA infections between 2005 and 2016, they remain concerning for SOT patients [7, 26•]. MRSA infections are most common in liver and lung transplant recipients [26•, 27•, 28], and the most common syndromes are bloodstream infections, pneumonia, surgical site infections, and intra-abdominal infections [29•]. In liver recipients with *S. aureus* bacteremia, the prevalence of MRSA ranged from 26.3 to 100% [28]. In a meta-analysis of 23 studies that evaluated infections of MRSA relative to colonization status, 17 (74%) pertained to liver recipients [30]. Pre-transplant, the pooled prevalence of MRSA colonization was 8.5% (95% CI 3.2–15.8%), compared to 9.4% (95% CI 3.0–18.5%) post-transplant [30]. MRSA colonization status was associated with increased risk of infections. The pooled risk ratio of infection was 5.5 (95% CI 2.36–12.90) from pre-transplant colonization and 10.56 (5.58–19.95) from post-transplant colonization [30]. In a recent single-center cohort study between 2008 and 2018 of 351 liver candidates, 5.4% (19/351) of the entire cohort were MRSA-positive, among whom two experienced infections [31]. In contrast, a single-center cohort of 369 pediatric SOT patients admitted between 2009 and 2014 found liver candidates to have the lowest risk of being colonized with MRSA (odds ratio 0.22, 95% CI 0.06–0.81), whereas lung candidates had the highest (odds ratio 18.7, 95% CI 1.9–182.3) [32]. Other risk factors for MRSA infections are summarized in Table 1 [26•, 33–37].

Vancomycin-resistant enterococcus (VRE) infections have been decreasing between 2012 and 2017 [7, 29•, 38]. A meta-analysis of VRE colonization status relative to infection rate in SOT patients estimated the pooled prevalence as 11.9% (95% CI 6.8–18.2) [30]. VRE colonization status was associated with infections, and liver recipients were the most commonly affected group [30]. Pre-transplant colonization was associated with VRE infection (risk ratio 6.65, 95% CI 2.54–17.41), as was post-transplant colonization (risk ratio 7.93, 95% CI 2.36–26.67) in a meta-analysis [30]. A single-center study of liver recipients identified 35% (123/351) of the entire cohort as VRE-positive, among whom 46% (57/123) experienced VRE infections [31]. A single-center cohort between 2008 and 2017 of 536 liver recipients reported 58 episodes of enterococcal bacteremia among 42 patients (7.8%), and VRE was the causative pathogen in 26

Table 1 Summary of risk factors for infections due to MDR pathogens in SOT patients

MDR pathogen	Risk factors	Most commonly affected SOT recipients
Methicillin-resistant *S. aureus*	Colonization status, alcoholic cirrhosis, decreased prothrombin ratio, recent surgical intervention, prolonged operating time, CMV seronegative status, primary CMV infection, prior antibiotic exposure, length of hospital and ICU stay, donor derived infection	Liver, lung, heart
Vancomycin-resistant enterococci (VRE)	Colonization status, post-transplant dialysis, length of hospital stay, donor-derived infection	Liver, heart
Extended spectrum beta-lactamase producing Enterobacterales (*E. coli*, *K. pneumoniae*)	Colonization status, history of infection due to ESBL-producing organism, post-transplant treatment with corticosteroid or treatment for acute rejection, exposure to antibiotics, including 3rd generation cephalosporin, renal replacement therapy post-transplant, donor-derived infection	Liver, kidney, heart
Carbapenemase-producing Enterobacterales, mainly *K. pneumoniae* (KPC)	Colonization status, renal replacement therapy post-transplant, high model for end-stage liver disease (MELD) score at transplant, ureteral stent placement, re-transplantation, donor-derived infection	Liver, lung, kidney, kidney-pancreas
Multidrug-resistant or extremely drug resistant *P. aeruginosa*	Colonization status, cystic fibrosis, prior transplant, intensive care admission, septic shock, donor-derived infection	Lung, liver
Carbapenem-resistant *A. baumanii* (CRAB)	High pre-transplant blood urea nitrogen, hypoalbuminemia, prolonged operating time, mechanical ventilation, intensive care admission, donor-derived infection	Abdominal organs, lung

episodes (45%) [39]. Post-transplant dialysis and length of post-transplant hospitalization were associated with VRE bacteremia, with odds ratio 3.95 (95% CI 1.51–10.34) and 1.03 (95% CI 1.01–1.04), respectively [39]. A recent analysis of surgical site infections in liver transplant patients reported to the National Health Care Safety Network between 2015 and 2018 found prevalence of VRE to be 69.4% (84/121) among *E. faecium* isolates [40]. As VRE remains mainly a nosocomial pathogen, unit-level outbreaks affecting SOT patients have been described, with biofilm formation as a contributing factor [41]. VRE colonization status was not a risk factor for infections in non-liver recipients in a large single-center cohort study [42]. See Table 1 for a summary of risk factors for VRE infections.

Gram-Negative Bacteria

Infections due to MDR Gram-negative bacilli (GNB), particularly extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing Gram-negative pathogens, have been on the rise in the last decade and affecting SOT patients [7, 23••, 27•, 43••, 44••, 45]. Prevalence of MDR GNB pathogens varies by organ group [9, 27•, 46••]. A meta-analysis of 1089 SOT patients from publications in 1994–2003 reported the pooled prevalence of ESBL Enterobacterales colonization to be 18% (95% CI 5–36%) [47•]. The pooled prevalence from 3 studies in Europe was 15% (95% CI 3–34%), and from one North American study, it was 31.4% [47•]. Liver recipients had a pooled prevalence of 17% (95% CI 3–39%), and in kidney recipients, it was 23.5% [47•]. A single-center study from China assessing prevalence of ESBL phenotype in SOT recipients between 2007 and 2010 identified 80 MDR Gram-negative isolates among 350 patients [48]. Phenotypic expression of ESBL was found in 52.5% of the isolates (42/80), and 42.3% (33/80) of patients had ESBL Gram-negative bacterial infections [48]. A 10-year cohort study from France between 2001 and 2010 of 710 recipients reported pre-transplant colonization rate to be 4.1% (29/710), and 5.5% (39/710) developed infections caused by ESBL Enterobacterales within 4 months post-transplant, with intra-abdominal infections being the most common syndrome [49]. In kidney recipients, urinary tract infection was the most common presentation (70.9% [129/182]), and 11.4% (19/166) of the causative Enterobacterales were ESBL-producing [50]. A multicenter cohort study of SOT patients with ESBL Enterobacterales bacteremia between 2005 and 2015 assessed 988 episodes of bacteremia due to Enterobacterales [44••]. Among them, 40% (395) were caused by ESBL-producing organisms [44••]. Risk factors for ESBL

bacteremia were history of ESBL-positive cultures (adjusted odds ratio [aOR] 12.57, 95% CI 3.23–50.33), post-transplant corticosteroid (aOR 1.30, 95% CI 1.03–1.65), acute rejection treated with corticosteroid (aOR 1.18, 95% CI 1.16–1.19) [44••]. Exposure to antimicrobials associated with ESBL bacteremia include 3rd generation cephalosporin (aOR 1.95, 95% CI 1.48–2.57), echinocandins (aOR 1.61, 95% CI 1.16–1.19), and trimethoprim-sulfamethoxazole (aOR 1.35, 95% CI 1.10–1.64) [44••]. A clinical prediction tool for ESBL Enterobacterales bacteremia was developed based on a multicenter cohort of 897 SOT patients admitted between 2005 and 2018 [45]. Predictors selected in the final model were prior colonization or infection with Enterobacterales, recent antimicrobial exposure, severity of illness, and immunosuppressive regimen, but the model had not been externally validated [45]. See Table 1 for a summary of risk factors for ESBL-Enterobacterales infections.

Carbapenemase-producing Enterobacterales (CPE) is a critical threat associated with healthcare-acquired infections affecting SOT patients early post-transplant [7, 23••, 46••]. CPE refers to the mechanism of resistance (genotype), while carbapenem-resistant Enterobacterales (CRE) refers to the phenotypic definition based on susceptibility pattern. *Klebsiella pneumoniae* is the most common CPE pathogen, with carbapenemase (KPC) being the most common mechanism of resistance [46••]. Colonization is reported in 2–18% of SOT patients, whereas acquisition after transplant was reported in 5–27% of patients [23••]. In a five-center serial point-prevalence survey conducted in the USA, 154 patients were screened for CPE between 2019 and 2020, among whom 92 (60%) were SOT patients, and 7 (8%) recipients were colonized [51]. The average rate of infection is estimated to be 10% in liver, 5–10% in lung, and around 5% in kidney recipients, although sources of data are limited to small, single-center studies [23••, 46••]. A retrospective study from Italy evaluated 828 SOT patients admitted in 2011–2014, among them KPC colonization was identified in 5.4% (45/828) of patients and 4.5% (35/828) had infections due to KPC [52]. Post-transplant colonization was reported in 88.9% (40/45) of patients [52]. In a multicenter international cohort study of 60 SOT patients with CRE colonization and/or infection pre-transplant (30 liver and 17 heart recipients), KPC was the most commonly detected CRE organism [53]. Post-transplant infection occurred in 40% (24/60) of the patients, with 62% having surgical site infection and 46% having bacteremia [53]. In a single-center cohort of kidney recipients between 2017 and 2019, prevalence of early (90-day post-transplant) KPC infection was 10.4% (43/419), which included pneumonia, surgical site infections, urinary tract infections, and bacteremia [54]. Site of infection are generally related to the type of graft, potentially with secondary bacteremia [9, 23••]. For liver recipients, intra-abdominal infections such as abscesses, infected bilomas, hematomas, or biliary complications (cholangitis, biliary leakage) are common presentations [9]. Risk factors for CPE infections are summarized in Table 1 [9, 23••].

The so-called difficult-to-treat resistant *Pseudomonas aeruginosa* remains a threat to SOT patients [7, 9, 46••, 55••]. Its mechanisms of resistance include efflux pump, plasmid-encoded extended-spectrum beta-lactamases, inducible chromosomal cephalosporinase AmpC, carbapenemases (metallo-betalactamases, and oxacillinase), and inactivation of OprD porin [9, 56]. Lung recipients are at high risk of *P. aeruginosa* colonization, with prevalence estimated to be 28% pre-transplant and 38% post-transplant [57]. Patients with cystic fibrosis (CF) have pre-transplant and post-transplant colonization risks as high as 70%, and re-colonization by the same strain post-transplant was 53% in one study [58–61]. For non-CF patients, colonization prevalence was reported to be 2.2% and 26% for pre- and post-transplant, respectively [59]. Pneumonia caused by MDR *P. aeruginosa* was reported in 33% of lung recipients early post-transplant in a retrospective study [62], and complications such as fatal empyema have been described [63•, 64]. SOT is a risk factor for antibiotic-resistant *P. aeruginosa* bloodstream infection [65], which accounted for 37–63% of *P. aeruginosa* bacteremia in SOT patients [66, 67]. The incidence of *P. aeruginosa* bacteremia in liver recipients ranged from 0.5 to 14.4%, and carbapenem- and quinolone-resistant *P. aeruginosa* was reported in 12.7% of patients, whereas the prevalence of XDR *P. aeruginosa* isolates was 9.3% [67–69]. Another study of abdominal transplant recipients with P. aeruginosa infections reported the prevalence of MDR isolates to be 46.3% (25/54) [70]. Risk factors for MDR or XDR *P. aeruginosa* infection are summarized in Table 1 [9].

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a critical threat in healthcare-associated infections [7]. Data describing the overall prevalence of CRAB colonization and infections in SOT patients are limited, and while geographical variation has been described, the prevalence in the USA appears to be low [9, 46••]. In a cohort of abdominal transplant recipients in China between 2013 and 2020, carbapenem-resistant Gram-negative pathogens were reported 10.5% (153/1452) of patients, and CRAB accounted for 31% (47/153) of the isolates [71]. A single-center study in Turkey of 41 SOT recipients with *A. baumannii* infections between 2011 and 2017 reported 58.5% and 41.5% of the isolates to be MDR and XDR, respectively [72]. In a cohort of lung recipients in South Korea between 2012 and 2016, 57% (55/96) had *A. baumannii* infections, and among those isolates, 93% (51/55) were MDR [73]. Risk factors for antibiotic-resistant *A. baumannii* infections are summarized in Table 1 [73, 74].

In patients with CF, *Burkholderia cepacia* complex (BCC), particularly *B. cenocepacia*, are associated with accelerated pulmonary function decline [75, 76]. Pre-transplant

colonization and infection with BCC is associated with post-transplant infection, chronic allograft dysfunction (CLAD), and poor survival outcomes compared to BCC-negative status [75, 76]. BCC tend to localize within macrophages, which may contribute to discordance between treatment response and in vitro susceptibility [75]. Resistance to aminoglycosides, fluoroquinolones, sulfamethoxazole-trimethoprim (SMX-TMP), ceftazidime, and meropenem necessitates combination therapy, including ceftazidime-avibactam [46••, 77]. Local epidemiology varies, with incidence of BCC in Canadian centers being higher than in the USA (7.2% vs. 4.5%) [75]. Facility outbreaks have been described, highlighting the risk of nosocomial transmission [75]. Similar to BCC, *Stenotrophomonas maltophilia* is a therapeutic challenge, with options for susceptible strains limited to SMX-TMP and levofloxacin, while potential alternatives for emerging resistance may include minocycline, levofloxacin, ceftazidime, or ceftazidime-avibactam [25••, 46••]. MDR *S. maltophilia* is associated with poor outcomes in patients who received lung transplant for CF; however, the true epidemiology of *S. maltophilia* and its impact is less clear due to limited data [46••, 60, 63•].

Impact of Donor-Derived MDR Pathogens on SOT Patients

Donor-derived infections are defined as any infection present in the donor that is transmitted to one or more recipient [78••]. There are several possible ways donors colonized or infected with MDR organisms may impact transplant recipients: acceptance for organ utilization, modification of peri-transplant surgical antibiotic prophylaxis regimens targeting MDR organisms, and selection of empirical antibiotic regimens for donor-derived infections [9, 78••, 79•, 80•, 81•, 82•, 83, 84, 85•]. In a retrospective cohort of 4 US transplant centers between 2015 and 2016, 15% (64/440) of deceased donors grew an MDR organism on culture [80•]. Risk factors for donors' acquisition of an MDR organism included hepatitis C viremia, need for dialysis, prior hematopoietic stem cell transplant, and exposure to antibiotics with a narrow Gram-negative spectrum [80•]. In a related study, among 440 donors, 7% (29/440) had MDR organism on hospital culture, with 2% (7/440) being MDR Gram-negative organisms, which was associated with a significant reduction in the number of organs transplanted per donor [82•]. Furthermore, organs were accepted significantly further down the match list, potentially reducing donor pool over time [82•]. The authors found that 14% (61/440) of donors received potentially redundant antibiotics, prompting suggestion for need for antimicrobial stewardship among donors during their terminal hospitalization [81•]. A multicenter retrospective cohort study evaluated 658 SOT patients identified 14% (93/658) to have had a donor with MDR organisms [86•]. Donor MDR status was associated with a significantly increased hazard of infection compared to those with negative donor cultures (adjust hazard ratio [aHR] 1.63, 95% CI 1.01–2.62) but were not associated with graft failure or death (aHR 0.45, 95% CI 0.15–1.36) [86•]. A single-center study of 28 abdominal transplant recipients in China between 2015 and 2020 reported a significantly lower survival rate if they had MDR Gram-negative (KPC, CRAB) donor-derived infections, compared with MDR Gram-positive (VRE) infections [87]. Isolation of resistant multidrug-resistant Gram-negative organisms from donor respiratory culture does not impact non-lung transplant recipient [88].

Mortality Associated with Antibiotic Resistance by Pathogen and Organ Type

Colonization and infections due to MDR organisms are associated with major impact on the outcomes of SOT recipients. However, in the absence of network-based, prospective registry data, the quality of available reports was limited by lack of standardized definitions to attribute morbidity and mortality to MDR organisms. Many were subject to bias due to retrospective, single-center design over varying study periods. For CPE infections, the reported mortality post-transplant rates varied. Driven by local epidemiology, depending on organ type, and infectious syndromes, the 1-year mortality ranged from less than 10% to over 80%, which was significantly higher than patients without CPE infections [23••, 43••, 52]. For ESBL-producing Gram-negative infections in liver and kidney transplant patients, bacteremia-related mortality was 26% [89]. Among patients with MRSA bacteremia, transplant status was not associated with higher 90-day mortality (adjusted odds ratio 0.74, 95% CI 0.44–1.25), but was associated with higher risk of septic shock and acute respiratory distress syndrome in a retrospective single-center study [90]. Others have reported higher long-term (1-year) mortality rate in lung recipients with MRSA infections compared with those who had methicillin-susceptible *S. aureus* infections [91]. Among heart transplant recipients, relative to those without infections, MDR pathogens and XDR pathogens infections were associated with 11-fold and 26-fold higher hazards of death, respectively [92•]. In a single-center study from 2011 to 2016, the most common MDR pathogens were ESBL-*E. coli* and *K. pneumoniae*, while *P. aeruginosa* and carbapenem-resistant *K. pneumoniae* were the most common XDR pathogens [92•]. In liver recipients, colonization and infection with MDR organisms were associated with increased risk of death (hazard ratio 2.57, $p < 0.001$) [31]. In kidney recipients, bacteremia due to *P. aeruginosa*, but not other MDR pathogens, was a significant risk factor for unfavorable outcome (defined as death, graft

nephrectomy, or return to dialysis), adjusted OR 46.11 (95% CI 3.9–552.2) [50]. Others reported carbapenem-resistant *K. pneumoniae* infection to be an independent risk factor for 1-year mortality, OR 6.75 (95% CI 1.05–43.4) [54].

Impact of the COVID-19 Global Pandemic on Antimicrobial Resistance and SOT Patients

SOT candidates and recipients have been affected by the direct risks of COVID-19 infection, as well as the secondary effects from the pandemic. Overall decrease in resources available at hospitals has led to reduction in non-urgent surgery and outpatient care, potentially adding to the negative impact on the mental status of SOT patients, contributing to decreased adherence to medical appointments [93–95]. Another potential impact has been a decrease in living and deceased organ donation worldwide, and its deleterious effect on transplant candidates' waitlist on morbidity and mortality [96–98]. Effects of the pandemic on AMR in general and subpopulations like SOT are difficult to predict. Increased antimicrobial use in COVID-19 patients could attribute to emergence of resistance [99, 100•]. The overall prevalence of bacterial coinfection was estimated to be approximately 7%, and higher at 8.1% in critically ill patients, yet 70% of patients received antibiotics [5, 6, 101•]. As a result of efforts to tackle the pandemic, resources for infectious diseases, antimicrobial stewardship (AMS), and infection prevention and control were stretched to their limits. In spite of that, recent European and UK surveillance data reported a decrease in AMU over the last 2 years [102, 103].

Severe COVID-19 infection with respiratory failure requiring prolonged mechanical ventilation or use of extracorporeal membrane oxygenation is associated with an increased risk of secondary infections and emergence of MDR pathogens [101•, 104, 105•]. Most studies addressing severely ill COVID-19 patients reported high rates of MDR pathogens [106•, 107]. Furthermore, COVID-19 patient unit-level outbreaks due to MDR pathogens have been reported [108–110]. In contrast, decline in MDR rates for the entire hospital was reported in an Italian hospital [111]. Lung transplantation has emerged as a long-term solution for COVID-19 patients with non-reversible lung fibrosis [112–114]. Since these patients have had heavy exposure to the healthcare environment and high pretransplant infection rates, MDR rates in this population is potentially higher than non-COVID lung recipients [112]. Although short-term outcome seems similar in the limited literature when compared to lung transplant for other indications, long-term data are missing and most studies did not specifically report on infections in the posttransplant period [112, 114]. The overall effect of the pandemic on AMR remains to be determined. Changes in the local epidemiology in healthcare settings could potentially lead to higher risks of acquisition of MDR pathogens among exposed individuals such as SOT recipients.

Challenges in Antimicrobial Stewardship in SOT Patients

Antimicrobial stewardship (AMS) is defined as a coordinated set of interventions to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial regimen including dosing, duration of therapy, and route of administration [115•]. While new antimicrobials targeting MDR pathogens have become available in the last few years, clinicians are urged to be judicious in prescribing these agents to preserve their effectiveness [24••, 25••, 116]. Furthermore, global shortage of antimicrobials remains an ongoing challenge in healthcare [117]. Facing MDR and antimicrobial shortage, clinicians have had to resort to less desirable antimicrobials with worse adverse effects profile, such as polymixins or tigecycline [24••, 25••]. Clinicians may also need to mitigate complex interactions between immunosuppressants and antimicrobials, carefully balancing the need to treat an infection with the goal of minimizing negative impact on the allograft. For it would be extremely unfortunate for a patient, after receiving a life-saving/altering organ transplant, only to lose the allograft or worse, succumb to an infection caused by an antibiotic-resistant pathogen. To ensure sustainability of safe and effective antimicrobials for current and future patients, coherent actions to promote responsible use of antimicrobials under the auspices of quality improvement are crucial [118].

Quality assurance programs from the US Center for Disease Prevention and Control (CDC), the Centers for Medicare and Medicaid, The Joint Commission, UK's National Institute for Health and Care Excellence, and Accreditation Canada, among others, have established quality standards for AMS programs across a wide spectrum of patient settings, including institutional and outpatient care [119••, 120•, 121•, 122•]. For example, the CDC's Core Elements of Antibiotic Stewardship encompass accountability structure, leadership, team membership, interventions, antimicrobial use monitoring and reporting for AMS programs in hospitals (Table 2) [119••]. However, there are no established standards on how to implement AMS programs specific to SOT patients, and clinical data evaluating the safety and effectiveness of AMS interventions in this population remain scarce [19••]. Diagnostic uncertainty and atypical presentation of infection in immunosuppressed patients are often the rationale for initiating antimicrobials [19••]. Guidelines for

Table 2 Summary of AMS interventions tailored to SOT patients

US CDC core elements of hospital-based AMS programs	Leveraging existing AMS framework	Suggested additional components to address the needs of SOT patients
Hospital leadership commitment	Dedicate necessary human, financial and information technology resources AMS program leadership report to hospital leadership	Resources to facilitate AMS interventions in SOT patients Engage SOT program leadership and key stakeholders Including clinical expertise in SOT and transplant infectious diseases to be a part of the interdisciplinary AMS team, with sufficient resources and support
Accountability	Appoint a leader or co-leaders, such as a physician and pharmacist, responsible for program management and outcomes	Reporting of AMS activities and key performance indicators that reflect interventions implemented in SOT patients
Pharmacy expertise	Appoint a pharmacist, ideally as the co-leader of the stewardship program, to lead implementation efforts to improve antibiotic use	Determine key performance indicators that are feasible, valid, and meaningful for local key stakeholders in SOT Ensure key performance indicators reflect interventions implemented in SOT patients
AMS interventions	Implement interventions, such as prospective audit and feedback or preauthorization, to improve antibiotic use Priority interventions include prospective audit and feedback, preauthorization, and facility-specific treatment recommendations. Facility-specific treatment guidelines can be important in enhancing the effectiveness of prospective audit and feedback and preauthorization Other priority interventions are infection- based, provider-based, pharmacy-based, microbiology-based, and nursing- based interventions	Establish process for audit and feedback with prescribers and clinicians in SOT patients Antibiogram for SOT patients Develop local guidelines specific for SOT patients using local epidemiology data. Start with a focused topic with a defined scope, and implement it and scale up as per local context. Refine the process before expanding to another topic or syndrome Engage pateint, caregiver, SOT prescribers, nursing and pharmacy to identify interventions that best meet local needs Examples of suggestions tailored to SOT patients' needs: • Antifungal stewardship • Asymtomatic bacteruria in kidney transplant recipients • Syndrome-based interventions on empirical and targeted therapy • Adding rapid diagnostics to part of a bundle of interventions to guide tailoring of antimicrobial therapy
Tracking antimicrobial prescribing, resistance and *Clostridioides difficile* infection rate	Monitor antibiotic prescribing, impact of interventions, and other important outcomes like C. difficile infection and resistance patterns	Track data from SOT unit. Adapt, validate and utilize existing data extraction process to meet the needs of SOT patients
Reporting	Regularly report information on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership Consider provider-level reporting (acknowledging that this has not been well studied for hospital antibiotic use)	Report data from SOT units, consider organ team level and/or provider level data reproting if feasible. Engage SOT clinicians in the process
Education	Educate prescribers, pharmacists, and nurses about adverse reactions from antibiotics, antibiotic resistance and optimal prescribing Case-based education, or "handshake stewardship"	Engage SOT clinicians using case-based format to discuss approach to infection management, including when to consult expertise from transplant infectious diseases team

Adapted from: CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019 and So M, Hand J, Forrest G, Pouch SM, Te H, Ardura MI, et al. White paper on antimicrobial stewardship in solid organ transplant recipients. Am J Transplant. 2022;22(1):96–112

management of certain infectious syndromes, such as those from the American Society of Transplantation, are available, but the heterogeneity of SOT patients makes defining appropriateness of antimicrobial regimen and identifying suitable outcome measures or key performance indicators difficult [19••, 123]. Clinical trials evaluating optimal duration of therapy tend to exclude SOT patients, limiting applicability of the evidence [19••]. Lastly, technical challenges in source control attainment, donor-derived infections, and the so-called net state of immunosuppression present additional barriers to designing and implementing AMS programs addressing the specific needs of SOT patients [19••, 124]. A 2016 survey of US transplant centers found that only 74% of institutional ASPs included coverage for adult SOT recipients [125•]. The extent to which CDC-recommended AMS interventions were implemented varied, and despite high needs for antimicrobials, strategies to assess antimicrobial prescribing quality in this population were limited [125•, 126]. A cross-sectional study of hospitals from 10 states in the USA evaluated the appropriateness of antimicrobial use in 1566 patients; immunocompromised patients (including SOT and stem cell transplant recipients) accounted for < 5% of the study cohort [126].

Potential Strategies to Optimize Antimicrobial Use and Mitigate the Threats of Antimicrobial Resistance

In 2020, 91% of hospitals in the USA have met all core elements of AMS programs recommended by the CDC [127••]. Therefore, leveraging existing framework and building on AMS programs already in place may be an efficient use of resources to address the unique AMS needs of SOT patients. Potential "add-on" components may include adding expertise in SOT and transplant infectious diseases to the interdisciplinary AMS team, monitoring and reporting antimicrobial use in SOT care units, and investing in resources to engage SOT leadership and clinicians to become stakeholders in SOT-specific AMS interventions [19••]. Locally developed guidelines constitute a key AMS strategy; therefore, focusing on organ-specific guidelines tailored to the SOT program's epidemiology could be a reasonable starting point [19••, 115•]. Adjudication of adherence to surgical prophylaxis guidelines in transplant procedures is another reasonable intervention, focusing on organ-specific guidance [128, 129•]. Specific to the USA, the current National Healthcare Safety Network Antimicrobial Use Option Report does not include data from SOT care units for benchmarking, although this may change in the future. Potential interventions tailored to SOT patients within an existing hospital-based AMS program are summarized in Table 2 [19••, 119••]. Beyond the in-patient setting, antimicrobial prescribed in the ambulatory clinics, where SOT patients receive often life-long care and follow-up monitoring, presents a crucial opportunity to explore the next horizon of AMS in SOT patients.

Conclusion

Rising antimicrobial resistance, particularly among difficult-to-treat Gram-negative pathogens, brings unique challenges to clinicians caring for SOT patients. While new antimicrobial agents targeting these pathogens have become available in recent years, without a coherent approach to ensure optimal and judicious use, they are at risk of losing their effectiveness due to emerging resistance. Antimicrobial stewardship programs tailored to the specific needs of SOT patients are important strategies to mitigate such threats to patient care.

Compliance with Ethical Standards

Conflict of Interest Miranda So and Laura Walti do not have any conflict of interests to disclose.

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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