Original Article

Perioperative antibiotic stewardship in the organ transplant setting

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Abstract

Background: Solid organ transplant (SOT) recipients can benefit from traditional antimicrobial stewardship (AMS) activities directed to improve judicious perioperative prescribing and management, but evidence is lacking. The aim of this expert opinion review is to provide an update on the current landscape of application of AMS practices for optimization of perioperative prophylaxis (PP).

Methods: We reviewed the available literature on early postoperative infectious complications in SOT and PP management, on modified perioperative approaches in case of infection or colonization in recipients and donors and on AMS in transplantation PP.

Results: SOT recipients are at high risk for early postoperative infectious complications due to the complexity of surgical procedures, severity of end stage organ disease, net state of immunosuppression in the posttransplant period and to the high risk for multidrug resistant organism. Moreover, SOT may be exposed to preservation fluid infections and expected or unexpected donor-derived infections. We summarize main factors to take into account when prescribing transplant PP.

Conclusion: Creating personalized PP to avoid unwanted consequences of antimicrobials while improving outcomes is an emerging and critical aspect in SOT setting. Further studies are needed to offer best PP tailored to SOT type and to evaluate interventions efficacy and safety.

Keywords

antimicrobial stewardship, donor derived infections, MDR, perioperative prophylaxis, preservation fluid, SOT

1 | Introduction

Solid organ transplant (SOT) recipients are at high risk for early postoperative infectious complications due to the complexity of surgical procedures, prior end stage organ disease, multiple comorbidities, the elevated net state of immunosuppression in the posttransplant period and to the high risk for colonization and infections caused by multidrug resistant organism (MDRO). In addition, perioperative infections in SOT recipients may be caused by preservation fluid infections (PFIs) and expected or unexpected donor-derived infections (DDIs), which may be graft specific or systemic.

According to the 2022 Centers for Disease Control and Prevention, surgical site infections (SSIs) are classified as superficial and deep incisional or organ/organ space infections occurring within 30 days from surgery or 90 days if a prosthetic device is used. In transplant
recipients, it is unclear whether early onset graft specific infections (e.g., early onset lower respiratory tract infection after lung transplantation) should also be considered SSI. Among most common infections occurring posttransplant, SSIs are reported between 3% and 53%, (up to 100% if a prosthetic device is used) with highest incidence in multivisceral transplant and lower in kidney transplant.5,6 SSIs in SOT setting have been associated with longer hospitalization, higher costs, increased graft failure, and mortality.5,7

It is important to underline that due to the wide range of etiologies, it is impossible to eliminate the risk of SSI in SOT setting, but creating personalized antimicrobial perioperative approaches to avoid unwanted consequences of antimicrobials while improving outcomes is an emerging and critical aspect of SOT medicine. The aim of this review is to evaluate the role of Perioperative Antibiotic Stewardship (PAS) in the specific setting of SOT taking into account the principles of antimicrobial stewardship (AMS).

1.1 AMS programs and perioperative AMS in SOT recipients

AMS programs lead institutional and individual efforts to promote responsible antimicrobial use to fight antimicrobial resistance and other consequences of antibiotic use, such as Clostridiodes difficile infection (CDI), drug interactions, and end-organ toxicities. AMS programs are multifaceted and affect both diagnostic programs, nonpharmaceutical interventions, and antibiotic prescriptions.

Diagnostic AMS involves adequate sampling measures before antimicrobial prescription, and it is of foremost importance in SOT due to the wide range of aetiologies of this special population.8 The fast expanding setting of molecular diagnostics is encouraging, but the clinical applicability of these diagnostic tools is uncertain.

Nonpharmaceutical interventions include strict adherence to infection prevention rules, and early withdrawal of invasive devices after surgery must be considered. Standard recommendation guidelines on nonpharmaceutical interventions include chlorhexidine gluconate 2% daily bathing during hospitalization, before and after transplant; minimal surgical time and optimal sterile technique; glucose and temperature control during surgery; minimizing blood loss; evaluation of local methicillin-resistant Staphylococcus aureus (MRSA) epidemiology, and the need for nasal and skin decontamination with topical nasal mupirocin and chlorhexidine bathing.1,9

There is the need for precision antimicrobial use. Antibiotic choice should be based not only on the antimicrobial spectrum but should take into account pharmacokinetic/pharmacodynamic characteristics according to the infection site and the patient end-organ failure, and potential allergies. After the prescription, duration and timing of administration should be clear, so as the need for redosing in long lasting surgeries. A multidisciplinary approach with collaboration with microbiologists and pharmacists contributes to the development of updated local guidelines with antibiotic susceptibility reports and evaluation of new available molecules.10

SOT recipients can benefit from traditional AMS activities directed to improve judicious perioperative prescribing and management, but evidence is lacking, although urgently advocated considering the great impact of MDRO in SOT population.11,12 AMS programs in immunocompetent hosts have shown good results in lowering antimicrobials use, improving patients’ outcome, appropriateness and duration of empiric and targeted therapy decreasing CDI rates, shortening length of hospital stay and, as final consequence, reducing health care costs.13–16 AMS programs in SOT should also make a step further into personalizing perioperative prophylaxis (PP) and treatments according to the type of transplantation and to the donor-recipient couple, always different and unique.

Measurements to evaluate success and failure in SOT have been categorized into three metrics: outcome measures, process measures, and balancing measures.11 Along with the well-known clinical, prescribing and health costs metrics, outcome measures in SOT should include graft impact and drug–drug interactions. Process measures, such as antimicrobial consumption and costs, are easier to collect than outcome measures. Lastly, balancing measures help avoiding a negative impact on aspects not directly involved in the AMS intervention (e.g., length of hospitalization vs. long-term impact on).

The result of the complexity of donor information, recipient clinical status, local epidemiology, availability of new antimicrobial molecules, and surgical techniques requires a face-to-face interaction between ASM staff members and other transplant physicians. A relatively recent concept in AMS, that is recommended in SOT setting, is the handshake stewardship (HS), based on daily rounds of members of AMS staff without any formulary restriction.17 HS has shown to reduce prescription rates, MDRO bacteremia incidence, antibiotic costs,18,19 with sustainable long-term effects.20 Due to its urgency, transplantation may occur at any time: in these cases, a phone or email consultation with an infectious disease (ID) physician would avoid under or overexposure to PP.21 but also in cases of living-donor, PP may be scheduled in an ID consultation. In the very early posttransplant, an active and proactive communication with microbiology is of main importance in order to modify prophylaxis or to turn it into therapy in cases of donor active infection.22,23 In addition, a regional and/or national network between transplant centers is the key to gather information about the donor.

1.2 Optimization of antimicrobial PP in SOT setting

PP during organ transplantation procedure is used mainly to prevent SSI as in nontransplant surgeries, but it may be beneficial to prevent DDI and graft specific infections as well.1 As a result, a one-size-fits-all kind of PP is not feasible in SOT populations as risk factors for acute posttransplant infections are different. According to the type of organ, pretransplant recipient condition, colonization and active infection at the time of transplant, donor infection and colonization at the time of procurement, local MDRO epidemiology and PF cultures, it is possible to tailor PP in order to mitigate early acute bacterial posttransplant infections (Tables 1 and 2).

As regards antimicrobials, their administration is crucial. To achieve therapeutic blood levels at the time of surgical incision and throughout
TABLE 1  Key elements of perioperative antibiotic stewardship in SOT recipients

- Transplantation surgery is unique as it involves an additional element of potential infection source: the graft
- Every type of organ entails different risk of SSI and different pathogens
- Donor management is essential to assist SOT recipients
- MDRO colonization of both recipient and donor should be known at the time of transplant
- Local epidemiology of recipient and donor areas should be taken into account
- Intraoperative redosing allows therapeutic blood levels throughout surgery
- End-organ failure or obesity should prompt antibiotic adjustment dose after loading dose
- Duration of PP should be adequate to the type of transplant and risk factors

Abbreviations: MDRO, multidrug resistant organism; PP, perioperative prophylaxis; SOT, solid organ transplant; SSI, surgical site infection.

surgery, antibiotics should be administered intravenously, within 60 min of surgical incision, and additional doses should be given when surgery lasts more than two half-lives of the drug, or if there is excessive blood loss during the procedure. In recipients affected by renal failure, hepatic failure, or obesity, dose should be adjusted following a standard loading dose. For lung transplant recipients, in the colonized donor or recipients, use of on-label or off-label nebulized antibiotics may also be considered in the immediate posttransplant.

Recommendations on standard PP of the joint members of American Society of Health-System Pharmacists (ASHP), the ID Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) compared to the 2019 updated American Society of Transplantation IDs (AST IDs) Community of Practice and our proposed approach are listed in Table 3.

Antimicrobials for PP should be adjusted according to donor and recipient colonization or infection at the time of transplant.

1.3  Antimicrobial PP by organs

Kidney transplant. SSIs rate in kidney transplant recipients is the lowest (3%–11%) among SOT recipients. Staphylococcus aureus, coagulase-negative Staphylococci (CoNS) and Enterococcus species are the most common organisms involved. First generation cephalosporins, namely cefazolin, has shown noninferiority to vancomycin and ceftiraxone in a randomized controlled trial (RCT), to ceftiraxone and to piperacillin/flucloxacillin in more recent retrospective studies. Duration of the PP should be limited to 24–48 h.

Pancreas, kidney-pancreas. In pancreas transplant or pancreas-kidney transplant recipients SSI rate is reported between 9% and 45% with the most frequent pathogens being S. aureus, CoNS, E. coli, and Klebsiella species in superficial SSI. In deep organ space SSIs enteric flora (Enterococci, Streptococci, anaerobes, Gram-negative organisms, and Candida) is more frequently involved. While IDSA/ASHP/SIS/SHEA suggests the use of first-generation cephalosporin, AST ID recommendations widen the spectrum to Staphylococci, anaerobes, and Candida with the use of ampicillin/sulbactam and fluconazole (Table 1). Only one RCT found no difference between vancomycin plus gentamicin versus ceftazolin plus gentamicin in preventing postoperative infections, and the role of antifungal prophylaxis is debated depending on the study design and the surgery technique. Our approach is in line with the use of fluconazole for 7–14 days, and we use a combination of Ampicillin-sulbactam 3 g for enteric Gram-positive and Gram-negative bacteria for 24–48 h after transplant. Fluconazole is added for 7–14 days as primary prophylaxis of yeasts infections.

TABLE 2  Factors influencing the choice of PP in SOT

| Type of organ | Donor | Recipient | Other |
|---------------|-------|-----------|-------|
| Most commonly involved microorganisms causing SSI and acute infections early post | Active infections at the time of procurement | Specific conditions of end stage organ disease affecting MDRO colonization (e.g., cystic fibrosis) | Allergy |
| Local epidemiology | Local epidemiology | Available molecules |
| Pre transplant colonization | PK/PD characteristics of the recipient (e.g., massive ascites, acute renal or hepatic failure) | Surgery-related risk factors (e.g., massive blood loss) |
| Preservation fluid culture |

Abbreviations: MDRO, multidrug resistant organism; PK/PD, pharmacodynamic/pharmacokinetic; PP, perioperative prophylaxis; SSI, surgical site infection; SOT solid organ transplant.
### TABLE 3

Recommendations for standard perioperative antibiotics by organ transplant type. All doses are intended intravenous

| Organ type       | 2013 IDSA/ASHP/SIS/SHEA guidelines | 2019 AST guidelines | Our approach                                      | Duration post op | Beta-lactams allergic |
|------------------|------------------------------------|---------------------|--------------------------------------------------|------------------|-----------------------|
| Kidney           | First generation cephalosporin      | Cefazolin 2 g       | Ampicillin-sulbactam 3 g                         | 24–48 h          | Ciprofloxacin 500 mg q12 |
|                  |                                    |                     | Piperacillin-tazobactam 4.5 g + fluconazole 400 mg (or Echinocandin or liposomal amphotericin B) if high risk for invasive fungal infections | 24–48 h          | Ciprofloxacin 500 mg q12 + Vancomycin |
|                  |                                    |                     | Ciprofloxacin 500 mg q12 + Vancomycin            |                  |                       |
| Liver            | Third-generation cephalosporin plus ampicillin or piperacillin-tazobactam alone | Ampicillin-sulbactam 3 g + fluconazole 400 mg x 1 or echinocandin or liposomal amphotericin B if high risk for invasive fungal infection (duration depends on the individual risk) | 24–48 h          | Ciprofloxacin 500 mg q12 + Vancomycin |
|                  |                                    |                     |                                                   |                  |                       |
| Heart            | Without prior VAD                   | Vancomycin plus cefazolin 2 g | Cefazolin 2 g If MRSA colonization: Vancomycin + cefazolin 2 g | 24–48 h          | Vancomycin            |
|                  | With prior VAD                      | Vancomycin plus either ceftriaxone 1 g or cefepime 2 g |                                                   |                  |                       |
| Lung             | First generation cephalosporin      | Vancomycin plus third-generation cephalosporin or cefepime 2 g | Ceftazidine 2 g + Vancomycin + fluconazole 400 mg or Echinocandin or Liposomal Amphotericin B if high risk for invasive fungal infections | 48–72 h          | Vancomycin plus levofloxacin 750 mg q24 |
|                  |                                    |                     |                                                   |                  |                       |
| Pancreas, kidney-pancreas | First generation cephalosporin | Ampicillin-sulbactam 3 g plus fluconazole 400 mg | Ampicillin-sulbactam 3 g + fluconazole 400 mg | 24–48 h          | Vancomycin + levofloxacin 750 mg q24 + Fluconazole 400 mg IV or Echinocandin or Liposomal Amphotericin B |
| Intestinal/multivisceral | N.A.                              | Vancomycin plus cefepime 2 g plus metronidazole 500 mg or vancomycin + piperacillin-tazobactam 4.5 g plus fluconazole 400 mg | Piperacillin-tazobactam 4.5 g + fluconazole 400 mg + Vancomycin or Echinocandin or Liposomal Amphotericin B | 48–72 h          | Vancomycin + levofloxacin 750 mg + tige 100 mg + h + Fluconazole 400 mg IV or Echinocandin or Liposomal Amphotericin B |

Note: Adapted and modified from Ref. (1).
Abbreviations: MRSA, methicillin-resistant Staphylococcus aureus; N.A., not applicable; VAD, ventricular assist device.

Liver. SSIs occur in 10%–37% of OLT patients. Due to the high exposure to intestinal microbiota, a narrow spectrum molecule such as first-generation cephalosporin is not sufficient to prevent postoperative infections as SSIs are most frequently caused by Gram-negative enteric infections. IDSA/ASHP/SIS/SHEA recommendations include the use of a third-generation cephalosporin plus ampicillin or piperacillin-tazobactam alone, while the AST ID suggests the use of ampicillin-sulbactam. In patients at risk for fungal infection (prolonged operative times, excessive blood transfusion, renal insufficiency requiring RRT, and re-operation), the addition of an azole, echinocandin, or liposomal amphotericin B may be considered. In line with this suggestion, we suggest the use of Piperacillin-tazobactam adding Fluconazole or a Echinocandin or liposomal amphotericin B if high risk for invasive fungal infections. Regarding the duration, we
Management of MDRO colonization in SOT recipient

MDRO colonization in SOT recipient has been associated with higher rate of related infections in several retrospective studies. An approach with topic decontamination and/or tailored PP should be considered on an individual basis.

Evaluation of local MRSA epidemiology and the need for nasal and skin decontamination with topical nasal mupirocin and chlorhexidine bathing is controversial but is usually recommended especially for cardiac and thoracic surgery. In patients with previous colonization with MRSA prophylaxis should be adjusted with the use of vancomycin especially in patients undergoing heart transplant and with cystic fibrosis patients undergoing lung transplant.

The use of targeted daptomycin PP in pretransplant Vancomycin-resistant Enterococci (VRE)-colonized recipient was effective in preventing posttransplant infections in a small cohort of liver transplant recipients. A modified PP in extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales-colonized patients has been observed to reduce the incidence of posttransplant ESBL infections after liver transplant (p = .04), and it is currently recommended by the Spanish guidelines. The use of amikacin has been found useful in a setting with a high prevalence of ESBL Enterobacterales infections.

The impact of gut decolonization with oral gentamicin with or without oral colistin has been observed to decrease carbapenem-resistant Enterobacterales (CRE) carriage rates in colonized patients but was associated with gentamicin and colistin resistance. However, to date there are insufficient data to support the systematic use of gut decontamination, and it is not supported by the current guidelines. When considering CRE, vancomycin-resistant Enterococcus, and carbapenem-resistant Acinetobacter baumannii, the use of targeted PP according to colonization was found to be the only protective factor for SSI after liver transplant (p = .01).

In lung transplant, recipient culture-oriented change in PP has not shown association with better outcomes in a low MDRO setting, while a prompt switch to donor colonization-targeted PP has been found to be a safe strategy in endemic MDRO areas. In Gram-negative MDRO-colonized recipient, the role of targeted PP according to MDRO colonization remains unknown, and thus it is not possible to recommend it. Pretransplant respiratory tract colonizing flora may be helpful in tailoring a PP in lung transplant recipients, especially in cystic fibrosis patients.

Data on PP modifications according to local epidemiology and specific MDRO prevalence threshold of the donor and recipient centers leading to adjusted prophylaxis are lacking, efficacy is unproven, and antibiotic pressure is a risk. Early empiric therapy in case of acute posttransplant infection may take into consideration MDRO epidemiology.
1.5 | Management of PF-related infections

PF cultures are not routinely performed worldwide. The modality of PF collection are not standardized, some centers collecting at three different stages of the transplant surgery, others only one. The role of PF cultures in predicting posttransplant infections and the relative mortality in transplant recipients is debated. In a recent meta-analysis, 13% of PF was found to be contaminated by a pathogenic organism (95% CI 9.0%–17.0%), with a low incidence of PF-related infections (4%), but a high mortality (35%) leading the authors to recommend routine PF cultures during procurement and transplantation. A Spanish multicentric study indicated that preemptive PF-driven antibiotic therapy decreases the incidence of PF-related infections and represents a protective factor against 90-day infection, although there is a concern for increased MDRO colonization and infections. Although not standardized, we recommend PF cultures whenever possible with a careful interpretation of the results made by a transplant ID specialist, particularly if a MDRO is isolated.

1.6 | Management of DDIs

Expected DDIs are an indication for modified PP. In donors with ongoing bacteremia at the time of organ procurement, prophylaxis should be prolonged up to 7–14 days. AST guidelines suggest modifying PP in lung transplant according to colonizing organisms of the respiratory tract of the donor. The impact of unanticipated DDI may be mitigated with a well-structured donor pre- and posttransplant management, which leads to a PP that takes into account data from donor culture and epidemiology. Early switch to appropriate treatment is crucial, especially in cases of MDRO infections, associated with high morbidity and mortality in SOT population. The use of rapid microbiology on donor and recipient cultures is crucial as it may lead to early modifications in the PP through a fast and effective communication from laboratory to the transplant ID physician. Indeed, it has been shown that a correct management and treatment of MDRO DDI leads to a safe transplantation.

2 | CONCLUSION

SOT recipients are at high risk for early postoperative infectious complications due to high risk for MDRO, donor, and recipient-related risk factors. Programs dedicated to stewardship in the organ transplant setting are vital as SOT may take a significant advantage from more precise and personalized perioperative management. Further studies evaluating intervention efficacy and safety are needed.

CONFLICT OF INTEREST
The authors have no conflict of interest to declare.

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EG, MP and PG performed the literature research and wrote the manuscript.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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