Title page

Perioperative Antibiotic Stewardship in the Organ Transplant Setting

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Proposed tweet

Solid organ transplant recipients can benefit from traditional antimicrobial stewardship principles creating personalized perioperative prophylaxis according to different risk factors.

Running title

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Keywords

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

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 post-operative 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

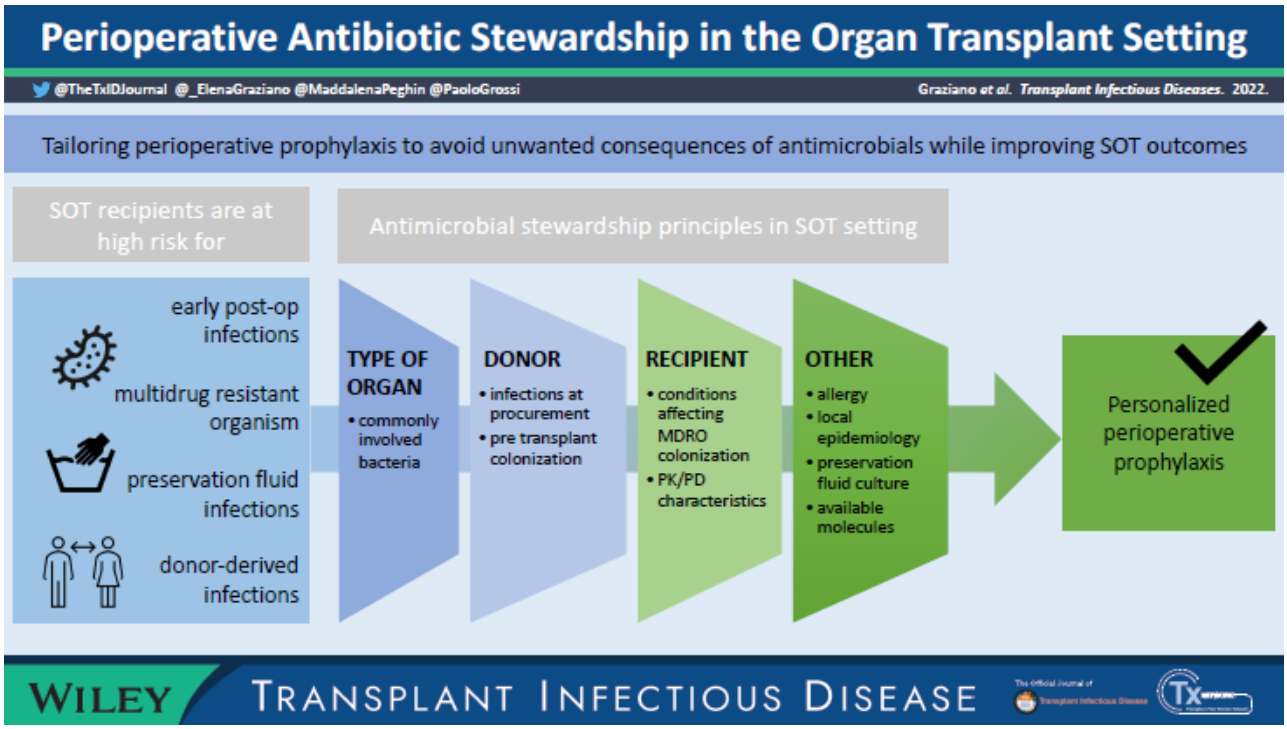
SOT recipients are at high risk for early post-operative infectious complications due to the complexity of surgical procedures, severity of end stage organ disease, net state of immunosuppression in the post-transplant period and to the high risk for multidrug resistant organism. Moreover, SOT may be 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.

Abbreviations: AMS, antimicrobial stewardship; CRE, carbapenem-resistant *Enterobacterales* (CRE); DDI, donor-derived infections; ECMO, extracorporeal membrane oxygenation; ESBL, extended-

spectrum beta-lactamase; HS, handshake stewardship; ID, infectious disease; MDRO, multidrug resistant organism; MRSA, methicillin resistant Staphylococcus aureus; PAS, Perioperative Antibiotic Stewardship; PFI, preservation fluid infections; PP, perioperative prophylaxis; SOT, solid organ transplant; VAD, ventricular-assist device.



Introduction

Solid organ transplant (SOT) recipients are at high risk for early post-operative infectious complications due to the complexity of surgical procedures, prior end stage organ disease, multiple comorbidities, the elevated net state of immunosuppression in the post-transplant period and to the high risk for colonization and infections caused by multidrug resistant organism (MDRO) [1] [2]. In addition, perioperative infections in SOT recipients may be caused by preservation fluid infections (PFI) and expected or unexpected donor-derived infections (DDI), which may be graft specific or systemic [3].

According to the 2022 Centers for Disease Control and Prevention (CDC), surgical site infections (SSI) 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 [4]. 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 post-transplant, SSI are reported between 3 to 53%, (up to 100% if a prosthetic device is used) with highest incidence in multivisceral transplant and lower in kidney transplant [5, 6]. SSI in SOT setting have been associated to 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).

AMS programs and perioperative AMS in Solid Organ Transplant 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, nonpharmacological 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.

Nonpharmacological interventions include strict adherence to infection prevention rules and early withdrawal of invasive devices after surgery must be considered. Standard recommendation guidelines on nonpharmacological 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, 14] [15] [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 post-transplant, 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.

Optimization of antimicrobial perioperative prophylaxis in SOT setting

PP during organ transplantation procedure is used mainly to prevent SSI as in non-transplant 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 post-transplant infections are different. According to the type of organ, pre transplant recipient condition, colonization and active infection at the time of transplant, donor infection and colonization at the time of procurement, local MDRO epidemiology and preservation fluid cultures it is possible to tailor PP in order to mitigate early acute bacterial post-transplant infections (Table 1 and 2).

As regards of antimicrobials, their administration is crucial. To achieve therapeutic blood levels at the time of surgical incision and throughout surgery, antibiotics should be administered intravenously, within 60 minutes 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 post-transplant.

Recommendations on standard PP of the joint members of American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS) and the Society for Healthcare Epidemiology of America (SHEA) [24] compared to the 2019 updated American Society of Transplantation Infectious Diseases (AST ID) Community of Practice [1] 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.

Antimicrobial perioperative prophylaxis 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 cephalosporin, namely cefazolin, has shown non inferiority to vancomycin and ceftriaxone in a randomized controlled trial (RCT) [25], to ceftriaxone and to piperacillin/flucloxacillin in more recent retrospective studies [26, 27]. Duration of the PP should be limited to 24 -48 hours.

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 suggest 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 vs cefazolin plus gentamicin in preventing post-operative infections [25] and the role of antifungal prophylaxis is debated [28] 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 hours after transplant. Fluconazole is added for 7-14 days as primary prophylaxis of yeasts infections.

Liver. SSI 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 post-operative infections [29] as SSI 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 suggest 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 suggest 24-48 hours as no benefit has been found in extending PP to 72 hours [30, 31]. If antifungal is added, a duration up to 14 days should be considered.

Heart. SSIs in HT recipients are reported between 4% and 19 and mediastinitis in 1.7%-7% of patients. The most common organisms involved are Gram positive (*Staphylococcus* spp included MRSA, *Enterococcus* SPP), lactose fermenting and non-fermenting Gram negative (*Enterobacterales*, *Pseudomonas aeruginosa, Stenotrophomonas*). Fungal infection caused by Candida species are reported as well. IDSA/ASHP/SIS/SHEA experts suggest using first generation cephalosporins, but data show no agreement on whether glycopeptides are superior to first generation cephalosporins in cardiac surgery [32, 33]. AST ID recommendation is to use both. Our approach is to use cefazolin for 24-48 hours, with an alternative regimen of Vancomycin plus Cefazolin if MRSA nasal pre-transplant colonization is detected. Heart transplant may come after the implantation of intracardiac devices such as ventricular-assist device (VAD) or extracorporeal membrane oxygenation (ECMO). In these cases, PP should be tailored to recent or ongoing infections and to local epidemiology due to invasiveness of such devices and the antibiotic regimen duration should be prolonged accordingly.

Lung. SSI in lung transplant recipients may be incisional, deep organ space or airway anastomosis infection. SSI have been reported in 5% -19% of lung transplant recipient and are most commonly caused by gram negative organisms such as *Pseudomonas aeruginosa* and *Enterobacterales*. Airway anastomosis may be at risk for Candida and Aspergillus infections. An international survey management of PP in lung transplant recipient showed a wide variation among centers worldwide. Interestingly even in recipients without colonization prior to transplant wide spectrum antibiotic was used, the most being piperacillin/tazobactam in 32.3% of centers with a median duration of 7 days. In cases of prior MDRO colonization PP was directed toward the pathogens and the duration increased to 14 days [34]. We recommend, in line with AST ID guideline, to broaden the first-generation cephalosporin spectrum suggested by the IDSA/ASHP/SIS/SHEA group, and to use an anti-Pseudomonal beta lactam and an anti MRSA molecule (i.e. piperacillin/tazobactam and vancomycin). The use of an anti-mold molecule such as voriconazole or inhaled/i.v. liposomal amphotericin B may be considered in cases of donor, recipient colonization or universal prophylaxis according to the presence of risk factors [35]. We use antimicrobial PP for 48-72 hours, unless ongoing infections in the donor or recipient and antifungal according to local protocol.

Multivisceral. Due to the inherent contaminated nature of the surgery, intestinal/multivisceral transplantation is the kind of transplant at highest infection risk, with higher rates in adults than in pediatric population [36] with rates up to 100% of cases if a mesh is used [1]. Organisms causing SSI are part of the enteric flora, mainly Gram negative, *Enterococcus* and Candida

species. While intestinal/multivisceral transplantation is not discussed in the IDSA/ASHP/SIS/SHEA guidelines, the AST ID recommendations cover the polymicrobial and fungal etiology of post-transplant infections suggesting an anti-Gram negative including *Pseudomonas*, Gram positive, anaerobic and fungal PP which we support simplifying the regimen with the use of piperacillin/tazobactam and fluconazole for a maximum of 72 hours.

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 methicillin-resistant *Staphylococcus aureus* (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 [1]. 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 [37].

The use of targeted daptomycin PP in pre-transplant VRE colonized recipient was effective in preventing post-transplant infections in a small cohort of liver transplant recipients [38].

A modified PP in extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales* colonized patients has been observed to reduce the incidence of post-transplant ESBL infections after liver transplant (P = 0.04) [39] and it is currently recommended by the Spanish guidelines [40]. The use of amikacin has been found useful in a setting with a high prevalence of ESBL *Enterobacterales* infections [41].

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 [42], but was associated with gentamicin and colistin resistance [43]. However, to date there are insufficient data to support the systematic use of gut decontamination and it is not supported by the current guidelines [40, 44-46]. 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 = 0.01) [47].

In lung transplant, recipient culture-oriented change in PP has not showed association with better outcomes in a low MDRO setting [48], while a prompt switch to donor colonization targeted-PP has been found to be a safe strategy in endemic MDRO areas [49, 50]. 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 [40]. Pre-transplant respiratory tract colonizing flora may be helpful in tailoring a PP in lung transplant recipients, especially in cystic fibrosis patients [51].

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 post-transplant infection may take into consideration MDRO epidemiology.

Management of preservation fluid 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 [52], others only one [53, 54].

The role of preservation fluid (PF) cultures in predicting post-transplant infections and the relative mortality in transplant recipients is debated [55]. 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 [56]. 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 [54], although there a is a concern for increased MDRO colonization and infections [57] [54, 58]. Although not standardized, we recommend PF cultures whenever possible with a careful interpretation of the results made by a transplant infectious disease specialist, particularly if a MDRO is isolated.

Management of donor derived infections

Expected DDI 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 [59] [9, 60]. AST guidelines suggest modifying PP in lung transplant according to colonizing organisms of the respiratory tract of the donor [51]. The impact of unanticipated DDI may be mitigated with a well-structured donor pre- and post-transplant management which leads to a PP that takes into account data from donor culture and epidemiology [21, 61]. Early switch to appropriate treatment is crucial, especially in cases of MDRO infections, associated with high morbidity and mortality in SOT population [62]. 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 infectious disease physician [13, 63]. Indeed, it has been showed that a correct management and treatment of MDRO DDI leads to a safe transplantation [23, 64].

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.

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The authors have no conflicts of interest to declare. Please refer to the accompanying ICMJE disclosure forms for further details.

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

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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
• Intra operative 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

MDRO multidrug resistant organism, PP Perioperative prophylaxis, SOT solid organ transplant, SSI surgical site infection

Table 2. Factors influencing the choice of PP in SOT

PERIOPERATIVE PROPHYLAXIS 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 Local epidemiology Pre transplant colonization	Specific conditions of end stage organ disease affecting MDRO colonization (e.g., cystic fibrosis) Local epidemiology PK/PD characteristics of the recipient (e.g., massive ascites, acute renal or hepatic failure)	Allergy Available molecules Surgery related risk factors (e.g., massive blood loss) Preservation fluid culture

MDRO multidrug resistant organism, PK/PD pharmacodynamic/pharmacokinetic, PP perioperative prophylaxis, SSI surgical site infection, SOT solid organ transplant

TABLE 3. Recommendations for standard peri-operative 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 hrs	Ciprofloxacin 500 mg q12
Liver		Third-generation cephalosporin plus ampicillin or piperacillin-tazobactam alone	Ampicillin-sulbactam 3 g ± fluconazole 400 mg × 1 or echinocandin or liposomal amphotericin B if high risk for invasive fungal infection (duration depends on the individual risk)	Piperacillin-tazobactam 4,5 g + fluconazole 400 mg (or Echinocandin or liposomal amphotericin B) if high risk for invasive fungal infections	24-48 hrs	Ciprofloxacin 500 mg q12 + Vancomycin
Heart	Without prior VAD	First generation cephalosporin	Vancomycin plus cefazolin 2 g	Cefazolin 2g If MRSA colonization: Vancomycin+cefazolin 2 g	24-48 hrs	Vancomycin
	With prior VAD	First generation cephalosporin	Vancomycin plus either ceftriaxone 1 g or cefepime 2 g			
Lung		First generation cephalosporin	Vancomycin plus third-generation cephalosporin or cefepime 2 g	Ceftazidime 2 g + Vancomycin + fluconazole 400 mgor Echinocandin or Liposomal Amphotericin B if high risk for invasive	48-72 hrs	Vancomycin plus levofloxacin 750 mg q24

			fungal infections		
Pancreas, kidney-pancreas	First generation cephalosporin	Ampicillin-sulbactam 3 g plus fluconazole 400 mg	Ampicillin-sulbactam 3 g + fluconazole 400 mg	24-48 hrs	Vancomycin + levofloxacin750 mg q24 h + Fluconazole 400 mg IV
Intestinal/multivisceral	N.A.	Vancomycin plus cefepime 2 g plus metronidazole 500 mg plus fluconazole 400 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 hrs	Vancomycin + levofloxacin 750 mg + tige 100 mg + h + Fluconazole 400 mg IV or Echinocandin or Liposomal Amphotericin B

Adapted and modified from (1)

MRSA methicillin-resistant Staphylococcus aureus, VAD ventricular assist device

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