Antimicrobial Stewardship in Solid Organ Transplant Recipients: Current Challenges and Proposed Metrics

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Abstract:

Background: Solid organ transplant (SOT) recipients are challenging populations for antimicrobial stewardship interventions due to a variety of reasons, including immunosuppression, consequent risk of opportunistic and donor-derived infections, high rates of infection with multi-drug resistant organisms and *Clostridioides difficile*, and need for prolonged antimicrobial prophylaxis. Despite this, data on stewardship interventions and metrics that address the distinct needs of these patients are limited.

Methods: We performed a narrative review of the current state of antimicrobial stewardship in SOT recipients, existing interventions and metrics in this population, and considerations for implementation of transplant-specific stewardship programs.

Results: Antimicrobial stewardship metrics are evolving even in the general patient population, while data on metrics applicable to the SOT population are even more limited. Standard process, outcomes, and balancing metrics may not always apply to the SOT population. A successful stewardship program for SOT recipients requires reviewing existing data, applying general stewardship principles, and understanding nuances of SOT patients.

Conclusion: As antimicrobial stewardship interventions are being implemented in SOT recipients; new metrics are needed to assess their impact. In conclusion, SOT patients present a challenging but important opportunity for antimicrobial stewards.

Abbreviations: Solid organ transplant (SOT), antimicrobial stewardship program (ASP), multi-drug resistant organism (MDRO), *Clostridioides difficile* infection (CDI), Centers for Disease Control and Prevention (CDC), Infectious Diseases Society of America (IDSA), prospective audit and feedback (PAF), hematopoietic cell transplant (HCT), cytomegalovirus (CMV), trimethoprim-sulfamethoxazole (TMP-SMX), surgical site infections (SSI), nucleic acid amplification testing (NAAT), days of therapy (DOT), defined daily dose (DDD), length of stay (LOS)

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Introduction

The impact of antimicrobial stewardship programs (ASPs) has been recognized in the general patient population[1-4]. However, limited data exist on appropriate antimicrobial stewardship interventions and metrics in immunocompromised patients, including in solid organ transplant (SOT) recipients. In SOT recipients, the degree of immunosuppression puts patients at risk of a variety of opportunistic infections and donor-derived infections[5]. This risk of infection changes over time depending on factors such as time since transplantation and de-escalating immunosuppression, necessitating a nuanced infectious disease approach. SOT recipients often have significant exposure to therapeutic and prophylactic antimicrobials both pre- and

post-transplantation, leading to higher rates of infection and colonization with multi-drug resistant organisms (MDROs) and associated poor outcomes[6-8]. This high degree of exposure to antimicrobials is also associated with increased risk of *Clostridioides difficile* infection (CDI), which in turn is associated with graft loss and mortality[9,10]. Additionally, complex medication regimens including immunosuppressive agents can lead to drug-drug interactions and other adverse drug effects. There is a paucity of data regarding optimal treatment of infections in these patients, including agent selection and antimicrobial duration. In addition, atypical presentations, diagnostic uncertainty, and a high degree of investment in patient outcomes, can lead to antimicrobial overuse.

Despite these critical differences from the general stewardship population, to our knowledge, no SOT-specific stewardship guidelines exist, and there is limited guidance related to SOT recipients in national and international recommendations for ASPs[11,12]. However, 74% of ASPs at transplant centers include transplant recipients in their recommendations[13]. Therefore, there is a critical need for guidelines that address the specific needs of this patient population. SOT patients require a bespoke stewardship approach and stand to benefit uniquely from stewardship interventions. This review provides an overview of the current state of stewardship in SOT recipients, including existing data for interventions and metrics specific to this population, as well as considerations for implementation of transplant-specific stewardship programs.

Methods:

This is a narrative review, and the following search strategy was employed to ensure an unbiased and comprehensive literature review. A search of the PubMed database was performed with the search terms “antimicrobial stewardship” or “antibiotic stewardship” and “immunocompromised” or “transplant” or “solid organ transplant” and “metrics” or “interventions” as well as search terms for resource-limited settings including “international” “long-term care” and “community.” We excluded non-human studies, pediatric studies (age <18), and studies where English language translation was not available. In addition, all references from selected articles were reviewed and included if relevant. There was no date limitation. Seventy-six articles were selected based on relevance per the search strategy as shown in Figure 1.

Current state of stewardship in SOT recipients

The Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) have published guidelines detailing optimal implementation and management strategies for ASPs. In 2016, the Centers for Medicare and Medicaid Services and The Joint Commission mandated that all hospitals, critical access hospitals, and nursing care centers have ASPs in place[11,12,14]. The CDC’s ASP guidelines, updated in 2019, highlight 7 core areas of antibiotic stewardship, including hospital leadership commitment, accountability, pharmacy expertise, action, tracking, reporting, and education[11]. Though there are increasing data on ASP interventions and metrics in the general population, data in SOT recipients are very limited and relatively few studies have focused on or even included this patient population. Table 1 provides a summary of existing data on ASP interventions in SOT recipients. This section will review current ASP interventions, related guidelines, and diagnostics in SOT recipients.

Antimicrobial stewardship interventions

Prospective audit and feedback (PAF) and preauthorization of formulary restricted antimicrobials

PAF and preauthorization of restricted antimicrobials are foundational ASP interventions with proven efficacy in the general population, and are key strategies recommended by national guidelines[11,12,15]. PAF was shown to be effective in SOT recipients in a recent study noting significant improvement in guideline-concordant prescribing after implementation of PAF, with no observed increase in antimicrobial cost or rates of CDI[16]. Though not directly applicable to SOT, other studies that have included hematopoietic cell transplant (HCT) recipients have also noted preauthorization and PAF to be associated with cost reduction and improvement in prescribing with no associated harms[17].

Transplant-specific antibiograms

While region and institution-specific antibiograms are extremely valuable in choosing empiric antimicrobial regimens, these typically are not specific to transplant recipients and may therefore underestimate the antimicrobial resistance seen in these patients. Previous studies examining urine cultures in renal transplant patients noted marked variability in antibiotic resistance patterns, including significantly more MDROs, as compared to the institutional antibiogram[18,19]. Another study examining Gram-negative resistance patterns from all bacterial isolates in SOT recipients also noted significant differences from the institutional antibiogram; again, higher rates of antibiotic resistance were noted among these patients, leading to decreased susceptibility to recommended first-line therapies[20]. These studies highlight the

potential utility of transplant-specific antibiograms in assisting with appropriate empiric prescribing of antimicrobials.

Parenteral to oral (IV to PO) conversion

Conversion from IV to PO antibiotics is recommended by current guidelines in many situations; this strategy is known to decrease drug costs, IV-associated complications, and reduce hospital length of stay.[21]. While the use of oral antibiotics has not been specifically studied in SOT recipients, a recent retrospective study of patients with *Enterobacterales* bacteremia included approximately 200 SOT recipients and found no difference in mortality between IV therapy and early step down to PO therapy[22]. The VICTOR trial, one of the few existing randomized controlled trials assessing antimicrobials specifically in SOT recipients, showed that oral valganciclovir was non-inferior to IV ganciclovir in treating cytomegalovirus (CMV) disease in SOT patients[23]. This strategy has been widely incorporated into disease-specific guidelines, including those for CMV and invasive fungal infections[24-26].

Allergy delabeling

Beta-lactam allergy delabeling has been shown to be tremendously impactful in improving appropriate antibiotic prescribing patterns[27-29]. SOT recipients, who often have significant exposure to antibiotics, are known to have high rates of reported antibiotic allergies. In one recent study, 29% of transplant (including both SOT and HCT) recipients reported an antibiotic allergy and 16% reported a beta lactam allergy. This study also showed that SOT patients with a listed beta lactam allergy were more likely to receive broad-spectrum antimicrobials than their non-allergic

counterparts[30]. Another retrospective study of liver transplant recipients demonstrated 16% had a labeled antibiotic allergy, with the majority of these being beta-lactam and sulfonamide allergies. Patients with antibiotic allergy labels in this study were found to have a trend toward increased rates of MDRO infection and CDI, which is consistent with the non-transplant population[31]. Studies in the non-transplant population have shown that allergy delabeling significantly improves antibiotic prescribing practices, but to date there are no similar studies in the transplant population[32-34]. However, a recent study in which SOT patients with sulfonamide allergies were desensitized to trimethoprim-sulfamethoxazole (TMP-SMX) demonstrated significant cost savings with no adverse effects, indicating that this may prove a useful strategy[35].

Individualizing prophylaxis strategies

Tailored prophylaxis approaches can lead to reductions in unnecessary antimicrobial exposures and related adverse effects. Recent studies in CMV prophylaxis demonstrate that the use of these strategies, including measuring cell-mediated immunity to CMV, are safe and feasible in SOT patients[36,37]. A study in lung transplant recipients showed that use of diagnostic tools including BAL fungal cultures and galactomannan assays to diagnose and pre-emptively treat invasive aspergillus infections significantly decreased the risk of these infections and decreased antifungal exposure when compared to a universal prophylaxis strategy[38].

Pre-operative prophylaxis

Though infection prevention bundles and standardization of preoperative antimicrobial prophylaxis are known to improve outcomes and decrease surgical site infections (SSI), few studies have evaluated these interventions in SOT recipients[39,40]. A recent retrospective study evaluating the implementation of an infection control bundle and standardizing recommendations for surgical prophylaxis in recipients of liver, kidney, pancreas, and kidney-pancreas transplantation demonstrated a significant reduction in SSI and increased compliance with antimicrobial protocols[41]. Additionally, the American Society of Transplantation has recently published guidelines for the management of SSI in SOT patients which address many of the critical differences between SOT patients and the general surgical population, and provide recommendations for prevention and treatment of these infections[42].

Diagnostics

Diagnostic uncertainty is common in SOT patients as they often have atypical presentations of common infectious syndromes, and are also at risk for uncommon infectious syndromes. Additionally, some commonly used diagnostic assays, such as serologic tests, may not be accurate in this population[43,44]. This diagnostic uncertainty can lead to indiscriminate use of broad-spectrum antimicrobials. Recent advances in rapid diagnostic tests, including point of care nucleic acid amplification tests, multiplex PCR panels which also report antimicrobial resistance genes, and the advent of metagenomic sequencing tests capable of detecting potential pathogens, can assist with accurate, speedy diagnosis and help minimize unnecessary antibiotic exposure[45]. Studies in the non-transplant population have shown that rapid diagnostics can reduce use of broad-spectrum antimicrobials and

treatment of contaminants; when paired with ASP interventions, these tests can be cost-effective interventions[21,46]. While most of these diagnostic tests have not been evaluated specifically in SOT recipients, a recent study evaluating a host gene expression panel—a gene expression signature produced by the host in response to infection--for bacterial, viral, and fungal infections demonstrated reduced accuracy in discriminating these infections in immunocompromised hosts (including SOT recipients) as compared to their immunocompetent counterparts[47]. Additionally, a study examining universal *C. difficile* screening of SOT recipients using nucleic acid amplification testing (NAAT) found that this strategy leads to overtreatment[48]. Further examination of the performance and applicability of newer diagnostic tests, including advanced molecular diagnostics, in the SOT population is needed to understand their best use in these patients.

Metrics

An understanding of valid metrics to assess the impact of ASP in SOT is critically important. Current data on ASP metrics are incomplete and evolving even in the general population, and data on metrics applicable to the SOT population are even more limited. Importantly, a recent survey of ASP interventions and outcomes in transplant centers (both SOT and HCT) noted that 23% of respondent programs did not utilize any specific metrics to assess the impact of ASP in SOT recipients. Among the 77% of programs that did use specific metrics, there was significant variability in which metrics were chosen[13]. This section discusses existing data on ASP metrics in SOT recipients, divided into process, outcome, and balancing metrics as shown in Table 2.

Process metrics

Process metrics are used to determine if an intervention is having the desired effect or impact. National guidelines recommend monitoring antimicrobial consumption by days of therapy (DOTs) or defined daily dose (DDD) (if DOT is not institutionally available) and comparing this data with institutional ASP recommendations to determine appropriateness of prescribing patterns (please see reference 49 for a thorough description of these metrics) [11,21]. This strategy represents a cornerstone process metric in general ASP and is also a commonly employed strategy in transplant programs, with 27% of SOT programs reporting monitoring antimicrobial use as an ASP metric[13]. However, use of consumption metrics like DOT and DDD have significant limitations in SOT patients considering the use of prolonged prophylaxis in many cases and therefore requires nuanced interpretation. Concordance with ASP guidelines is also a commonly used process metric. A recent study examining stewardship-concordant prescribing practices in SOT found 30% of prescriptions were not consistent with stewardship recommendations; the most common reasons for discordance were lack of de-escalation, inappropriate length of antibiotic therapy, and empiric antibiotics that were too broad. The majority of guideline-discordant cases did not have transplant infectious diseases consultation. This study used the CDC's guidelines to define best stewardship practice in the absence of national, international, or institutional SOT-specific guidelines[50]. Studies of antifungal stewardship interventions which have included transplant patients have utilized appropriateness of antifungal therapy, duration of therapy, and adherence with antifungal guidelines as relevant process measures[51,52].

Outcome metrics

Measurement of patient outcomes that truly reflect ASP interventions is challenging. Rates of CDI, antimicrobial resistance, length of stay (LOS), mortality, readmission rates, duration of parenteral therapy, and days of central venous access have all been proposed but each have their limitations, primarily inability to adjust for confounding variables that impact these metrics[53-56]. Monitoring for adverse events including toxicities and drug-drug interactions can also be considered as useful outcome metrics. Many of these measures, including CDI, readmission, and mortality, have been proposed as metrics to assess the quality of transplant programs in general[57]. CDI rates may represent a particularly salient metric, as SOT recipients are known to have higher rates of infection and increased morbidity, mortality, and costs associated with CDI than the general population[58,59]. Additionally, CDI is one of the few outcome measures in the general stewardship population where ASP have consistently been shown to have a positive impact, including on mortality[3]. Accordingly, CDI rates are the most commonly utilized outcome metric in SOT programs, with 56% of programs in a recent survey using this metric[13].

Metrics specific to antifungal and antiviral interventions in SOT patients have also been reported. Useful outcome measures related to antifungal stewardship include antifungal resistance rates, recurrent fungal infections, LOS, and mortality or fungal-infection free survival[24,51,52]. Similarly, viral-related hospital admissions and antiviral resistance rates have been documented as outcomes in antiviral stewardship studies, primarily in patients with CMV infection[26,36,37,60].

An important caveat in SOT recipients is that most of these outcome variables are likely to be more frequently affected by confounders and less responsive to ASP interventions than in the general population[9]. Therefore, more data on SOT-specific outcome metrics are needed, and a careful interpretation of existing metrics as applied to SOT patients is necessary.

Balancing metrics

Balancing measures assess whether a given intervention designed to improve one aspect of stewardship may inadvertently cause negative repercussions in another aspect of care. Many process metrics (such as antibiotic use) and outcomes metrics (including readmission rates, mortality, and drug-related adverse events) can also be assessed as balancing metrics.

One study mentioned above examining the impact of PAF in SOT recipients utilized stewardship-concordant prescribing as their primary outcome, with antimicrobial consumption and CDI as secondary outcome measures. They also examined LOS, readmission rates, and mortality as balancing measures[16].

The desirability of outcome ranking and response adjusted for duration of antibiotic risk (DOOR/RADAR) tool is a novel method involving first categorizing patients into an overall clinical outcome, and subsequently ranking those patients on desirability of outcomes[61]. This strategy seeks to overcome limitations of typical ASP metrics to assess advantages and disadvantages of different antibiotic use strategies, and has been used in recent studies in SOT recipients[62].

Feasibility and Usefulness of Metrics

Given the difficulty and complexity of identifying and implementing accurate, clinically meaningful metrics for assessing the impact of ASP, defining the feasibility and usefulness of these metrics is necessary. Recently, an expert panel identified 6 metrics for assessing ASP interventions in acute care settings using a modified Delphi approach[63], according to the following criteria:

1. If the metric is associated with improved antimicrobial prescribing.

2. If the metric is associated with improved patient care.

3. If the metric is useful in targeting antimicrobial stewardship efforts.

4. If the metric is feasible to monitor in any hospital with an electronic health record.

Metrics were considered feasible if electronic definition development, data collection, and analysis were completed within the two-year project timeline. Metrics were considered useful if pilot sites and investigators felt that analyses using the metric could inform decisions about their ASP goals and development. For example, days present or antibiotic days per patient days are both feasible and useful. However, this metric requires the ability to track individual patients' movements between hospital units in order to count calendar days of hospital and unit exposure[63]. These data can be complex, and require a mapping procedure to ensure consistency with units identified in the pharmacy data source as well as the patient movement data source. This approach can provide a framework for selecting appropriate ASP metrics, both at the institutional and national level, in the absence of robust data to guide these decisions.

Recommendations for the creation and implementation of SOT-specific ASPs

Interpreting existing data in combination with general ASP principles and nuances of the patient population of interest can be used to model successful SOT ASPs.

A multidisciplinary team approach is the first critical step in a successful SOT-specific ASP[64,65]. This should include at minimum, transplant infectious disease specialists, infectious disease trained pharmacists, organ-specific transplant physicians relevant to the institution, as well as representatives from nursing, microbiology, and infection prevention (Figure 2). A close relationship with the microbiology laboratory is also vital to facilitate understanding of diagnostic testing strategies in SOT patients, interpretation of microbiologic data, and timely communication of test results. Collaboration between ASPs and microbiology labs in the non-SOT population has been shown to clarify microbiologic results, reduce unnecessary testing, and optimize antimicrobial therapy[66,67].

Recommended ASP interventions in SOT mirror general ASP interventions to some extent, with some important considerations. The implementation of PAF has been shown to be effective and safe in SOT recipients[16]. This strategy is viewed more favorably among transplant physicians compared to formulary restriction and has also been found to be more impactful than restriction in decreasing antibiotic use[15,68]. The implementation of transplant-specific antibiograms can assist in defining and tracking SOT-specific resistance patterns and in choosing empiric antimicrobials tailored to this population[18-20]. Pharmacy expertise in dosing antimicrobials for this special population, with an eye to drug-drug interactions and toxicities, can maximize the benefits of antimicrobials while reducing harms[69]. The use of advanced diagnostics can also assist in personalizing prophylaxis regimens to avoid unnecessary drug exposure[45]. A concerted allergy de-labeling strategy can also help

improve prescribing patterns and minimize indiscriminate broad-spectrum antimicrobial use[27,30].

Organ and disease state guidelines specific to transplant recipients are already known to be effective in antiviral and antifungal stewardship but should be expanded to include other infectious disease states as well[24,25]. These guidelines should incorporate transplant antibiograms if possible, which can improve empiric prescribing and help minimize unnecessary antibiotic exposure.

Lastly, education of stakeholders is an essential component to the success of SOT ASPs. The unique relationship of SOT recipients with the medical system can lead to a high degree of emotional investment in patient outcomes, which paired with the perception that these patients are often more ill than their non-transplant counterparts can lead to challenges for the successful implementation of ASPs. Education about ASPs has been shown to change attitudes and improve prescribing practices and should be applied to SOT ASPs as well[70,71].

The right metrics by which to measure the success of these interventions in SOT patients remain largely unknown. However, process metrics including defined daily dose and concordance with stewardship guidelines, outcomes measures including rates of MDRO, CDI, LOS, readmission rates, and mortality have all been used to study stewardship in this population. Additionally, intriguing new strategies such as the DOOR/RADAR methodology may help address the complexities of these patients to move toward a more comprehensive understanding of the impact of ASPs.

International perspective

The vast majority of studies on antimicrobial stewardship have been conducted in high-income countries in the US, Europe, and Australia. However, antimicrobial resistance is an urgent worldwide problem, prompting the World Health Organization to release a global action plan to combat resistance in 2015[72]. Developing countries face unique challenges in antimicrobial stewardship, but efforts to address these challenges are evolving in many places[73]. For example, India has worked on national policy to improve antimicrobial use and has begun to formalize infectious diseases fellowship programs. Despite this, a number of barriers still exist for antimicrobial stewardship in India depending on the region including availability of diagnostics, lack of ID-trained pharmacists and physicians and unregulated antibiotic use in the community[74]. However in India, as of 2019, 550 transplant centers were already in operation with more than 12,000 solid organ transplants performed annually[75]. As solid organ transplants are increasingly performed around the world, more data is needed on the feasibility and applicability of ASP interventions and metrics globally.

Conclusion and future directions

The field of antimicrobial stewardship is evolving rapidly and has made significant impacts in the responsible use of antimicrobials, including decreasing antibiotic resistance and improving patient outcomes. Within this field, SOT recipients comprise a complex patient population that presents unique challenges and opportunities. Despite this, these patients are not included in societal ASP guidelines, and data on ASP interventions and metrics by which to assess their

impact are sparse and poorly defined. Most existing data have been derived from the general population, or other immunocompromised patients, and must therefore be substantiated in SOT recipients.

The first important step toward comprehensive ASP for SOT recipients is a more complete understanding of the current state of stewardship in SOT and existing barriers to implementation of ASPs. Current data is limited to single center studies and therefore studies with greater generalizability are needed. As SOT recipients are often not included in clinical trials which inform infectious disease guidelines, there is limited guidance related to treatment of infections in these patients. Current recommendations, where they exist, are largely based on expert opinion. Inclusion of SOT recipients in future large-scale trials is an important step toward developing disease state-specific guidelines that accurately address the specific needs of this population. Other next steps will be to perform a modified expert panel similar to the STEWARDs panel to assess usability and feasibility of ASP metrics in SOT[63].

As our understanding of ASP in SOT patients progresses, appropriate metrics to assess the impact of ASP in SOT patients must evolve as well. Standard process, outcomes, and balancing metrics may not always apply to the SOT population. As unique ASP interventions are being developed in this population, new metrics may need to be generated to assess their impact. In conclusion, while SOT patients present singular opportunities for antimicrobial stewardship, there are currently more questions than answers in how best to address their specific needs.

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Table 1: Summary of available literature on antimicrobial stewardship interventions in solid organ transplant patients

Intervention	Population	Results	Reference
Prospective audit and feedback	179 SOT † recipients with infection	Increased antimicrobial-stewardship concordant prescribing	So et al 2019[16]
Transplant-specific antibiograms	66 renal transplant recipients with UTI	High rates of antimicrobial resistance to empiric agents recommended per institutional antibiogram	Korayem et al 2018[18]
	100 renal transplant recipients with UTI ‡	High rates of antimicrobial resistance to empiric agents recommended per institutional antibiogram	Halim et al 2020[19]
	1889 positive blood and urine cultures from SOT recipients	High rates of antimicrobial resistance to empiric agents recommended per institutional antibiogram	Rosa et al 2016[20]
Optimizing antimicrobial dosing	53 SOT recipients receiving ganciclovir or vanganciclovir prophylaxis	Population pharmacokinetic modeling optimizes antiviral dosing vs. manufacturer recommendations	Padulles et al 2016[24]

	79 SOT recipients receiving isavuconazole prophylaxis	Population pharmacokinetic modeling optimizes antifungal dosing vs standard dosing, specifically for candidal infection	Wu et al 2020[26]
IV to PO conversion	1478 total patients including 217 SOT recipients with Enterobactericiae bacteremia	No difference in mortality between oral step down in first 5 days vs. entire duration with parenteral therapy	Tamma et al 2019[28]
	321 SOT recipients with CMV § disease	Oral valganciclovir was non-inferior to IV ganciclovir in treating CMV disease	Asberg et al 2007[29]
Allergy delabeling	1410 SOT recipients	Reported beta lactam allergies were more likely to receive non-beta lactam antibiotics	Imlay et al 2020[36]
	313 Liver transplant recipients	Reported antibiotic allergies were associated with a trend toward increased antimicrobial resistance and Cdifficile infections	Khumra et al 2017[37]
	52 SOT recipients with sulfa allergy	Desensitization was associated with significant cost savings with no adverse impacts on patient care	Pryor et al 2019[41]
Personalized prophylaxis	27 SOT recipients with CMV viremia	CMV-specific cell-mediated immune assay can be utilized to determine duration of antiviral therapy	Kumar et al 2017[42]

	519 Lung transplant recipients	BAL culture and galactomannan-directed pre-emptive therapy significantly reduced the risk of invasive Aspergillus infection and reduced the need for anti-fungal prophylaxis	Husain et al 2018[44]
Pre-operative prophylaxis	1424 surgical procedures on SOT recipients	Implementation of infection prevention bundle and standardized antimicrobial prophylaxis led to decreased surgical site infections and increased compliance with stewardship recommendations	Frenette et al 2016[47]

† SOT- Solid Organ Transplant,

‡ UTI – Urinary Tract Infection

§ CMV- Cytomegalovirus

Table 2: Examples of proposed antimicrobial stewardship (ASP) metrics for solid organ transplant patients

Type of metric	**Examples**
Process metrics	Antimicrobial consumption (daily dose (DDD), length of therapy, or days of therapy (DOT) Parenteral to oral conversion rates Duplicate antibiotic therapy

	Adherence to prescribing guidelines Provider acceptance of ASP recommendations
Outcome metrics	Rates of antimicrobial resistance Clostridium difficile infection rates Financial impact/cost savings Length of stay Readmission rates Mortality
Balancing metrics	Antimicrobial consumption (DOT or DDD) Drug-related adverse events Readmission rates Mortality Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR)

Figure legends:

Figure 1: Flow diagram detailing search and article selection strategy.

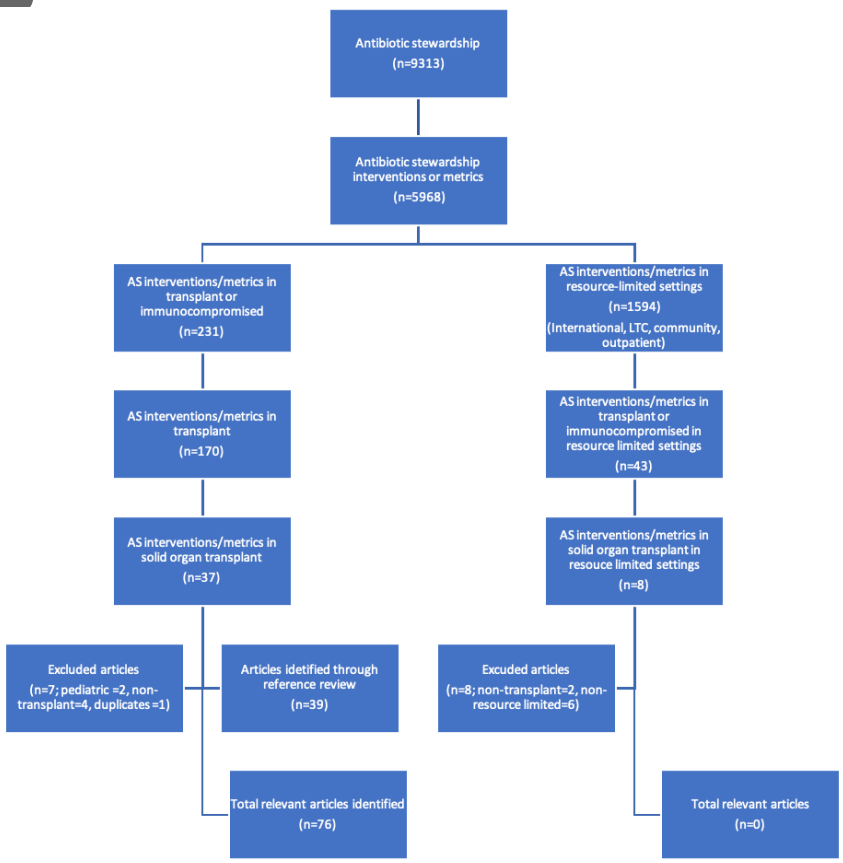

Figure 2. Multidisciplinary approach to antimicrobial stewardship in solid organ transplant patients.