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Surgical site infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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Abstract

These guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the diagnosis, prevention, and management of post-operative surgical site infections (SSIs) in solid organ transplantation. SSIs are a significant cause of morbidity and mortality in SOT recipients. Depending on the organ transplanted, SSIs occur in 3%-53% of patients, with the highest rates observed in small bowel/multivisceral, liver, and pancreas transplant recipients. These infections are classified by increasing invasiveness as superficial incisional, deep incisional, or organ/space SSIs. The spectrum of organisms implicated in SSIs in SOT recipients is more diverse than the general population due to other important factors such as the underlying end-stage organ failure, immunosuppression, prolonged hospitalizations, organ transportation/preservation, and previous exposures to antibiotics in donors and recipients that could predispose to infections with multi-drug-resistant organisms.

In this guideline, we describe the epidemiology, clinical presentation, differential diagnosis, potential pathogens, and management. We also provide recommendations for the selection, dosing, and duration of peri-operative antibiotic prophylaxis to minimize post-operative SSIs.

KEYWORDS

antibacterial, antibiotic, antibiotic prophylaxis, infection, infectious agents, surgical infection, solid organ transplantation

1 | INTRODUCTION

Surgical site infections (SSIs) account for a majority of infections in the early post-transplant period in part due to the complexity of these operations (violation of multiple anatomic barriers), immunosuppression, and patient comorbidities. These infections are classified by increasing invasiveness as superficial incisional SSI, deep incisional SSI, or organ/space SSI.¹ The spectrum of organisms implicated in SSIs in SOT recipients is more diverse than the general population due to other important factors such as underlying end-stage organ failure, immunosuppression, prolonged hospitalizations, organ

transportation/preservation, and previous exposures to antibiotics in donors and recipients that could predispose to infections with multidrug-resistant organisms.

According to the Centers for Disease Control and Prevention (CDC), approximately 80 million operative procedures were performed in the United States (US) in 2006 (46 million in acute care hospitals).² In January 2019, the Organ Procurement and Transplantation Network (OPTN) reported that 36 527 solid organ transplants were performed in the US in 2018 from both deceased and living donors.³ To date, more than 750 000 organ transplants have been performed since 1988 in the US, the first full year national transplant data were collected.

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Though there has been progress in infection control practices, surgical site infections (SSIs) remain one of the most common healthcare-associated infections. SSIs are a significant issue in transplant recipients with higher rates of SSIs among SOT recipients than among non-SOT recipients who undergo comparable clean or clean-contaminated procedures.⁴ Depending on the

organ transplanted and the era of the report, SSIs have been reported to occur in 3%-53% of patients transplanted with the highest rates observed in small bowel/multivisceral transplants (where SSI rates can reach over 90% when prosthetic mesh is employed), followed by liver, and pancreas transplant recipients (Table 1).^{5,6} SSIs have been found to extend the average hospital stay by seven

TABLE 1 Predominant pathogens causing SSIs by organ transplant type

Organ transplant type	Incidence of SSIs (%)	Predominant pathogens causing SSIs	Secondary pathogens causing SSIs
Renal	3-11	<i>Staphylococcus aureus</i> CoNS <i>Enterococci</i>	Gram-negative organisms (Enterobacteriaceae, <i>Pseudomonas</i>) Yeast
Pancreas and pancreas-kidney	9-45	<i>Staphylococcus aureus</i> CoNS <i>Enterococci</i>	Gram-negative organisms (Enterobacteriaceae, <i>Pseudomonas</i>) <i>Streptococci</i> <i>Candida</i> spp <i>Mycoplasma hominis</i>
Liver	10-37	Gram-negative organisms (Enterobacteriaceae, <i>Acinetobacter</i> , <i>Pseudomonas</i>) <i>Enterococci</i> <i>Staphylococcus aureus</i> CoNS <i>Candida</i> spp	
Intestinal/ Multivisceral	14-53 Up to 100 if mesh used	Often polymicrobial Gram-negative organisms (<i>Pseudomonas</i> , <i>Escherichia coli</i> , <i>Klebsiella</i> spp) <i>Candida</i> spp Anaerobes <i>Enterococci</i>	<i>Staphylococcus aureus</i> CoNS
Heart	4-19	CoNS MRSA <i>Enterococci</i>	Gram-negative organisms (Enterobacteriaceae, <i>Pseudomonas</i> , <i>Stenotrophomonas</i>) <i>Candida</i> species
Lung	5-19	<i>Pseudomonas</i> spp <i>Escherichia coli</i> <i>Klebsiella</i> spp <i>Candida</i> spp <i>Staphylococcus aureus</i> <i>Enterococci</i> CoNS <i>Burkholderia</i> spp	<i>Stenotrophomonas</i> <i>Aspergillus</i>

Abbreviations: CoNS, coagulase-negative *Staphylococci*; MRSA, methicillin-resistant *Staphylococcus aureus*; spp, species; SSI, surgical site infection.

days, increase readmission rates, and increase the cost of hospitalization by nearly 100%.^{7,8} SSIs have also been associated with increased graft failure as well as mortality in SOT recipients.⁹⁻¹³ Thus, it is crucial to minimize SSIs.

SOT recipients are also at high risk of developing infections with antibiotic-resistant organisms.¹⁴⁻¹⁶ Infections with multidrug-resistant organisms (MDROs) have been associated with increased morbidity and mortality, particularly in SOT recipients.^{15,17} For example, one study evaluating outcomes among liver and kidney transplant recipients found that among those infected with a carbapenem-resistant *Acinetobacter baumannii*, 67% died due to the infection.¹⁷ The increased risk for infection, including SSIs, with MDROs is likely related to the high degree of pre-transplant exposure to antibiotics and hospitals, which are known risk factors for development of MDRO colonization and infection.^{16,18} SSIs account for \$3.2 billion USD in attributable cost per year in acute care hospitals with an estimated additional eleven days of hospitalization per SSI per patient¹⁹ and represent the most frequent cause of unplanned readmissions after surgery.²⁰ No data are published to date regarding the overall cost (nationally or internationally) of SSIs in transplanted organs.

1.1 | Clinical presentation and definitions

According to the 2019 Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) Patient Safety Manual, Surgical Site Infections,²¹ surgical site infection (SSI) definitions include superficial and deep incisional infections, and organ/organ space infections that occur within 30 days of the surgical procedure or 90 days if a prosthetic implant is used. Superficial and deep wound infections do not differ between general surgical and transplant surgical patients. Nevertheless, the spectrum of pathogens implicated in surgical site infections in solid organ transplant recipients is much more diverse²²⁻²⁴ due to various factors, such as underlying illness, end-stage organ failure and colonization of the organ recipient, colonization or active infection in the organ donor, and the use of immunosuppressive therapy. Organ/space infections include any part of the body that is opened or manipulated during an operative procedure. In addition, at least one of the following must also be present: purulent drainage from a drain placed through a stab wound to the organ space (which plays no role in transplant surgery); organisms isolated from a culture of the fluid or tissue in the organ space; an abscess or other evidence of infection found on direct examination, during re-operation, or by histopathologic or radiologic examination; or clinical diagnosis of surgical site infection by a surgeon or attending physician. This definition has some limitations in transplantation as the graft itself may become a source of infection. One has to bear in mind that human allografts may be contaminated and once transplanted, infection may develop within the graft. It is not clear whether early onset pneumonia after lung transplantation, pyelonephritis after kidney transplantation, or cholangitis after liver transplantation should be considered surgical site infections.

1.2 | Differential diagnosis

Local signs of pain, swelling, erythema, and purulent drainage provide the most reliable information in diagnosing a SSI. In addition, many patients with a SSI will develop fever and/or leukocytosis. However, local signs and symptoms may not always be present, nor are they necessarily due to infection when they are present. Flat, erythematous skin changes can occur around or near a surgical incision during the first week without swelling or wound drainage and most resolve without any treatment. The cause is unknown but may relate to tape sensitivity or other local tissue insult not involving bacteria. The presence of purulence within a surgical incision generally serves as initial evidence of a SSI, but culture results of surgical wounds or exudates should be used as a guide to the presence or absence of infection.

Deep SSIs also have a broad differential diagnosis; some patients develop non-infectious hematomas, seromas, urinary leaks (kidney or kidney/pancreas SOT), biliary or pancreatic leaks, and sterile drainage from abdominal or cardiothoracic surgeries. In all of these scenarios, it is important to remember that suspicion of possible SSI alone does not justify use of antibiotics, but requires a careful clinical, laboratory, physical examination and diagnostic imaging, comprehensive evaluation of the patient. The surgical transplant team and infectious diseases consultants should be in close communication to decide when a surgical exploration or percutaneous drainage is indicated to control the source of infection.

1.3 | Potential pathogens

The most common bacterial pathogens vary according to the type of transplant and are described in detail in the following paragraphs and Table 1. *Staphylococcus aureus*, coagulase-negative staphylococci, and enterococci are most frequently involved in SSIs in heart, kidney, and pancreas-kidney transplantation while Gram-negatives are prevalent following liver, intestinal, and lung transplantation. However, over the past decade, the microbiology of SSIs is evolving because of the emergence of various multidrug-resistant pathogens, particularly multidrug-resistant Gram-negative organisms.

1.4 | Risk factors and preventive strategies

Reducing SSIs requires a multi-faceted approach; antimicrobials alone are insufficient to prevent this complication. Individual organ risks will be discussed in subsequent sections of this guideline. Overall, minimizing surgical operative time and optimizing sterile technique, surgical technique, and peri-operative management of patient comorbidities as well as glucose and temperature regulation are imperative to limit SSIs.²⁵⁻²⁹ Normothermia, oxygenation, and glycemic control protocols are beyond the scope of this manuscript. The 2017 Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection provides evidence-based graded recommendations for the general population that are applicable to solid organ transplantation.³⁰

Transfusion of packed red blood cells has an immunosuppressive role and serve as an indirect marker of intra-operative complication (from two units of blood to massive transfusion protocols).³¹ Patient's hemoglobin should be maintained at levels just sufficient to provide adequate oxygenation to the tissues. The peri-operative management goal should be always focused toward safe transfusion-free transplantation and minimizing blood loss of any kind. Minor bleeding should not be always managed by simple packing only but more dependable measures such as argon beam electrocautery and suture ligation whenever required. The role of the anesthesiologist in blood management is critical in maintaining central venous pressures, glycemic control below 200 mg/dL, and avoidance of hypothermia that can help to prevent temperature-related coagulopathy.³²

Chlorhexidine gluconate (CHG) is a potent, safe, and effective topical disinfectant agent that has been used for over 50 years for skin antisepsis and bathing. It has multiple applications including skin antisepsis before surgery or central line insertions and as pre-operative and post-operative daily chlorhexidine bathing/showering in patients older than two months of age. Preadmission whole-body cleansing and peri-operative skin prepping with 2% or 4% CHG has been documented to be a safe and effective risk reduction strategy for preventing SSI by a wide range of pathogens in particular Gram-positive organisms.³³⁻³⁶ A recent study by Patel et al³⁷ did not identify the same benefit in preventing healthcare-associated infections with Gram-negative organisms, but the study was focused on healthcare-associated infections not specific to SSIs or SOT recipients. Several studies have been reported in bone marrow transplant centers evaluating the efficacy of daily bathing/showering of patients with 2% CHG and demonstrating a reduction in hospital-associated infections with multidrug-resistant Gram-positive organisms.^{38,39} A recent case report of anaphylaxis to CHG in a patient undergoing LVAD and transplantation highlights the importance of careful allergy history before using this product and potential that some patients might rarely develop hypersensitivity or anaphylaxis.⁴⁰ We are not aware of studies focused on the use of CHG skin antisepsis or bathing in solid organ transplant recipients to prevent SSIs.

- We recommend daily bathing with CHG 2% in SOT in hospitalized patients pre-transplant during the hospital stay; at the time of organ offer before going to the operating room; and post-operatively during the entire hospitalization to reduce colonization and infections with Gram-positive organisms including SSIs as standard of care (strong, low).

Staphylococcus aureus nasal or rectal colonization is frequent in transplanted patients, and an important cause of SSIs as well as sepsis. Additionally, cirrhotic patients show greater *S aureus* colonization rates, and the association between staphylococcal colonization and infection has been demonstrated in several studies.⁴¹ In a retrospective cohort, both methicillin-sensitive and methicillin-resistant *S aureus* colonization was also an independent factor for post-transplantation infection ($P = 0.0004$ and $P < 0.0001$; respectively).⁴² Hashimoto et al⁴³ demonstrated that transplant recipients colonized

with MRSA had higher infection rates (odds ratio 3.5) compared to those non-colonized ($P = 0.001$).

Decolonization strategies to prevent post-operative Staphylococcal infections including SSIs using topical nasal mupirocin have been evaluated in several studies with controversial results.⁴⁴ Paterson et al⁴⁵ evaluated decolonization with nasal mupirocin in a cohort liver transplant candidates and recipients colonized by *S aureus*; during the study, 37% patients were recolonized. Seven of these patients, previously colonized by methicillin-sensitive *S aureus*, were recolonized by MRSA. The authors emphasized that intestinal MRSA could be a source that cannot be eliminated by nasal mupirocin and chlorhexidine bathing. Besides, mupirocin resistance has been described.

Lee et al⁴⁶ reported preliminary results using universal decolonization with topical mupirocin and daily CHG bathing in kidney transplant recipients with a reduction in Staphylococcal infection rates in the intervention group compared to a small control. Because the intervention was a bundle, we cannot attribute the effectiveness to the nasal decolonization alone as it was not evaluated. In a meta-analysis by van Rijem et al⁴⁷, nasal mupirocin reduced colonization and *S aureus* infection after transplantation ($P = 0.02$, RR 0.55, and 95% CI 0.34-0.89). Clancy et al⁴⁸ used a computer simulation model to estimate the cost-effectiveness of routine *S aureus* screening and decolonization among lung and heart-lung transplant recipients. The baseline rates of *S aureus* colonization, infection, and decolonization efficacy were 9.6%, 36.7%, and 31.9%, respectively. Screening and decolonization were economically dominant for all scenarios tested, providing more cost savings and health benefits than no screening. Savings per case averted (2012 \$US) ranged from \$73 567 to \$133 157 (hospital perspective) and \$10 748 to \$16 723 (third party payer perspective), varying with the probability of colonization, infection, and decolonization efficacy. According to that study, the authors reported that screening and decolonization led to cost savings per case averted of \$240 602 (hospital perspective) and averted 6.7 *S aureus* infections (4.3 MRSA and 2.4 MSSA); 89 patients needed to be screened to prevent one *S aureus* infection in lung and heart-lung transplant patients.

- We recommend that transplant centers evaluate the local prevalence of *S aureus* colonization and SSIs and tailor the use of nasal decolonization to their individual population. In some centers, the heart and lung transplant population might be at higher risk than kidney or pancreas recipients although in other centers, all transplant patients might be at increased risk based on the local prevalence of MRSA in the community or the local hospital (strong, moderate).

1.5 | Peri-operative antibiotic prophylaxis

Another strategy is the use of peri-operative antibiotic prophylaxis to minimize the bacterial load in the surgical wound and thereby optimizing the environment for healing. It is the standard of care

for nearly all surgical procedures including SOT. Although there have been intermittent reports that question its efficacy,^{5,49} evidence points to a benefit of peri-operative antibiotic prophylaxis in reducing post-operative SSIs in SOT recipients.⁵⁰⁻⁵⁶ However, specific antibiotic regimens and durations vary widely across transplant centers and SOT procedures, and the quality of the evidence supporting specific practices is varied.⁵⁷ Currently, there are no formal recommendations on peri-operative antibiotic prophylaxis in SOT outside of the “Clinical practice guidelines for antimicrobial prophylaxis in surgery” by the Infectious Diseases Society of America, American Society of Health-System Pharmacists, Surgical Infection Society, and Society for Healthcare Epidemiology of America (IDSA/ASHP/SIS/SHEA guidelines). A recent review by Anesi et al⁵⁸ proposes changes and more structured formal recommendations for antimicrobial prophylaxis in transplantation as there is a need to address the unique circumstances of the transplant population in many parts of the world such as recipient colonization with a multidrug-resistant organism (MDRO) pre-transplantation or the presence of a ventricular assist device (VAD) prior to heart transplantation.⁵⁹

Considering the morbidity, mortality, frequency, and increased risk for SSIs due to MDROs among SOT recipients, the peri-operative antibiotic prophylaxis given to SOT recipients should be optimized to prevent and minimize the risk of these infections and personalized for selected cases based on history of donor or recipient infection or colonization. In SOT recipients, peri-operative antibiotic prophylaxis should be optimized for each organ type and each patient. The choice of antibiotic regimen depends on the type of SSIs that are most common (superficial, deep, or organ space infections), the organisms that most often cause SSIs in each population, and the specific risk factors that each patient has going into surgery that may alter their risk for SSIs or SSIs with specific organisms. Unfortunately, there have been only two prospective randomized clinical trials assessing the impact of antibiotic prophylaxis on SSIs in SOT recipients, and both included fewer than 125 patients.^{60,61} Further, only one compared different regimens, and neither evaluated the impact of the duration of prophylaxis on recipient outcomes. To our knowledge, there are no randomized trials that have evaluated the duration of peri-operative antibiotic prophylaxis in SOT recipients.

Though the choice of antibiotic regimen is of great significance, accurate timing of antibiotic dosing is equally important. Peri-operative antibiotics have the most impact on reducing SSIs when administered within 60 minutes of surgical incision.⁶² However, in a recent meta-analysis of 14 studies including over 54 000 patients, the authors point out that there is no strong evidence to substantiate the 60-min timeframe and concluded that the lowest risk of SSIs is within <120 minutes.⁶³ The rationale for the timing is to achieve appropriate antibiotic tissue levels at the time of incision and at the time of wound closure. If the antibiotic must be administered over 1-2 hours (eg, vancomycin or levofloxacin), the infusion should be started 120 minutes before the incision.⁵⁹ All peri-operative antibiotics should be given intravenously rather than enterally, as the time to therapeutic blood levels is faster and

more predictable with the intravenous route. The peri-operative dose should be weight-based, particularly in obese patients (including cefazolin, which should be increased to 3 g when the patient's weight is over 120 kg⁵⁹). During the procedure, re-dosing of antibiotics may be necessary, especially in the setting of cardiopulmonary bypass, depending on the half-life of the agent(s) being employed. It has been shown that SSIs are less common when the peri-operative antibiotics still have detectable levels in tissue at the conclusion of the procedure.^{62,64-66}

The current recommendation is that antibiotics should be re-dosed intra-operatively if the procedure lasts more than two half-lives of the drug or if there is excessive blood loss during the procedure.^{59,62,64-66}

In the following sections, we will review the epidemiology and risk factors for SSIs in each organ transplant type, as well as any data related to the use of specific prophylaxis regimens in each organ type.

2 | EPIDEMIOLOGY, RISK FACTORS, AND RECOMMENDED PERI-OPERATIVE ANTIBIOTIC PROPHYLAXIS FOR SOLID ORGAN TRANSPLANT RECIPIENTS BY ORGAN

Given the complexities of SOT and the unique risks for SSIs, guidance that is more customized to each SOT scenario is needed. Consequently, in this guideline, we describe the epidemiology and risk factors for SSIs and evidence-based recommendations for peri-operative antibiotic prophylaxis regimens individualized by organ transplant type.

2.1 | Renal transplantation

2.1.1 | Epidemiology of SSIs

Renal transplant (RT) recipients experience the lowest rate of SSIs among all SOT types, with rates estimated between 3% and 11% (Table 1).^{5,9,67,68} However, when they do occur, SSIs have significant impact on RT recipient outcomes with reduced graft survival.^{9,69}

Risk factors for SSIs in RT recipients (Table 2) include host factors such as diabetes mellitus (DM), obesity, chronic glomerulonephritis (GN), re-operation; surgical factors such as ureteral leak, hematoma, intra-operative blood transfusion; allograft factors including acute graft rejection, delayed graft function (DGF), donor factors such as donor infection; and immunosuppression factors including use of antithymocyte globulin (ATG), azathioprine, mycophenolate mofetil (MMF), or sirolimus.^{9,69-72}

The most common organisms causing SSIs among RT recipients (Table 1) are Gram-positive organisms including *S aureus*, coagulase-negative *Staphylococci* (CoNS), and *Enterococcus* species. Less commonly, Gram-negative organisms and yeast can also cause SSIs.^{5,70,73,74} As with most SOT types, there have been reports of increasing MDROs causing SSIs in renal transplantation including methicillin-resistant *S aureus* (MRSA), drug-resistant *Escherichia coli*, and MDR *Klebsiella pneumoniae*.^{5,70,75}

TABLE 2 Risk factors for SSI by organ transplant type

Organ transplant type	Risk factor categories			
	Host factors	Surgical factors	Donor/allograft factors	Immunosuppression
Renal	DM	Ureteral leak	DGF	Azathioprine
	Obesity	Hematoma	Contamination of kidney perfusate	ATG
	Chronic GN	Blood transfusion	Acute graft rejection	MMF
	Re-operation			Sirolimus
Pancreas, pancreas-kidney	Re-operation	Prolonged operative time	Donor > 55 y old	
		Prolonged ischemic time	ATN in transplanted kidney	
		Enteric drainage	Graft rejection	
		Post-transplant fistula		
		Hand sewn anastomosis		
		Blood transfusion		
Liver	Prolonged ICU or hospital stay	Prolonged duration of surgery	Donor infection	Muromonab-CD3
	Prior hepato-biliary surgery	Anastomotic leak	Acute rejection	
	Prior liver or renal transplantation	Roux en Y biliary anastomosis		
	Antibiotic use in the prior 3-4 mo	Blood transfusion		
	High pre-transplant MELD score	Entry into GI tract		
	Ascites	Post-transplant RRT		
	Obesity			
	DM			
	Hemochromatosis			
Intestinal/multivisceral	Increased age	Use of surgical mesh		Daclizumab
	Hospitalization before transplantation	Re-intervention in the first month		MMF
	Re-transplantation	Contamination of the surgical field		
		Entero-cutaneous fistulas		
		Skin flaps		
		Post-transplant RRT		
		Staged procedures		
Heart	Increased age	Prolonged ischemic time	Donor colonization (particularly with Gram-negative organisms)	mTOR inhibitors
	Ciprofloxacin alone for prophylaxis	Use of bilateral internal mammary arteries		
	Prolonged mechanical ventilation			
	Positive wire cultures			
	Obesity			
	Prior cardiac procedure			
	Prior VAD			
	DM			
	Recipient colonization/infection			
	Re-operation			
	Re-transplantation			

(Continues)

TABLE 2 (Continued)

Organ transplant type	Risk factor categories			
	Host factors	Surgical factors	Donor/allograft factors	Immunosuppression
Lung	Impaired renal function	Re-exploration post-transplant due to bleeding	Colonization of the donor (particularly with a Gram-negative organisms)	
	Prior sternotomy	Prolonged ischemic time		
	Recipient colonization	Blood transfusions		
	DM			
	Repeat transplantation			

Abbreviations: ATG, antithymocyte globulin; ATN, acute tubular necrosis; DGF, delayed graft function; DM, diabetes mellitus; GI, gastrointestinal; GN, glomerulonephritis; ICU, intensive care unit; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil; mTOR: mechanistic target of rapamycin; ppx, prophylaxis; RRT, renal replacement therapy; VAD, ventricular assist device.

2.1.2 | Peri-operative antibiotic prophylaxis

There have been two prospective randomized controlled trials evaluating antibiotic prophylaxis in renal transplantation. The first trial found that there was a significantly lower rate of SSIs during the first five days post-transplant in the group that was given prophylaxis compared to the group that did not receive antibiotic prophylaxis; this difference did not persist at 14 days post-transplant.⁶⁰ The second trial compared the use of vancomycin plus ceftriaxone to cefazolin alone for peri-operative prophylaxis and found no difference in the rate of post-operative infections between groups.⁶¹ There have also been several retrospective studies among RT recipients that have reported a lower rate of SSIs when antibiotic prophylaxis is used peri-operatively.^{50,76–80} Studies have not shown any improvement when multiple agents are used (rather than a single agent).^{60,61,78} Further, studies have shown no difference in SSI rates between those who are given an anti-*Staphylococcal* penicillin and those who are given a cephalosporin.⁷⁹ Rates of SSIs were also not found to be notably different in a study using a third-generation cephalosporin (ceftriaxone) as compared to studies in which first-generation cephalosporins were used.^{61,81} In contrast to these studies, however, there was one recent study that found a significant reduction in SSIs when amikacin was used in peri-operative prophylaxis as compared to a cephalosporin⁷¹; this may have been related to the fact that the predominant organisms causing SSIs in this study were extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, which were resistant to cephalosporins but susceptible to amikacin. These data suggest that in most cases, a single first-generation cephalosporin is adequate for peri-operative prophylaxis.

Given these data, the recommendation in the IDSA/ASHP/SIS/SHEA guidelines is to use a single first-generation cephalosporin for RT recipients.⁵⁹ We agree with this approach and would similarly limit the prophylaxis to ≤ 24 hours. (See Table 3 for dosing details and for alternatives for penicillin-allergic patients). However, we would consider altering this approach if the recipient is being treated for an infection at the time of SOT, as that prior infection should likely

continue to be covered during the peri- and intra-operative period. Further research is needed to determine whether pre-transplant colonization in the donor and/or recipient should impact the peri-operative antibiotic prophylaxis selection. (See section below on recipient/donor infection or colonization with MDROs for further details.)

- We recommend a first-generation cephalosporin for ≤ 24 hours for peri-operative antibiotic prophylaxis in renal transplantation (strong, low).
- We recommend for patients known to be colonized with an organism resistant to first-generation cephalosporin to use a third-generation cephalosporin or an appropriate alternative agent passed on individual susceptibilities and local formulary for ≤ 24 hours for peri-operative antibiotic prophylaxis in renal transplantation (strong, low).
- We recommend for patients with severe allergy to cephalosporins to use an alternative agent such as a fluoroquinolone or aztreonam (weak, low).
- We recommend that if the patient is being treated for an active infection at the time of organ transplantation, the antibiotic regimen should be altered to target specific pathogens based on the current infection and individual risk factors (strong, moderate).

2.2 | Pancreas and pancreas-kidney transplantation

2.2.1 | Epidemiology of SSIs

SSIs are reported to occur in between 9% and 45% of pancreas transplant (PT) or simultaneous pancreas-kidney (SPK) transplant recipients (Table 1).^{10,82–90} This higher rate may be explained by the clean-contaminated nature of these procedures and the presence of DM in all PT recipients, which is a known risk factor for infections post-transplant. The type of SSI varies by the pancreatic duct drainage technique. When enteric drainage is used, SSIs involving intra-abdominal spaces are more common; when bladder drainage

TABLE 3 Recommendations for peri-operative antibiotics by organ transplant type

Organ type	IDSA/ASHP/SIS/SHEA guidelines	An alternative approach	Intra-op re-dosing	Post-op dosing	PCN-allergic	Duration post-op
Renal	Single first-generation cephalosporin (eg, cefazolin)	Cefazolin 2 g IV	Every 4 h	Cefazolin 2 g q8h	Vancomycin ^b or clindamycin 900 mg IV plus gentamicin 5 mg/kg IV	≤24 h
Pancreas, pancreas-kidney	Single first-generation cephalosporin (eg, cefazolin)	Ampicillin-sulbactam 3 g IV plus fluconazole 400 mg IV	Every 2 h (fluconazole not re-dosed)	Ampicillin-sulbactam 1.5 g q6h	Vancomycin ^b or clindamycin 900 mg IV and gentamicin 5 mg/kg IV and fluconazole 400 mg IV	Antibacterial ≤48 h, Antifungal ×1 dose, unless high risk in which case ≤14 d
Liver	Third-generation cephalosporin plus ampicillin or piperacillin-tazobactam alone	Ampicillin-sulbactam 3 g IV ± fluconazole 400 mg IV × 1 or echinocandin or liposomal amphotericin B if high risk for invasive fungal infection (duration depends on the individual risk)	Every 2 h (fluconazole not re-dosed)	Ampicillin-sulbactam 1.5 g q6h	or echinocandin or liposomal amphotericin B if high risk for invasive fungal infection (duration depends on the individual risk)	and antifungal agent and duration depends on the individual risk
Intestinal/multivisceral	None given	Vancomycin ^b plus cefepime 2 g IV plus metronidazole 500 mg IV plus fluconazole 400 mg IV or vancomycin ^b plus piperacillin-tazobactam 4.5 g IV plus fluconazole 400 mg IV	Every 4 h (fluconazole not re-dosed)	Cefepime 2 g q8h, metronidazole 500 mg q8h, fluconazole 400 mg q24h, piperacillin-tazobactam 4.5 g q6h, Vancomycin per weight/GFR ^b	Vancomycin ^b plus levofloxacin 750 mg IV plus metronidazole 500 mg IV	≤72 h, if infected mesh or fistulas, then extend to 7 d
Heart	With prior VAD Without prior VAD	Single first-generation cephalosporin (eg, cefazolin) Vancomycin ^b plus either ceftriaxone 1 g IV or cefepime 2 g IV Vancomycin ^b plus cefazolin 2 g IV	Every 4 h Every 4 h	Cefepime 2 g q8h, Vancomycin per weight/GFR ^b Cefazolin 1 g q8h, Vancomycin per weight/GFR ^b	Vancomycin ^b plus levofloxacin 750 mg IV q24h Vancomycin ^b plus levofloxacin 750 mg IV q24h	≤48 h ≤48 h
Lung	Single first-generation cephalosporin (eg, cefazolin)	Vancomycin ^b plus third-generation cephalosporin or cefepime 2 g IV	Every 4 h	Cefepime 2 g q8h, Vancomycin per weight/GFR ^b	Vancomycin ^b plus levofloxacin 750 mg IV q24h	≤72 h

Abbreviations: g, grams; GFR, glomerular filtration rate; h, hours; IV, intravenous; kg, kilograms; mg, milligrams; PCN, penicillin; q, every; VAD, ventricular assist device.

^aAll dosing regimens should be modified based on the patient's renal and liver function.^bVancomycin doses should be calculated based on the patient's weight and renal function.

is used, SSIs involving the genitourinary tract, for example urinary tract infections (UTIs), are more common.^{82,87} If bladder drainage is used, UTI rates within the first 3 months post-transplant have been reported as high as 48%.^{87,91} SSIs have a significant impact on PT and SPK transplant recipient outcomes, as SSIs that involve the deep organ space have been associated with longer hospital length of stay, increased graft loss, and increased patient mortality.^{10,88-90,92}

Risk factors for SSIs following PT or SPK transplantation (Table 2) include host factors such as re-operation; surgical factors including SPK, prolonged operative time, prolonged ischemic time (>4 hours), enteric drainage (rather than bladder drainage), post-transplant fistula, hand sewn anastomoses (rather than stapled anastomoses), blood transfusion; donor factors such as an organ donor over 55 years old; and allograft factors such as acute tubular necrosis (ATN) in the allograft or graft rejection.^{10,92-94} Bladder exocrine drainage has been associated with higher risk of infection in some studies.^{89,95-97} Of note, use of peritoneal dialysis (rather than hemodialysis) pre-transplantation has not been associated with an increased risk for intra-abdominal infections post-transplantation,⁹⁸ and there was no difference found in the SSI rate between patients who were given tacrolimus vs cyclosporine.⁹⁹

The most common organisms causing SSIs in pancreas transplantation depend on the location of the SSI (Table 1). In superficial SSIs, *S aureus*, CoNS, and Gram-negative organisms, particularly *E coli* and *Klebsiella* species, are most common.^{10,92} In deep organ space SSIs, *Enterococci*, *Streptococci*, anaerobes, Gram-negative organisms, and *Candida* species are more common.¹⁰ Overall, Gram-positive organisms dominate (about 66% of SSIs) with Gram-negative organisms and *Candida* occurring less frequently (around 19% and 15% of SSIs, respectively).¹⁰⁰ As with other SOT types, there are reports of increasing MDROs including one study published in 2009 that found the majority of SSIs at their center were due to *Klebsiella* species, and 42% of the *Klebsiella* species produced an ESBL.⁹² *Mycoplasma hominis* is less frequent but should be considered as a potential etiological agent in the differential diagnosis of post-transplant surgical site infection when there is no response to broad-spectrum β -lactams.^{101,102}

2.2.2 | Peri-operative antibiotic prophylaxis

There has been one prospective randomized controlled trial evaluating antibiotic prophylaxis in PT transplantation. This trial included predominantly RT recipients, but there were also 24 PT recipients included; this study found no difference between vancomycin plus gentamicin vs cefazolin plus gentamicin when evaluating post-operative infections.⁶¹ Outside of this trial, there are only retrospective studies evaluating surgical prophylaxis in PT recipients. These retrospective studies have shown a reduction in the rate of SSIs with the use of prophylaxis from 7%-50% to 7%-33%.^{10,85,91,103-105} In a single observational study, fluconazole has been shown to reduce the risk for *Candida* SSIs from 10% to 6% in PT.⁵²

Since the most common type of SSI is superficial and caused by Gram-positive skin flora, the recommendation by the IDSA/ASHP/SIS/SHEA guidelines is to use a first-generation cephalosporin.⁵⁹

In our experience, however, based on the diverse array of possible etiologies of SSIs, broader coverage may be indicated; a possible alternative would be to use ampicillin-sulbactam plus fluconazole (Table 3). There is, however, only anecdotal experience supporting this. As with every organ transplant type, we would also consider revising this regimen based on recipient and donor infection as described below.

Most studies among PT and SPK transplant recipients use a duration between 48 and 72 hours for antibiotic prophylaxis.^{10,85,91,103-105} Fluconazole use has ranged from 1 to 28 days in studies and clinical practice.⁵² There are no data to specifically support a prolonged duration of antibacterial or antifungal prophylaxis, so we typically limit the ampicillin-sulbactam to ≤ 48 hours and the fluconazole to ≤ 14 days. In most cases, fluconazole does not need to be extended beyond a single dose; more prolonged durations should be reserved for patients with specific risk factors for fungal infection such as enteric drainage, vascular thrombosis, post-perfusion pancreatitis, post-perfusion pancreatitis, acute rejection, poor initial allograft function, anastomotic problems, hemodialysis, laparotomy after transplantation^{106,107} (see Table 3 for dosing details and for alternatives for penicillin-allergic patients).

- We recommend ampicillin-sulbactam for ≤ 48 hours and a single dose of fluconazole. We recommend the use of longer durations of fluconazole for patients with specific risk factors for fungal infection from 7 to up to 14 days (strong, low).
- We recommend that if the patient is being treated for an active infection at the time of organ transplantation, the antibiotic regimen should be altered to target specific pathogens based on the current infection and individual risk factors (strong, moderate).

2.3 | Liver transplantation

2.3.1 | Epidemiology of SSIs

SSIs in liver transplantation (OLT) can involve the superficial soft tissue as well as deep organ space including peritonitis. SSIs are relatively common in liver transplant recipients, occurring in 10%-37% of patients (Table 1).^{12,108-115} SSIs post-OLT have been associated with increased graft loss and mortality at one year.^{12,113}

Risk factors for SSIs in liver transplantation (Table 2) include host factors such as prolonged intensive care unit (ICU) or hospital stay, antibiotic use in the prior 3-4 months, DM, hemochromatosis, high pre-transplant model for end-stage liver disease (MELD) score, ascites, obesity, prior hepato-biliary surgery, prior liver or renal transplantation; surgical factors such as prolonged duration of surgery (>8-12 hours), Roux en Y biliary anastomosis, bacterial contamination due to entry into the GI tract, >4 units of red blood cells required in surgery, anastomotic leak; donor factors such as donor infection; allograft factors such as acute rejection after liver transplant; need for renal replacement therapy (RRT) post-transplant; and

immunosuppression factors such as use of muromonab-CD3 within the first week after transplantation.^{12,108-118} There was no difference found in the rate of SSIs between those patients given tacrolimus and those given cyclosporine immunosuppression.¹⁰⁹

The most common organisms causing SSIs in OLT recipients are Gram-negative organisms (predominantly Enterobacteriaceae, *Acinetobacter* species, and more rarely *Pseudomonas*); there are also high rates of infection with Enterococci, *S aureus*, coagulase-negative *Staphylococcus* spp, and *Candida* species (Table 1).^{108,110,114,115,119} OLT recipients have particularly high rates of MDROs reported, predominantly with vancomycin-resistant Enterococci (VRE), ESBL Enterobacteriaceae,⁷⁴ and carbapenem-resistant Enterobacteriaceae^{120,121}; one study reported 13% ESBLs among Enterobacteriaceae isolates.¹¹⁹ Use of pre-transplant antibiotics (eg, for spontaneous bacterial peritonitis prophylaxis) has been associated with lower overall rates of SSIs but an increased risk for intra-abdominal infection post-transplant with an MDRO.^{114,115}

2.3.2 | Peri-operative antibiotic prophylaxis

Due to the high rate of SSIs in OLT recipients, peri-operative prophylaxis is routinely employed although there are no prospective randomized controlled studies evaluating antibiotic prophylaxis in this population. Further, studies have come to differing conclusions regarding whether there is any benefit to broader antibiotics over a first-generation cephalosporin. One study published in 2008 found no difference in the rate of SSIs when comparing amoxicillin-clavulanate to a first-generation cephalosporin.¹¹⁶ A second study, however, showed that there was an increased risk for *Enterococcal* SSIs when cefotetan was used rather than ampicillin-sulbactam.¹¹⁸ A larger study published in 2008 found that use of cefazolin was associated with a significantly higher risk for SSI than the combination of a glycopeptide plus aztreonam, suggesting broader coverage is beneficial.¹⁰⁸ Taking this all together, the IDSA/ASHP/SIS/SHEA guidelines recommend a third-generation cephalosporin plus ampicillin or piperacillin-tazobactam alone.⁵⁹ We would propose that using ampicillin-sulbactam is another alternative with sufficient coverage of the relevant organisms (Table 3). There are no studies comparing these different broad-spectrum regimens. Duration of prophylaxis should be ≤48 hours as there is no evidence to suggest a benefit of prolonged prophylaxis.¹²² Of note, some centers also employ antifungal prophylaxis peri-operatively in liver transplant patients. Though clinical practice varies, if the patient has risk factors for fungal infection, then it should be considered.¹²³ Risk factors for fungal infections include prolonged operative times, excessive blood transfusion, renal insufficiency requiring RRT, and re-operation.¹²³ Post-transplant antifungal prophylaxis is crucial to consider but is outside the scope of this article. Antifungal prophylaxis is detailed in the invasive fungal infections section of the updated guidelines.¹²⁴ (See Table 3 for dosing details and for alternatives for penicillin-allergic patients.).

Of note, there has been no conclusive benefit demonstrated from use of selective bowel decontamination prior to liver transplantation, and this intervention is not currently

recommended.¹²⁵⁻¹²⁷ There have been several small studies that have found a benefit from pre-transplant pre- and pro-biotics (with pre-biotics referring to non-digestible fiber) although the small sample sizes and case reports describing secondary infection with the organisms contained in pro-biotics limit support for their use.¹²⁸⁻¹³⁰ As such, the IDSA/ASHP/SIS/SHEA guidelines do not make any recommendations about this practice, and we do not recommend the use of pro-biotics.

- We recommend a third-generation cephalosporin plus ampicillin or piperacillin-tazobactam alone for up to 24 hours for peri-operative antibiotic prophylaxis in liver transplantation (strong, low).
- Another alternative would be ampicillin-sulbactam or in countries where available intravenously amoxicillin-clavulanate for ≤48 hours; antifungals may be considered based on individual patient risk.¹³¹(strong, high).
- The use of selective bowel decontamination prior to liver transplantation is not recommended (strong, low).
- The use of pro-biotics is not recommended (strong, low).
- We recommend that if the patient is being treated for an active infection at the time of organ transplantation, the antibiotic regimen should be altered to target specific pathogens based on the current infection and individual risk factors (strong, moderate).

2.4 | Intestinal and multivisceral transplantation

2.4.1 | Epidemiology of SSIs

SSIs in small bowel/multivisceral (SB/MV) transplantation can include superficial or deep soft tissue infections as well as intra-abdominal collections. The rates of SSIs in SB/MV transplantation are extremely high; between 14% and 53% of patients develop SSI (Table 1).^{6,132,133} If prosthetic mesh is used to close the abdomen, SSI rates between 25.7% and 100% have been reported.¹³² Infection during the first month post-transplant, particularly intra-abdominal infection, is associated with increased mortality in these patients.¹³

Risk factors for SSIs after SB/MV transplantation (Table 2) include recipient factors such as increased age, hospitalization before transplantation, re-transplantation; surgical factors including use of surgical mesh, re-operation in the first month, contamination of the surgical field, entero-cutaneous fistulas, skin flaps, staged procedures; need for post-transplant RRT; and immunosuppressive choice, especially the use of daclizumab and MMF.^{13,133}

SSIs following SB/MV transplantation are often polymicrobial and predominantly involve Gram-negative organisms including *Pseudomonas* species, *E coli*, and *Klebsiella* species.^{134,135} Less frequently, Gram-positive organisms are found including Enterococci and *Staphylococci*.¹³³⁻¹³⁵ Fungal infections including *Candida* species as well as anaerobic organisms are commonly reported (Table 1).^{136,137} Extremely high rates of MDROs among SB/MV recipients are reported with one study noting 31% of Enterobacteriaceae isolates produced an ESBL, 36% of *Pseudomonas* isolates were

multidrug-resistant, 75% of *Enterococci* were VRE, and 100% of *S aureus* were MRSA.¹³⁴

2.4.2 | Peri-operative antibiotic prophylaxis

Although there are limited data concerning peri-operative antibiotic prophylaxis for SB/MV transplantation, it is routinely utilized due to the exceedingly high rates of SSIs. In one study in which 43% of patients were given a standard regimen of ampicillin-sulbactam plus fluconazole, and the remainder were given a customized antibiotic regimen by infectious diseases consultants, they found no difference in SSIs between the two groups.¹³⁴ Notably, many patients were given prophylaxis with an agent that covered the organism that was ultimately causative in the infection, suggesting that antibiotic prophylaxis is not sufficient to fully prevent SSIs in these patients.¹³⁴ The IDSA/ASHP/SIS/SHEA guidelines do not provide recommendations for SB/MV transplantation. Due to the high rate of SSIs and the broad array of causative organisms, we would suggest a possible approach using a combination of antibiotics targeting Gram-positive (including *Enterococcus*), Gram-negative (including *Pseudomonas*), anaerobic, and fungal organisms (Table 3). Options include vancomycin plus cefepime, metronidazole, and fluconazole; or vancomycin plus piperacillin-tazobactam and fluconazole or an echinocandin in cases of fluconazole resistance. There is no consensus on duration, though there is no evidence to suggest prolonging the duration beyond 72 hours is beneficial in uncomplicated cases. In patients with infected mesh or fistulas, prolonging the duration up to 7 days may be needed.

- We recommend using of one of the following regimens (strong, low):
 - o vancomycin, cefepime, metronidazole, and fluconazole or
 - o vancomycin, piperacillin-tazobactam, and fluconazole or an echinocandin in cases of fluconazole resistance.
- Duration of antibiotic prophylaxis should be 48-72 hours in most cases. Prophylaxis should be continued in these settings until complication such as pancreatitis, anastomotic leak, or fistula contaminations peri-operatively has been surgically addressed or resolved (strong, low).
- We recommend that if the patient is being treated for an active infection at the time of organ transplantation, the antibiotic regimen should be altered to target specific pathogens based on the current infection and individual risk factors (strong, moderate).

2.5 | Heart transplantation

2.5.1 | Epidemiology of SSIs

SSIs in heart transplant (HT) recipients can range from superficial soft tissue infections to sternal infections and mediastinitis. SSIs occur in between 4% and 19% of HT recipients, and mediastinitis has been reported in 1.7%-7% (Table 1).^{4,11,138-142} Development of a post-transplant SSI or nosocomial infection among HT recipients is associated with increased risk for mortality.¹¹

Risk factors for SSIs in HT patients (Table 2) include host factors such as increased age, obesity, DM, prior cardiac procedure, prior ventricular assist device (VAD), prolonged mechanical ventilation, positive wire cultures or other sites of recipient colonization (especially with Gram-negative organisms), and re-operation or re-transplantation; surgical factors such as prolonged ischemic time, use of bilateral internal mammary arteries; donor factors such as donor colonization (particularly with Gram-negative organisms); immunosuppression including early use of mammalian target of rapamycin (mTOR) inhibitors; and ciprofloxacin monotherapy for prophylaxis.^{4,11,138,141,143,144}

The most common organisms causing SSIs in OHT recipients are coagulase-negative *Staphylococcus* spp, *S aureus* including MRSA, *Enterococcus*, Enterobacteriaceae including ESBL organisms, *Pseudomonas aeruginosa*, *Stenotrophomonas*, and *Candida* species (Table 1).^{138,141,142}

2.5.2 | Peri-operative antibiotic prophylaxis

There are little data in HT recipients regarding peri-operative antibiotic prophylaxis. However, there have been studies performed in patients undergoing other cardiac procedures from which data may be extrapolated. In those studies, prophylactic antibiotics resulted in a significant reduction in post-operative SSIs.⁵³⁻⁵⁶ With regard to antibiotic choice, there is significant controversy. Studies have found no difference in SSI rates between anti-*Staphylococcal* penicillins (eg, oxacillin or methicillin) and cephalothin.⁵³ However, when evaluating vancomycin vs cephalosporins, some studies show no difference¹⁴⁵⁻¹⁴⁷ while others show a benefit of vancomycin over cephalosporins.^{148,149} The impact of vancomycin on SSI rates may be related to the prevalence of MRSA colonization and infection at each institution. The Society of Thoracic Surgeons practice guidelines recommend that the primary prophylactic antibiotic for adult cardiac surgery to be a first-generation cephalosporin, which is usually cefazolin. Vancomycin (one pre-operative with or without one additional dose) may be reasonable as an adjuvant agent to the cephalosporin. They also recommend that the duration for routine post-operative administration of prophylactic antibiotics has to be no longer than 48 hours.^{150,151} The IDSA/ASHP/SIS/SHEA guidelines recommend using a first-generation cephalosporin alone for up to 24 hours. However, because of the controversy regarding the superiority of vancomycin over cephalosporins, another option would be the use of vancomycin *and* a first-generation cephalosporin (Table 3). The optimal duration of prophylaxis is unclear. In non-HT cardiac surgery, it has been shown that 56 hours of prophylaxis is not superior to 36 hours¹⁵²; and in several studies, it has been shown that prolonging antibiotics beyond 48 hours does not reduce SSIs but does increase the rate of antimicrobial resistance.^{56,153} Our approach would thus extend antibiotics up to 48 hours post-operatively.

- The use of a first-generation cephalosporin alone for up to 24 hours is recommended for peri-operative antibiotic prophylaxis in heart transplantation (strong, moderate).

- We recommend for patients colonized or previously infected with MRSA, the use of vancomycin plus a first-generation cephalosporin for up to 48 hours (weak, low).
- We recommend that if the patient is being treated for an active infection at the time of organ transplantation, the antibiotic regimen should be altered to target specific pathogens based on the current infection and individual risk factors (strong, moderate).

There are several unique situations in HT that require customization of recommendations:

- For patients who have been maintained on suppressive antibiotics for VAD infection, antibiotic therapy should be continued post-transplant, with length of therapy dependent on severity of infection.
- If there is a history of VAD infection, then coverage of that organism should be included in the peri-operative antibiotic regimen (strong, moderate). Longer duration of prophylaxis is recommended according to the type and severity of pre-HT infection.
- After explant of the VAD at the time of heart transplant, antimicrobials should be continued in the immediate post-transplant period, with the length of therapy dependent on the severity of infection (strong, very low).
- If there is no history of VAD infection, we recommend to use the standard regimen for heart transplant surgical prophylaxis (strong, moderate).

For those patients on ECMO as a bridge to HT:

- If there is no evidence of active infection or colonization of the ECMO circuit, we recommend using standard peri-operative prophylaxis (strong, low).
- If there is evidence of an active infection or colonization of the ECMO circuit, we recommend covering the infecting/colonizing organisms as part of the peri-operative antibiotic regimen (strong, moderate).
- For patients with an open chest post-HT which is a significant risk factor for infection.¹⁵⁴⁻¹⁵⁶ We recommend individualizing peri-operative prophylaxis to account for individual patient and scenario based on risk factors and timing of closure to determine whether extended duration of antimicrobial therapy is indicated (strong, low).

2.6 | Lung transplantation

2.6.1 | Epidemiology of SSIs

SSIs in lung transplant (LT) recipients can present in a variety of fashions including superficial soft tissue infection, mediastinitis, and airway anastomosis infection. SSIs are relatively common post-LT and have been reported in between 5% and 19% of patients (Table 1).^{11,22,139} If all pneumonias in the early

post-operative period are included, then the SSI rate is as high as 40%.¹¹ Development of a post-transplant SSI is associated with increased mortality (approximately 35% mortality at one-year post-transplant).^{11,22}

Risk factors for SSIs following LT (Table 2) include host factors such as pre-transplant colonization, DM, impaired renal function, prior sternotomy, repeat transplantation; surgical factors including prolonged ischemic time, blood transfusions, re-exploration due to bleeding; and donor factors such as colonization of the donor bronchus and/or perfusate (particularly with a Gram-negative organism).^{11,22,157} A study of 115 LT recipients showed that LT recipients had significantly worse outcomes including longer ICU time, longer time on mechanical ventilation, and worse survival when the donor bronchoalveolar lavage (BAL) culture grew bacteria.^{11,158}

In contrast to other transplant types, the most common organisms causing SSIs in lung transplant recipients are Gram-negative organisms, particularly *Pseudomonas* species, *E coli*, and *Klebsiella* species.^{22,157} Fungal organisms including *Candida* and *Aspergillus* species are also more common among lung transplant recipients than other SOT recipient types.^{22,157} Gram-positive organisms including *S aureus*, *Enterococcus* species, and CoNS are still important but slightly less common.^{22,157} More rarely, *Stenotrophomonas* and *Aspergillus* may also cause SSIs^{22,157} (Table 1).

2.6.2 | Peri-operative antibiotic prophylaxis

There are few studies evaluating peri-operative and post-operative antibiotics for lung transplantation and no randomized controlled trials. Retrospective studies have shown a reduction in post-transplant pneumonia with prophylaxis, but there is little guidance in the literature regarding either specific regimens or durations.^{159,160} Because of this, the IDSA/ASHP/SIS/SHEA guidelines recommend a single first-generation cephalosporin for prophylaxis.⁵⁹ Due to the frequency of Gram-negative and fungal SSIs in lung transplant recipients, however, many centers in the US and Europe utilize broader coverage. One potential approach would be to use vancomycin plus a third-generation cephalosporin or cefepime (Table 3). Antifungals may also be indicated; if there is a history of fungal colonization or infection in the donor or recipient, then the risk of fungal infection is increased and the use of an anti-mold azole may be considered.^{161,162} If neither donor nor recipient had pre-transplant infection or colonization with bacterial or fungus, then the antibacterial prophylaxis may be limited to 48-72 hours.

For routine peri-operative prophylaxis in lung transplantation:

- We recommend to use vancomycin plus an anti-Pseudomonal beta-lactam for 48-72 hours (weak, low).
- We recommend that if the patient is being treated for an active infection at the time of organ transplantation, the antibiotic regimen should be altered to target specific pathogens based on the current infection and individual risk factors (strong, moderate).

3 | CUSTOMIZATION OF ANTIBIOTICS BASED ON UNIQUE CIRCUMSTANCES AND RECIPIENT AND DONOR COLONIZATION/INFECTION

There are several unique situations that require customization, for example patients on Extracorporeal Membrane Oxygenation (ECMO). If the patient was on ECMO as a bridge to lung transplantation, there is no evidence to suggest that the antibiotic regimen needs to be altered, unless there is an active infection or colonization of the circuit, in which case, the infecting/colonizing organisms may be covered in the peri-operative antibiotic regimen.

Open chest: Delayed chest closure post-transplant is a significant risk factor for infection.¹⁵⁴⁻¹⁵⁶ Although there are no data to support broadening coverage in this scenario, the authors' routine practice includes Gram-positive (including MRSA), Gram-negative (including *Pseudomonas*), and fungal coverage until the chest is closed, due to the higher risk for infection.

- We recommend in patients with delayed chest closure to maintain the first line surgical prophylaxis regimen for cardiac or lung transplant and avoid the unnecessary use of broad-spectrum antibiotics unless there is evidence of active infection (weak, low).

3.1 | Recipient colonization or infection

When the SOT recipient is colonized (airway/respiratory and or rectal/GI tract) or being treated for an active infection at the time of transplantation, the surgical prophylaxis regimen may need to be re-evaluated. This is largely due to the fact that colonization with certain organisms may confer an increased risk for SSIs. For example, in lung and heart transplantation, it has been shown that recipient colonization with a Gram-negative organism increases the risk for post-transplant SSI and pneumonia.¹¹ Another study evaluating rectal screening for MRSA and VRE in liver transplant patients found that colonization with either organism was a risk factor for infection.¹⁶³ In renal transplant recipients, it has also been shown that pre-transplant colonization with a carbapenem-resistant *K pneumoniae* (CRKP) isolate is associated with post-transplant CRKP bacteriuria, though it is not clear whether this is associated with CRKP infection.¹⁶⁴ It can be difficult to ascertain a patient's colonization status without routine rectal and nasal swabs. Since it is not yet clear that treating colonizers is of substantial benefit to the patient, there is no basis to recommend routine pre- or post-transplant surveillance for MDROs, though further study in this area is needed.

A single center study by Chatani et al¹⁶⁵ compared the outcome (bloodstream infection and mortality) of thirty-one pediatric intestinal and multivisceral transplant recipients with tailored antibiotic prophylaxis based on previous infection or colonization vs. standard of care (cefazolin 1 g peri-operatively and continued for seven days until fascia closure). Patients in the standard group had both shorter times to and higher rate of bacteremia, which was statistically significant ($P < 0.001$). The time to development of an MDRO in the

tailored group was 52.6 days compared to 63.9 in the standard group ($P = 0.677$). Although not statistically significant, the tailored group had a propensity to present with Gram-negative pathogens after transplant as compared to the standard regimen group, which presented with Gram-positive pathogens ($P = 0.103$). Children with a history of an MDRO held a 7.3 ($P < 0.01$) times more likelihood of death within a year of transplant. A tailored prophylactic antibiotic regimen in the post-transplant period had no effect in mortality. Surgical site infection rates were not described in the results and we cannot determine whether tailored antimicrobial therapy had a protective effect in SSIs in this population. Nonetheless, considering that the majority of post-operative bacteremias in multivisceral and intestinal transplants could be secondary to gut translocation, deep abdominal post-operative collections, the role targeted antibiotic prophylaxis preventing secondary bacteremias could also reduce SSIs and further studies are needed.

3.1.1 | Pulmonary pre-transplant colonization

If the donor or recipient has a history of pre-transplant pulmonary colonization/infection, as is often the case particularly in patients with cystic fibrosis (CF), those organisms that colonize the donor or recipient may need to be covered by the prophylaxis regimen. There are no data to suggest an optimal duration of coverage, though most centers use at least 7 days of treatment post-operatively. This is based primarily on reports of comparable outcomes among CF patients and non-CF patients when the CF patients were treated for 7 days based on their pre-transplant cultures.¹⁶⁶ Individual assessment should be conducted in each case to determine the optimal selection of antibiotic agents, the right dose, and appropriate targeted duration based on clinical and microbiological response post-operatively. Further studies are needed in this area to determine what is the appropriate selection and duration of tailored antibiotic therapy for surgical prophylaxis and the outcomes of the recipients.

- We recommend donor and recipient pre-transplant colonization/infection evaluation in centers located in endemic areas where organ transplants are being performed in high-risk patients (weak, low) Considering the increased number of infections and reports of colonization with MDROs, surveillance of respiratory and rectal anatomical sites in organ recipients at risk of colonization (traveling from endemic areas for MDROs or previously exposed to prolonged and or broad-spectrum antibiotics) might be appropriate. Infection prevention measures and targeted antimicrobial stewardship for prophylaxis and or treatment will need to be individualized to each patient and case scenario (weak, low).
- We recommend in cases of recipient with active or previously treated infection or known colonization with a multidrug-resistant organism (eg, carbapenem-resistant and/or carbapenemase-producing Gram-negative organisms) pre- and post-transplant consultation with transplant infectious disease specialists to facilitate selection of the most appropriate regimen and duration on an individual basis (strong, low).
- We recommend that if the transplant recipient is being treated for a prior active infection, that treatment should continue in the

operating room and post-operatively as originally planned (strong, moderate).

4 | THE CONSEQUENCES OF BROADENING PERI-OPERATIVE PROPHYLAXIS

With the high risk of SSIs in SOT recipients, and a rising incidence of MDROs in SOT donors and recipients, it seems logical to progressively broaden and extend peri-operative antibiotic prophylaxis. As such, it is worth noting the costs related to overuse of peri-operative antibiotic prophylaxis and emphasizing how imperative it is to limit antibiotic exposure whenever possible. Despite the fact that peri-operative antibiotic prophylaxis is only given for 24-48 hours in most cases, this antibiotic exposure may have significant downstream effects on quality of care and patient safety including (a) increased financial costs, (b) increased rates of *Clostridioides difficile* colonization and colitis,¹⁶⁷⁻¹⁶⁹ (c) increased rates of antimicrobial resistance,¹⁷⁰ and (d) increased adverse drug events. Thus, targeted antibiotics should be used in each case based on individual risk factors and local patterns of resistance. Given the many gaps in data-driving peri-operative prophylaxis in organ transplantation, future prospective studies are warranted to determine optimal regimens for transplant recipients.

5 | MANAGEMENT OF SURGICAL SITE INFECTIONS

Post-surgical nosocomial infections, including SSIs, have been studied extensively in the general surgical population and in several specialty surgical populations. However, very few studies have investigated SSIs among SOT recipients and most of them have described the epidemiology and risk factors but no recommendation about treatment has been published thus far.^{4,22,140,171-176} Most of the following recommendations are therefore borrowed by the non-transplant population.

All clearly infected wounds should be opened, irrigated, debrided, and treated with basic wound care. All SSIs should always be cultured in SOT recipients. However, wound swab cultures often reveal polymicrobial growth, making it difficult to distinguish colonization from true infection. Ideally, cultures should be sterile aspirations or tissue, but swabs are useful if cautious interpretation of the results is used. The culture results should be used to guide antibiotic choice, particularly if the patient is at high risk of having resistant pathogens.

6 | SUPERFICIAL INCISIONAL SSIS

Superficial SSIs involve only skin and subcutaneous tissue of the incision. These infections can be managed by opening the wound sufficiently for adequate visualization of the underlying tissue to insure

that no additional processes, such as fascial dehiscence, drainage from an organ/space SSI, or enteric fistula, are occurring.

Infected incisional wounds should be irrigated with an isotonic solution such as a saline solution to remove loose, dead tissue and exudate, and mechanical debridement with sharp excision or pressure irrigation may be indicated to remove devitalized tissue. Once the wound has stabilized and most of the devitalized tissue has been removed, consideration can be given to placement of a negative pressure wound therapy device ("wound vac"). Although the overall outcome may not change, placement of such a device generally speeds closure and may be particularly helpful in larger wounds and those in which dressing changes are difficult.^{174,177}

The need for antimicrobial therapy is determined by magnitude of the infection, evidence of systemic involvement, presence of prosthetics, and status of the patient, including comorbidities. While in immunocompetent individuals, uncomplicated superficial SSIs that have been managed with incision and drainage usually can be managed without antibiotics, in solid organ transplant recipients, a targeted antimicrobial treatment is recommended to avoid dissemination.

- We recommend to select systemic antibiotic treatment under antimicrobial stewardship principles and tailor the duration based on the individual patient's clinical response (strong, low).
- Empiric treatment should be started using broad-spectrum antibiotics with coverage of Gram-positive cocci from the skin as well as the expected flora at the site of operation according to the local epidemiology, type of transplant procedure, colonization status, individual patient risk factors for difficult to treat pathogens,¹⁷⁸ clinical severity of infection, infection source, and recent infections (Strong, low).
- A first-generation cephalosporin or an anti-staphylococcal penicillin for MSSA, or an active antibiotic agent (eg, vancomycin) when risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended (strong, low).
- Broad-spectrum agents are recommended if the patient has risk factors for MDROs (pre-transplant colonization; peri-operative prophylaxis; prolonged tracheal intubation; long-term hospitalization; urologic manipulation; kidney-pancreas transplantation; renal replacement therapy after transplantation; post-transplant urinary obstruction; recurrent UTI) (strong, low).
- Definitive antimicrobial treatment is guided by the clinical response of the patient and results of Gram stain, wound culture, and sensitivity (strong, moderate).
- Topical antibiotics and additional agents such as antiseptics (hydrogen peroxide, povidone-iodine) have an unclear role in the management of infected wounds and should be avoided (strong, low).

7 | DEEP INCISIONAL SSIS

Deep incisional SSI involves deep soft tissues of the incision (for example, fascial and muscle layers).

- For moderate to severe SSIs, including those associated with systemic toxicity, significant cellulitis (>2 cm beyond the incision), purulent drainage, fascial dehiscence, and deep drainage, antibiotics should be administered empirically in addition to surgical treatment. Empiric initial selection of antibiotics should follow the same criteria described for superficial SSIs (strong, low).

8 | ORGAN/SPACE

Organ space or deep seated infections are defined when infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure. Very few studies have addressed this topic in the transplant setting.

- Source control is imperative for organ/space SSIs, including mediastinitis, empyema, and intra-abdominal abscess, and requires either percutaneous or operative drainage (strong, high).
- Empiric initial selection should follow the same criteria described for superficial SSIs (strong, low).

CONFLICT OF INTEREST

The authors report no conflict of interest related to this work. Dr Abbo has served as speaker for Pfizer Latin America, MSD Brazil, and Merck Latin America and as a consultant in Advisory Boards for Roche Diagnostics, Nabriva Therapeutics and Paratek. Dr Grossi has served as a speaker for Merck, Sharp and Dohme, Biotest, Pfizer, Angelini, Novartis, Gilead and as a consultant in Advisory Boards for Merck, Sharp and Dohme, Biotest, Becton Dickinson, Angelini, Gilead, Paratek, Shire.

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