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Thank you for your submitted edits, they have improved the manuscript. I deleted your previous responses; your explanations were very helpful. We have a few additional queries below. We made edits in the text below, please review and indicate whether these edits are acceptable.

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Antimicrobial Resistance in Organ Transplant Recipients

Maddalena Giannella^{1,2}, Matteo Rinaldi^{1,2}, Pierluigi Viale^{1,2}

¹Infectious Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

²Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy

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Key words: multidrug resistant bacteria, difficult to treat bacteria, prevention, surveillance, antibiotic prophylaxis, early treatment, graft failure, mortality

Corresponding author:

Maddalena Giannella, MD, PhD

Associated Professor of Infectious Diseases

Department of Medical and Surgical Sciences, University of Bologna

Via Massarenti 11, 40137 Bologna, Italy

Email: maddalena.giannella@unibo.it

Alternate corresponding author

Matteo Rinaldi, MD

Clinical researcher of Infectious Diseases

Department of Medical and Surgical Sciences, University of Bologna

Via Massarenti 11, 40137 Bologna, Italy

Email: matteo.rinaldi23@unibo.it

Abbreviations

AKI acute kidney injury

AST American society transplantation

CPE/CRE carbapenem-producing/resistant Enterobacterales

CR-AB carbapenem-resistant *Acinetobacter baumannii*

CR-GNB carbapenem-resistant Gram-negative bacteria

DDI donor-derived infection

DT decolonization treatment

DTR difficult to treat

ESBL extended spectrum β -lactamase

ESCR-E extended spectrum cephalosporin resistant Enterobacterales

GCP good clinical practice

HT heart transplant

ICU intensive care unit

KT kidney transplant

LT liver transplant

LTRI lower tract respiratory infection

Lu-T lung transplant

MDRO multidrug resistant organism

MDR-PA multidrug resistant *Pseudomonas aeruginosa*

MRSA methicillin-resistant *Staphylococcus aureus*

MV mechanical ventilation

PCR polymerase chain reaction

SOT solid organ transplant

SSI surgical site infection

T-PAP targeted perioperative antibiotic prophylaxis

UTI urinary tract infection

VRE vancomycin-resistant Enterococci

Key Points

- SOT candidates and recipients are highly susceptible to acquire multidrug resistant organism (MDRO) colonization and/or infection with a significant impact on graft/patient survival;
- Optimal management of the MDRO burden in solid organ transplant (SOT) patients should consist in individualized preventive strategies, fully integrated with infection control and antimicrobial stewardship activities, with the goals of improving patient outcome as well as to minimize environmental damage;
- Infection control and antimicrobial stewardship activities (i.e. surveillance screening for MDRO colonization, local guidelines for the management of main infectious syndromes and/or perioperative antibiotic prophylaxis, implementation of rapid diagnostics to improve the time to appropriate therapy) should be adapted to the context of SOT according to local epidemiology;
- In this framework, patient risk stratification tools and rapid diagnostic tests may be useful in improving therapeutic management of MDRO in SOT population.

Synopsis

The overall burden of the main clinically relevant bacterial MDROs (e.g. MRSA, VRE, ESBL or ESCR-E, CRE or CPE, MDR *P. aeruginosa* and CR-Ab) in SOT populations are summarized showing prevalence/incidence, risk factors and impact on graft/patient outcome according to the type of SOT. The role of such bacteria in donor-derived infections is also reviewed. As for the management, main prevention strategies and treatment options are discussed. Finally, non-antibiotic-based strategies are considered as future directions for the management of MDRO in SOT setting.

INTRODUCTION

In 2017 WHO released a list of 12 bacteria requiring new antibiotic treatments and classified as responsible of severe infections with high mortality rates. *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacterales were identified as critical threats, while *Staphylococcus aureus* and *Enterococcus faecium* were considered as high priority. This global warning was due to a progressive widespread pattern of resistance in such bacteria, impacting patient survival mainly among vulnerable populations. Indeed, multi-drug resistant organisms (MDRO) have a dramatic impact in solid organ transplant (SOT) recipients.

The present review will focus on the most clinically relevant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE), extended spectrum β -lactamase producing or extended spectrum cephalosporin resistant Enterobacterales (ESBL or ESCR-E), and carbapenem resistant or carbapenemase producing Enterobacterales (CRE or CPE), multi-drug-resistant (MDR) *Pseudomonas aeruginosa* and carbapenem-resistant *Acinetobacter baumannii* (CR-AB).

EPIDEMIOLOGY

Colonization and incidence rates of MDRO infections depends on local epidemiology, host factors, and selective pressure from antibiotic exposure. In SOT, the type of organ is a major determinant of the type of infection and associated pathogens, influencing the burden of specific MDR bacteria in each graft setting (see Table 1). Indeed, cutaneous and/or upper respiratory colonizing bacteria such as *S. aureus* and *P. aeruginosa* more frequently cause infections in patients after heart and/or lung transplantation, whereas organisms colonizing gut microbiota such as *Enterococci* and *Enterobacterales* more frequently cause infections after liver and/or kidney transplantation.

Regarding timeline, infections with MDR bacteria have traditionally been considered to most frequently occur within the early period (1-2 months) after SOT. However, recent studies have shown that the prevalence of bacterial infection remains high even later (> 6 months) after SOT (1,2). A recent report from the Swiss Transplant Cohort (1) including 2761 adult recipients (kidney 58%, liver 21%, lung 10%, heart 8%, and kidney-pancreas 3%), enrolled between 2008 – 2014, underlined that bacteria were responsible for 63% of post-SOT infections prevailing throughout the year, with a predominance of Enterobacterales (54%), *Enterococcus* spp. (20%), and *Pseudomonas aeruginosa* (9%). Due to rising rates of antibiotic resistance among these pathogens, the authors emphasized the need for new preventive strategies.

Deep surgical site infections (SSIs), lower respiratory tract infections (LRTI) and central venous catheter bloodstream infections due to MDROs are relevant in all types of SOT. In the kidney transplant (KT) setting, the management of urinary tract infections (UTIs) due to MDRO can be challenging. In particular,

uncertainties and heterogeneity exist in the approach to asymptomatic bacteriuria when MDROs are isolated (3).

The incidence /prevalence of, the risk factors for and the impact on clinical outcome of overall MDRO and of each clinically relevant MDR bacteria are summarized in Table 1.

Donor-derived MDRO infections

The risk of bacterial transmission from donor to recipients is related to the presence of bloodstream infection and/or bacterial isolation at the graft level (e.g. from urine in KT, from lower respiratory sample in Lu-T) (4). A 2012 nationwide study investigated the rate of carbapenem resistant Gram negative bacteria (CR-GNB) isolation in brain-dead donors from 190 Italian ICUs over 4-month period. In one third of donors a Gram-negative bacteria was isolated from blood, urine and/or LRT and 15% were CR-GNB. Such information was available and communicated before transplantation in only 15% of cases. Risk factors for isolation of CR-GNB included age <60 years, ICU stay \geq 4 days, fever, and local epidemiology (5).

When a MDRO is recognized in the donor, early management of the recipient is necessary in order to reduce the risk of infection, graft impairment, and mortality (6, 7). In fact, several reports highlighted the importance of an early communication and the effectiveness of an appropriate targeted therapy in preventing transmission of MDRO infection in the recipients (4,8). A recent review evaluated all published cases of MDRO donor derived infections (DDIs) (6). For MRSA bacteremic donors, a 70% risk of infection transmission in the recipients without a targeted perioperative prophylaxis was reported, with an associated mortality rate of 14% (6). Seventeen out of 33 (52%) recipients receiving graft from donors with prior isolation of MDR-GNB (mostly CRE or CR-Ab) developed MDR-GNB infection after SOT. In most of the described cases information about donor cultures was acquired after transplant, so a targeted perioperative prophylaxis was not performed. Regarding outcome, 59% of infected recipients either died or suffered allograft loss.

APPROACH TO PREVENTION AND MANAGEMENT

MDRO infection management in SOT recipients is largely based on prevention strategies aimed at reducing the risk of infection, and its consequences on graft/patient survival, in the most vulnerable patients (e.g. carriers), settings (e.g. high endemic and/or outbreaks), and periods (e.g. early post-transplant period and/or ICU stay). Active surveillance for each type of MDRO pathogen, targeted antibiotic perioperative prophylaxis, decolonization and early-targeted treatment are potential preventive strategies that are reviewed in this section.

Active surveillance

Active surveillance consists of superficial cultures performed in asymptomatic patients to exclude colonization with a MDRO. Sites to be cultured vary according to the specific MDRO (i.e. nasal swab for MRSA, rectal swab for VRE, ESBL-E and CRE). Sampling multiple sites (i.e. throat, axilla, inguinal in addition to nasal and rectal swabs) may improve screening accuracy, mainly for pathogens as MDR *P. aeruginosa* and CR-Ab (9). Timing of surveillance is not standardized. It is usually performed before transplant at the inclusion in waiting list, at regular intervals during stay in waiting list, and/or at the moment of surgery. Few studies have investigated relationship between timing of acquisition MDRO colonization before SOT and the risk of developing MDRO infection after SOT. In a recent series of 60 CRE carriers undergoing different types of SOT, closer pre-transplant carriage acquisition (0.9 vs. 4.2 months), along with LT as type of SOT, were significantly associated with higher rate of post-transplant CRE infection (10). Post-operative screening during the hospital stay is also encouraged as it revealed that more than two-thirds of CRE colonization acquisitions were detected after LT in a large multinational study (11). Finally, an important issue to be considered is the local epidemiology. Any change in screening procedures should follow a careful assessment of the local prevalence of a specific MDRO colonization and infection in patients undergoing a specific graft transplantation. Although a prevalence threshold is not clearly defined to recommend the implementation of screening procedures, it is reasonable to consider a prevalence $\geq 10\%$ as a cut-off for implementation evaluation according to previous recommendation (12). The targets of surveillance efforts include MRSA, VRE, and MDR Gram negatives and surveillance efforts can be used to inform cohorting/infection control interventions and individual preventive strategies.

MRSA

As for MDR-Gram positive bacteria, current guidelines recommend active MRSA screening in centers with high prevalence or during outbreak settings (13,14). However, in a study Clancy et al (15) using a computer simulation model to estimate the cost-effectiveness of routine *S. aureus* screening and decolonization among lung and heart-lung transplant recipients showed that screening and decolonization were economically dominant for all scenarios tested, providing more cost savings and health benefits than no screening. The baseline rates of *S. aureus* colonization and infection among carriers were 9.6% and 36.7%, respectively. Screening averted 6.7 *S. aureus* infections (4.3 MRSA and 2.4 MSSA); 89 patients needed to be screened and decolonized to prevent one *S. aureus* infection. Thus, some experts recommend careful consideration of MRSA screening in heart and lung transplant population (16).

VRE

Despite the strong correlation between VRE carriage and the risk of progression to VRE infection after SOT (17,18), there are not specific indications about screening for VRE colonization in SOT candidates, and the approach varies across centers (19,20).

MDR-GNB

Three recent guidelines have addressed the issue of active screening for ESBL/ESCR-E, CRE/CPE, MDR *P. aeruginosa* and CR-Ab in SOT (Table 2) (21–23). As for ESBL/ESCR-E, the American Society Transplantation (AST) guidelines consider screening necessary during outbreaks or periods of high prevalence to increase infection control activities (22), whereas the European documents endorse ESBL/ESCR-E screening also to inform perioperative antibiotic prophylaxis and/or empirical treatment (21,23). Such recommendation is principally based on six prospective studies evaluating abdominal surgery, three of them including LT recipients (24–29). Due to a lack of evidence, the role of screening for ESBL-E in other types of SOT remains controversial, and should be evaluated according to local epidemiology (23). All available guidelines endorse active screening for CRE/CPE carriage in LT recipients mainly in centers with high prevalence (21–23). Such recommendation is based on several studies highlighting the relationship between CRE colonization at LT and increased risk of CRE infection in the post-transplant period, with a significant impact on graft survival and mortality (9,30–32). In other types of SOT, current guidelines consider good clinical practice (GCP) to perform an active screening before surgery, according to local epidemiology (23). Few data are available regarding the effectiveness of MDR-PA screening in SOT recipients. Major concerns raise from colonized Lu-T recipients, in which MDR-PA infection is associated with BOS development, the principal limitation for long-term survival after transplantation (33). Although active screening through respiratory, rectal and urinary swab sampling may lead to earlier detection of carriers, a retrospective study failed to demonstrate an improvement in term of infection rates with carbapenem-resistant *P. aeruginosa* before and after the implementation of screening measures, associated with contact isolation and cohorting of positive patients. (34). Thus, guidelines do not recommend an active screening of MDR-PA colonization. Such practice should be evaluated case-by-case, especially in Lu-T showing risk factors for severe MDR-PA infection as previous transplantation, history of nosocomial infection and/or septic shock, previous ICU admission (35–38). Considering that CR-Ab has been identified in contaminated equipment or fomites of patients, leading to in-hospital outbreaks, an active surveillance should be employed in settings with increased incidence (22,39). In this context, European guidelines consider GCP to perform an active surveillance for CR-Ab in all types of SOT (23). Well-designed studies focusing on this topic are lacking, but two different studies conducted in LT recipients showed a significant association between CR-Ab colonization at transplantation and subsequent infection (31,40). Therefore, current guidelines conditionally recommend implementing active surveillance for CR-Ab before LT according to local prevalence (23).

Targeted perioperative antibiotic prophylaxis

Targeted perioperative antibiotic prophylaxis (T-PAP) in MDRO carriers has been proposed as a strategy to reduce the risk of infection, especially SSIs, in the early post-transplant period. Similar to standard prophylaxis, T-PAP should be administered within 60 minutes before the incision (for fluoroquinolones and vancomycin the infusion should be started 120 minutes prior to incision); intraoperative redosing may be necessary depending on the duration of the procedure, the half-life of the antibiotics employed, and if significant blood loss during surgery occurs (41). There is currently no formal consensus on standard PAP duration in transplant surgery due to a lack of comparative trials (16). To minimize the risk of further resistance selection, in our opinion T-PAP should not be prolonged more than the duration of standard PAP per each SOT type established at local level. In patients on treatment for an active well controlled MDRO infection at the moment of transplant, that treatment should continue in the operating room and post-operatively as originally planned (16).

MRSA / VRE

Few data and no recommendation about T-PAP for MDR Gram positive bacteria are available, however could be considered on a case by case basis known to be colonized.

MDR-GNB

Recommendations exist for some MDR Gram negative bacteria, but these are based on low quality evidence, are not endorsed by all professional societies, and are considered controversial. For example, AST guidelines do not recommend T-PAP for ESBL/ESCR-E colonization (42) and note potential for negative microbiologic impact secondary to carbapenem exposure (22). In contrast, the European guidelines suggest the use of T-PAP in ESCR-E carriers, with detection obtained within 1 month before transplant, possibly avoiding carbapenems if alternative molecules with *in vitro* activity against the colonizing ESCR-E are available (21,23). This recommendation principally refers to LT recipients (LTR) and is based on the results from Logre et al (42). They analyzed 100 ESCR-E carriers undergoing LT in France, 35 developed a postoperative ESCR-E infection (11 SSIs, 10 urinary tract infections, nine pulmonary infections, and five sepsis) at day 30. Only 68 patients could be assessed according to PAP, showing higher rates of ESCR-E postoperative infections among LTR receiving routine (7/11, 63%) compared with T-PAP (17/57, 30%) ($p=0.04$). T-PAP included ceftazidime (40%), a carbapenem (31%), or piperacillin/tazobactam (29%). Although the results favored T-PAP, the quality of the study was low, with high risk of bias because of the retrospective nature, the limited sample size (with only 11 patients receiving routine prophylaxis), and the lack of outcome according to each regimen.

As for CRE/CPE and CR-Ab, since the quality of published studies is low and the effectiveness of T-PAP remains unproven, current guidelines do not recommend for or against T-PAP in CRE/CPE and/or CR-Ab carriers undergoing SOT (21,23). In an eight-year retrospective study, after the first 4 years standard PAP was

implemented with amikacin in LTR at high risk for CR-GNB infection (colonization, exposure to antibiotics in the prior 30 days, MELD >24, renal replacement therapy before LT) (31). The rate of SSIs caused by any CR-GNB (i.e. Enterobacterales, *P. aeruginosa*, *A. baumannii*) decreased in the intervention period from 30% to 13%. However, in another study including different SOT, mainly LT, with a previous CRE colonization, T-PAP was more common in the group of patients who developed a CRE infection after SOT (10). In addition, a small single-center experience evaluating T-PAP vs. standard PAP in 7 LT pediatric recipients colonized with CRE observed a progressive restoration of gut microbiota in the standard group, meanwhile in the T-PAP (consisting in both intravenously and orally colistin based regimens) group persistent dysbiosis was recorded even after 12 months of follow-up (43).

Finally, colonization with MDR-PA is a concern in Lu-T candidates (21), especially in those affected by cystic fibrosis where MDR-PA colonization could be as high as 75% and it has been associated with worse outcome (44). Thus, in Lu-T an extended T-PAP could be adopted awaiting donor and, if repeated, recipient culture results. 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 old 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 (45).

Decolonization

MRSA

The role of mupirocin for MRSA decolonization in SOT candidates remains controversial. A study conducted among LT candidates showed that decolonization procedures failed to prevent infection and almost 40% of decolonized carriers became recolonized (46). Therefore, the long-term effectiveness of decolonization procedure in transplant candidates may be limited. However, the combination of active surveillance, decolonization with mupirocin and the use of contact precautions was shown to significantly decrease MRSA infections and bacteremia during post-transplant hospital stay (47). In addition, universal daily bathing with chlorhexidine 2% 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 is recommended to reduce colonization and infections with Gram-positive organisms including MRSA (16).

MDR-GNB

Several studies, including randomized trials, have evaluated the efficacy of a decolonization strategy in ESBL/ESCR-E or CRE/CPE carriers, especially in hematological and in ICU patients (48–53). Although in some studies a reduction in infection rates has been reported, the long-term benefit of this intervention has yet to be defined (54) and selection of resistance is a concern.

In a multicentre randomized controlled trial conducted in Spain (55), 768 SOT recipients were screened for MDR-Enterobacterales colonization (extended-spectrum β -lactamase or carbapenemase producing) before transplantation and +7 and + 14 days after transplantation; 105 were randomized 1:1 to receive oral treatment with colistin sulfate plus neomycin sulfate for 14 days (decolonization treatment (DT) group, n=53) or no treatment (no decolonization treatment (NDT) group, n=52). No significant decrease in the risk of infection by MDR-E was observed in the DT group (9.4%, 5/53) compared to the NDT group (13.5%, 7/52) (relative risk 0.70; 95% confidence interval 0.24-2.08; p 0.517) but the number of events was small. Four patients (5.6%), three (5.6%) in the DT group and one (1.9%) in the NDT group, developed colistin resistance. Adverse events including diarrhea, skin rash, nausea and vomiting were more common in the DT than NDT groups (27% vs. 3.8%). Thus, since a net benefit in general and SOT population has not been determined, to date there is no evidence to support gut decolonization in SOT recipients colonized with MDR Gram negative bacteria (27).

Airway colonization with CRE/CPE, MDR-PA or CR-AB remains a significant issue after lung transplant. The efficacy of inhaled antibiotics, such as colistin or tobramycin, has been evaluated in small cohorts of non-SOT patients, with discordant results (56–60). Since *P. aeruginosa* carriage in the immediate post-transplant period may lead to infection of the bronchial anastomosis and dehiscence of the suture, it is a common practice to prescribe nebulized antibiotics if such pathogen is isolated from respiratory secretions of a Lu-T recipient in the immediate post-transplant period. Conversely, inhaled antimicrobial therapy has not demonstrated any benefit in preventing infections caused by CR-Ab in both colonized donors and Lu-T recipients (21).

Pre-emptive approach

Since previous colonization is the main risk factor for MDRO infection in the post-transplant period, in presence of signs/symptoms of infection, a prompt empirical treatment active against the colonizing strain is commonly adopted. In this regard, individual risk models and new rapid molecular tests may improve identification of patients at high risk and allows for early confirmation or exclusion of MDRO involvement at infection level optimizing the use of antibiotics, especially of the new drugs according to diagnostic and antimicrobial stewardship principles. Thus, along with the classical preemptive approach based on serial surveillance cultures and targeted antibiotic initiation upon symptoms onset, we may improve patient management using tools able to stratify the individual risk of developing infection in order to guide the use of diagnostic procedures (imaging studies as well as microbiological investigations) and antimicrobial use.

With this aim, a recent study conducted among 840 LT recipients, colonized with CRE before or after LT, in 15 different transplant centers investigated risk factors for developing CRE infection in the post-transplant period and further proposed a stratification tool including those variables independently associated with CRE

infection (11). The score was designed to be used in the immediate post-transplant period, ideally from the day of transplantation up to 3-4 weeks after transplantation. The cumulative risk of CRE infection within 30-60 days after liver transplant was assessed using a prediction model composed of the carriage status, the presence of multisite colonization after OLT, the need of prolonged MV, the development of AKI, and/or the need of re-intervention—Exploring the potential clinical utility of this prediction model using a decision-curve analysis, a “net benefit” of applying model-directed interventions was found when the overall CRE infection threshold probability exceeded 10%. These interventions could consist of intensification in diagnostic investigations including imaging to identify an infectious focus potentially amenable to source control, and the use of rapid molecular tests (i.e. multiplex-PCR) to rule out the presence of CRE in clinical specimens such blood and/or lower respiratory samples. In addition, since in a further multistate analysis, the same score was also shown to predict mortality when the CRE infection risk approached 30%, it has been hypothesized that for threshold probabilities $\geq 30\%$ initiation of empirical treatment waiting for the results of diagnostic investigations could be considered regardless of symptoms. However, the impact of such risk stratification tool in improving antimicrobial use, decreasing mortality and further resistance selection is currently under investigation (NCT05594901).

Molecular diagnostic testing has gained attention in the last several years due to a rapid turnaround time and high sensitivity, potentially improving time to effective antibiotics and decreasing the duration unnecessarily broad therapy.. In 2018 Liang et al. highlighted the potential role of a multiplex polymerase chain reaction (PCR) able to differentiate Gram-positive from Gram-negative bacterial DNA in a 3.5-hour time period in blood specimens (61). Thereafter, different multiplexed PCR has been developed in order to rapidly detect specific resistance patterns as MEC, VAN, CTX-M, KPC, VIM, OXA-48 from blood cultures with a turnaround varying from 1 to 2.5 hours (62,63). These novel tests showed a high concordance with standard of care in overall 88.3% blood cultures, specifically in 92% and 96% of all samples growing Gram-positive and Gram-negative pathogens, respectively (64). Although the presence of polymicrobial bacteremia could reduce sensitivity of these assays, concordance for detecting resistance mechanisms could reach 100% (65). Furthermore, some new molecular assays have been developed considering specific syndromes, such as lower respiratory tract infections. Indeed, several studies highlighted the potential role of syndromic molecular tests in improving antibiotic use mainly in the management of critically ill patients with hospital acquired/ventilator associated pneumonia (66,67), and in settings with high prevalence of MDROs. A recent study demonstrated an increase in detection of potential pneumonia pathogens compared to standard of care methods, pointing out the importance of semi-quantification of bacterial load that ideally could assist physicians in understanding its clinical role (68). Gram-negative resistance markers were detected in all cases. Considering the turnaround time of approximately 1 hour, it has the potential to improve antimicrobial stewardship. A randomized trial evaluating its benefit compared to standard of care is ongoing (69). Thus, in

immunosuppressed or critically ill patients this approach may lead to a quasi-targeted treatment, based on detecting or ruling out specific patterns of resistance.

THERAPEUTIC OPTIONS

Recommendations regarding antibiotic treatment for documented MDRO infection in SOT recipients do not differ from that for general population. The pivotal role of source control to improve graft/patient survival and reducing the risk of infection relapse should be emphasized.

MRSA

IDSA guidelines for the treatment of MRSA bloodstream infection has been published in 2011 (70), an update of that document is ongoing with the collaboration of ESCMID, while UK guidelines on the treatment of MRSA infections have been recently updated (71). The choice of a specific treatment should be based on strain susceptibility and infection site. For MRSA bacteremia or endocarditis, intravenous vancomycin and daptomycin are considered first options. Linezolid, as well as ceftaroline and ceftobiprole, are considered good options for the treatment of MRSA pneumonia (72,73).

VRE

Linezolid and daptomycin are used for VRE infection treatment with several limitations. Linezolid has a bacteriostatic effect, and retrospective studies suggest an underexposure of daptomycin at standard dosage (4-6 mg/kg). (74–76). In fact, lower 30-day mortality rate and improved microbiological clearance in patients treated with high-dose (≥ 10 mg/Kg) daptomycin compared with medium or standard dose daptomycin was reported in one study (77). Another study confirmed that the clinical response of daptomycin was dose-dependent (78). Thus, treatment options for VRE are limited and mortality rates in historical cohorts remain high (up to 40%) (79), suggesting that new drugs are needed. In this regard, the long-acting lipoglycopeptide oritavancin, recently introduced in Europe for the treatment of ABSSSI in adults, was shown to have good *in vitro* activity against VRE strains (including those resistant to daptomycin) (80). Clinical data on its efficacy and safety for the treatment of monomicrobial VRE surgical site infection after SOT are needed.

MDR-GNB

IDSA and ESCMID have been recently published guidance documents and guidelines, respectively, for the treatment of MDR-GNB infections (81–83). Recommendations of such documents are summarized in Table 3. The main differences between the two documents include: i) the application the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system in the European Guidelines thus limiting the indication for some drugs recently introduced in the clinical practice (i.e.

imipenem/relebactam), while the US guidance was based on a consensus of experts; ii) classification of resistance for *P. aeruginosa*, European guidelines addressed the treatment of carbapenem resistant strains that could maintain in some cases susceptibility to piperacillin/tazobactam and/or ceftazidime, cefepime. While IDSA guidance adopted the more innovative definition of difficult to treat resistant (DTR) *P. aeruginosa* more appropriate to depict strains with limited treatment options; iii) recommendations regarding the drug of choice were declined according to clinical severity and to infection site in European and US documents, respectively.

Along with the choice of the drug, the dosage and the administration modality (i.e. intermittent vs. prolonged/continuous infusion) are key to ensure PK/PD target attainment. Indeed, even more real-life data underline that appropriate administration schedules (i.e. loading dose followed by prolonged or continuous infusions of beta-lactams), supported by a therapeutic drug monitoring (TDM) and pharmacological advice approach is associated with better microbiological and clinical outcome, especially in the management of immunocompromised patients with severe MDRO infections (84–86).

Finally, it should be remarked that antibiotic resistance *per se* does not require a prolonged treatment duration (81,82), this may be necessary only in case of inappropriate initial treatment and/or source control with delayed clinical and/or microbiological response.

FUTURE DIRECTIONS

Previous microbiome studies demonstrated that an increase in relative abundance of CPE is associated with subsequent bacteremia (87), suggesting a crucial role for a dysregulated gut microbiota in infection development. Similarly, Enterococcus and Proteobacteria dominance has been correlated with an increased risk of bacteremia with VRE and Gram-negative bacteria, respectively (88). Fecal microbiota transplantation (FMT) has been proposed as a way to restore protective intestinal microbiome diversity. Indeed, it has been observed that patients undergoing FMT for recurrent *C. difficile* infection cleared also MDRO colonization. FDA decided to allow its use for such purpose under an enforcement discretion policy. A recent systematic review focused on such issue (89). Overall, 10 studies including one randomized open-label clinical trial were pooled. Among 112 FMT recipients colonized by CRE, decolonization was reported up to 60% and 79% at 1 and at 6-12 months, respectively. However, little is known about the efficacy and safety of FMT in SOT recipients, even if preliminary results, mainly regarding *C. difficile* infection, appears promising (90).

SUMMARY

The burden of MDRO infections in SOT may vary according to local prevalence and type of SOT. Poorer impact on graft/patient outcome has been observed, in particular for CR-GNB infections where mortality rates were as high as 40-60% before the introduction of new drugs. New drugs have improved patient survival in the general population, but a significant percentage of microbiological failure with persistent or relapsing

infection and/or emergence of further resistance has already been observed with their use. Thus, infection control and antimicrobial stewardship activities aimed at the reducing the spread and optimizing therapeutic management of MDRO in SOT recipients are needed. Screening strategies should be based on the careful assessment of local epidemiology. Protocols for targeted perioperative antibiotic prophylaxis should consider the low level of evidence currently sustaining this approach and potential harmful consequences on gut dysbiosis. For the same reason, prolonged prophylaxis or treatment duration should be avoided. Predictive tools able to stratify patients according with their risk of developing MDRO infection and/or dying combined with the use of new rapid diagnostic tests may support clinicians in the appropriate use of antibiotic therapy. Finally, efficacy and safety of new non-antibiotic based strategies, such as FMT, to reduce MDRO burden, in SOT population should be investigated.

CLINICS CARE POINTS

- SOT candidates and recipients are highly susceptible to acquire MDRO colonization and/or infection with a significant impact on graft/patient survival;
- Optimal management of the MDRO burden in SOT patients should consist in individualized preventive strategies, fully integrated with infection control and antimicrobial stewardship activities, with the goals of improving patient outcome as well as to minimize environmental damage;
- Patient risk stratification tools and rapid diagnostic tests may be useful in improving diagnostic and therapeutic management of MDRO in SOT population;
- New data should be acquired on the efficacy and safety of FMT in reducing the burden of MDRO in SOT patients.

Table 1. Incidence, risk factors and outcome for MDRO infections in each type of SOT.

Micro-organism	Organ	Burden (incidence/ prevalence)	Risk factors	Outcome	
				Mortality	Graft complications/loss
All MDRO	Liver	21.7-25%	Hematoma, biloma, complicated intraabdominal infection, cholangitis and recurrent biliary infection	38.6%	NA
	Kidney	8.4%	Recurrent urinary tract infection Renal cyst infection Surgical site infection Peri-graft infected hematoma	NA	NA
	Lung	NA	Previous recipient-related colonization, previous exposure to broad-spectrum antibiotics, tracheostomy, ICU stay >14 days	NA	NA
	Heart	29.7-37%	Deep surgical site infection, hospital-acquired pneumonia, diabetes, antibiotic treatment within 1 month before transplant	30-day 14.3%	Early graft failure 21.4%
MRSA	Liver	4-7.3%	Preoperative nasal carriage, alcoholic cirrhosis, decreased prothrombin ratio	0-21%	0%
	Kidney	1.25-1.9%	Preoperative nasal carriage, steroid treatment during the previous 4 weeks	30-day 10%	10%
	Lung	14.8-35%; 26% of early-onset pneumonia	Preoperative nasal carriage, mechanical ventilation for > 5 days	30-day 10-17.6%	Acute rejection 13-37% Chronic rejection 23%
	Heart	6.2-38%	Preoperative nasal carriage	NA	NA
VRE	Liver	0-16%	Immunosuppression, antibiotic exposure, indwelling catheters, manipulation of the gastrointestinal tract, ERCP, anti-anaerobic antibiotics, re-operation	30-day: 9-54% 1-year: 56-80%	Rejection 20%
	Kidney	0-13.6%	Continuous ambulatory peritoneal dialysis, vancomycin use	NA	NA
	Lung	0-19%	Renal failure, diabetes	NA	NA
	Heart	0.8-7%	Renal failure, diabetes	NA	NA
ESBL/ESCR-E	Liver	8-13.2%	Previous 3GC exposure, pre-transplant colonization, prolonged tracheal intubation, long-term hospitalization, post-transplant renal	2.6%	NA

			replacement therapy, acute rejection, MELD \geq 25, preoperative spontaneous bacterial peritonitis prophylaxis		
	Kidney	26-45%	Urinary tract obstruction and instrumentation, kidney-pancreas transplantation, recurrent urinary tract infection	2.9-6.7%	NA
	Lung	2-20.5%	Previous antibiotic exposure, pre-transplant colonization, prolonged tracheal intubation	In-hospital: 18-27%	NA
	Heart	5-14.2%	Previous antibiotic exposure, pre-transplant colonization, prolonged tracheal intubation	NA	NA
CRE/CPE	Liver	1-16%	CRE carriage before/after transplant, high MELD score, multi-organ transplant, reintervention, AKI or RRT, prolonged mechanical ventilation, graft rejection	45%-58%	NA
	Kidney	1-11%	Ureteral stent, pre-transplant CR-KP infection/colonization	28%	NA
	Lung	1-8.1%	Length of hospital stay, deceased donor allograft, diabetes mellitus	30-day 36% 1-year 64%	Re-transplantation 18.2%
	Heart	0.4-6%	Carbapenem exposure, pre-transplant CR-KP infection/colonization	NA	NA
CR-AB	Liver	2.2-10.5%	Length of post-transplant ICU stay	30-day: 28.6-66.7%	NA
	Kidney	1.1-4.3%	NA	30-day: 12.5-40.8%	66.7% graft loss
	Lung	NA	High blood urea nitrogen before LT, long duration of surgery, hypoalbuminemia	30-day: 5.9% 90-day: 19.6% 1-year: 66.7%	NA
	Heart	1.9-3.1%	NA	30-day: 13%	NA
MDR <i>P. aeruginosa</i>	Liver	0.3-7.2%	Prior transplantation or ICU admission, nosocomial acquisition, septic shock	30-day: 30%	NA
	Kidney	0.9%	NA	NA	NA
	Lung	NA	Previous recipient-related colonization, empirical exposure to broad-spectrum antibiotics	NA	BOS in 22.7% of colonized Lu-T
	Heart	0.8%	NA	NA	NA

Abbr: MDRO multidrug resistant organisms, MRSA methicillin-resistant *Staphylococcus aureus*, VRE vancomycin-resistant Enterococci, ESBL/ESCR-E extended spectrum beta-lactamase *Enterobacterales*, CRE/CPE carbapenem resistant/producing *Enterobacterales*, CR-AB carbapenem-resistant *Acinetobacter baumannii*, MDR-*P. aeruginosa* multidrug-resistant *Pseudomonas aeruginosa*, NA not available, BOS bronchiolitis obliterans syndrome

Table 2. Main recommendation statements for management of Gram negative colonization in SOT recipients.

	GESITRA (2018)(21)	AST (2019)(22)	ESCMID (2022)(23)
ESBL-E/ESCR-E			
Screening	Yes	Controversial outside outbreaks	Yes in LT (conditional, low) GCP in all SOT* (expert opinion)
Targeted antibiotic prophylaxis	Yes, but avoid carbapenems	Undefined	Yes in LT (conditional, very low) GCP in all SOT* (expert opinion)
Decolonization	No	No	NA^
CRE/CPE			
Screening	Yes	Yes	Yes in LT (conditional, low) GCP in all SOT* (expert opinion)
Targeted antibiotic prophylaxis	No, but consider if high incidence of CPE SSI	Undefined	Insufficient evidence
Decolonization	No	No	NA^
MDR-PA			
Screening	No except in Lu-T recipients	NA	NA
Targeted antibiotic prophylaxis	No in non-Lu-T recipients	NA	NA
Decolonization	Nebulized antibiotics in Lu-T	NA	NA
CR-Ab			
Screening	NA	In high endemic settings or outbreak	Yes in LT* (conditional, low) GCP in all SOT* (expert opinion)
Targeted antibiotic prophylaxis	No	NA	Insufficient evidence

Decolonization	No	NA	NA
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*according to local epidemiology

Abbr. ESBL-E, extended-spectrum Beta-lactamase Enterobacterales, CPE carbapenem-resistant Enterobacterales, MDR-PA multidrug resistant Pseudomonas aeruginosa, CR-AB carbapenem-resistant Acinetobacter baumannii, SOT solid organ transplant, Lu-T lung transplant, LT liver transplant, GCP good clinical practice, NA not available.

^Issue addressed in another ESCMID-EUCIC guideline (91).

Table 3. Main guidelines recommendations for MDRO treatment.

IDSA (81,82)				
	UTI	cUTI	non-UTI	Notes
ESBL-E	Nitrofurantoin TMP-SMX	ERTA, MEM, IMP FQs, TMP-SMX	CARBAPENEM	If BL/BLI was initiated as empiric therapy for UTI with clinical improvement no change is necessary
CRE	FQs, TMP-SMX, single dose AG, HD MEM (or new drugs)	FQs, TMP-SMX, single dose AG, HD MEM (or new drugs)	KPC: CAZ-AVI, MEM-VAB, IMP-REL OXA-48: CAZ-AVI MBL: CAZ-AVI+AZT, CFD	
DTR-PA	TOL/TZB, CAZ/AVI, IMP/REL, CFD	CFO/TZB, CAZ/AVI, IMP/REL, CFD	TOL/TZB, CAZ/AVI, IMP/REL	If strain is susceptible to multiple traditional beta-lactams or FQs carbapenem-sparing options are preferred
CR-AB	HD sulbactam (6-9 g/day) as monotherapy for mild infections		HD sulbactam (6-9 g/day) combined with other in vitro active drug (minocycline, tigecycline)	Cefiderocol should be limited to refractory infections and as a part of combination regimen.
ESCMID (83)				
	Severe infection	Non-severe infection	cUTI	Notes
ESCR-E	CARBAPENEM, ERTAPENEM (if no septic shock)	BL/BLI, FQs, TMP-SMX	AG, IV FOSFOMYCIN	New BL/BLIs should be reserved for XDR bacteria
CRE	KPC: CAZ-AVI, MEM-VAB OXA-48: CAZ-AVI MBL: CAZ-AVI+AZT, CFD	Old antibiotics (combination)	AG	No evidence to recommend for or against IMP-REL

CR-PA	TOL/TZB	Old antibiotics	Old antibiotics	No evidence to recommend for or against combination with new BL/BLIs Combination suggested for old antibiotics
CR-AB	Combination therapy including two <i>in vitro</i> active antibiotics	Ampicillin/sulbactam if susceptible If resistant, polymyxin or HD tigecycline	Ampicillin/sulbactam if susceptible If resistant, polymyxin or HD tigecycline	Cefiderocol is conditionally not recommended. If meropenem MIC \leq 8 mg/L, consider carbapenem combination regimen

Abbr: ESBL extended spectrum beta-lactamase, CRE carbapenem-resistant Enterobacterales, DTR-PA difficult-to-treat *P. aeruginosa*, CR-AB carbapenem-resistant *A. baumannii*, 3GCephRE third generation cephalosporin-resistant Enterobacterales, UTI urinary tract infections, cUTI complicated urinary tract infection, ERTA ertapenem, MEM meropenem, IMP imipenem, BL/BLI beta-lactam/beta-lactamase inhibitor, TMP/SMX trimethoprim/sulfamethoxazole, FQ fluoroquinolones, AG aminoglycosides, HD high-dose, MEM/VAB meropenem/vaborbactam, IMP/REL imipenem/relebactam, CAZ-AVI ceftazidime/avibactam, CFD cefiderocol, TOL/TZB ceftolozane/tazobactam.

BIBLIOGRAPHY

1. van Delden C, Stampf S, Hirsch HH, Manuel O, Meylan P, Cusini A, et al. Burden and Timeline of Infectious Diseases in the First Year After Solid Organ Transplantation in the Swiss Transplant Cohort Study. *Clin Infect Dis* [Internet]. 2020 Oct 23 [cited 2023 Jan 9];71(7):e159–69. Available from: doi.org/10.1093/cid/ciz1113
2. Hamandi B, Husain S, Grootendorst P, Papadimitropoulos EA. Clinical and microbiological epidemiology of early and late infectious complications among solid-organ transplant recipients requiring hospitalization. *Transpl Int Off J Eur Soc Organ Transplant*. 2016 Sep;29(9):1029–38.
3. Coussement J, Maggiore U, Manuel O, Scemla A, López-Medrano F, Nagler EV, et al. Diagnosis and management of asymptomatic bacteriuria in kidney transplant recipients: a survey of current practice in Europe. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2018 Sep 1;33(9):1661–8.
4. Mularoni A, Bertani A, Vizzini G, Gona F, Campanella M, Spada M, et al. Outcome of Transplantation Using Organs From Donors Infected or Colonized With Carbapenem-Resistant Gram-Negative Bacteria. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2015 Oct;15(10):2674–82.
5. Procaccio F, Masiero L, Vespasiano F, Grossi PA, Gagliotti C, Pantosti A, et al. Organ donor screening for carbapenem-resistant gram-negative bacteria in Italian intensive care units: the DRIn study. *Am J Transplant* [Internet]. 2020 [cited 2023 Jan 9];20(1):262–73. Available from: onlinelibrary.wiley.com/doi/abs/10.1111/ajt.15566
6. Lewis JD, Sifri CD. Multidrug-Resistant Bacterial Donor-Derived Infections in Solid Organ Transplantation. *Curr Infect Dis Rep*. 2016 Jun;18(6):18.
7. Miller R, Covington S, Taranto S, Carrico R, Ehsan A, Friedman B, et al. Communication gaps associated with donor-derived infections. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2015 Jan;15(1):259–64.
8. Ariza-Heredia EJ, Patel R, Blumberg EA, Walker RC, Lewis R, Evans J, et al. Outcomes of transplantation using organs from a donor infected with *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae*. *Transpl Infect Dis Off J Transplant Soc*. 2012 Jun;14(3):229–36.
9. Freire MP, Villela Soares Oshiro IC, Bonazzi PR, Pierrotti LC, de Oliveira LM, Machado AS, et al. Surveillance culture for multidrug-resistant gram-negative bacteria: Performance in liver transplant recipients. *Am J Infect Control*. 2017 Mar 1;45(3):e40–4.
10. Taimur S, Pouch SM, Zubizarreta N, Mazumdar M, Rana M, Patel G, et al. Impact of pre-transplant carbapenem-resistant Enterobacterales colonization and/or infection on solid organ transplant outcomes. *Clin Transplant*. 2021 Apr;35(4):e14239.
11. Giannella M, Freire M, Rinaldi M, Abdala E, Rubin A, Mularoni A, et al. Development of a Risk Prediction Model for Carbapenem-resistant Enterobacteriaceae Infection After Liver Transplantation: A Multinational Cohort Study. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2021 Aug 16;73(4):e955–66.
12. World Health Organization. Global guidelines for the prevention of surgical site infection [Internet]. World Health Organization; 2018 [cited 2023 Feb 10]. 184 p. Available from: apps.who.int/iris/handle/10665/277399

13. Pereira MR, Rana MM, AST ID Community of Practice. Methicillin-resistant *Staphylococcus aureus* in solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019 Sep;33(9):e13611.
14. Calfee DP, Salgado CD, Milstone AM, Harris AD, Kuhar DT, Moody J, et al. Strategies to prevent methicillin-resistant *Staphylococcus aureus* transmission and infection in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014 Jul;35(7):772–96.
15. Clancy CJ, Bartsch SM, Nguyen MH, Stuckey DR, Shields RK, Lee BY. A computer simulation model of the cost-effectiveness of routine *Staphylococcus aureus* screening and decolonization among lung and heart-lung transplant recipients. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol*. 2014 Jun;33(6):1053–61.
16. Abbo LM, Grossi PA, AST ID Community of Practice. Surgical site infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019 Sep;33(9):e13589.
17. Ziakas PD, Pliakos EE, Zervou FN, Knoll BM, Rice LB, Mylonakis E. MRSA and VRE colonization in solid organ transplantation: a meta-analysis of published studies. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2014 Aug;14(8):1887–94.
18. Simkins J, Morris MI, Camargo JF, Vianna R, Beduschi T, Abbo LM. Clinical outcomes of intestinal transplant recipients colonized with multidrug-resistant organisms: a retrospective study. *Transpl Int [Internet]*. 2017 Sep 1 [cited 2023 Jan 1];30(9):924–31. Available from: <https://doi.org/10.1111/tri.12987>
19. Nellore A, Huprikar S, AST ID Community of Practice. Vancomycin-resistant *Enterococcus* in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019 Sep;33(9):e13549.
20. Malinis M, Boucher HW, AST Infectious Diseases Community of Practice. Screening of donor and candidate prior to solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019 Sep;33(9):e13548.
21. Aguado JM, Silva JT, Fernández-Ruiz M, Cordero E, Fortún J, Gudiol C, et al. Management of multidrug resistant Gram-negative bacilli infections in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations. *Transplant Rev Orlando Fla*. 2018 Jan;32(1):36–57.
22. Pouch SM, Patel G, Practice the AIDC of. Multidrug-resistant Gram-negative bacterial infections in solid organ transplant recipients—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant [Internet]*. 2019 [cited 2022 Dec 28];33(9):e13594. Available from: onlinelibrary.wiley.com/doi/abs/10.1111/ctr.13594
23. Righi E, Mutters NT, Guirao X, Dolores Del Toro M, Eckmann C, Friedrich AW, et al. ESCMID/EUCIC clinical practice guidelines on perioperative antibiotic prophylaxis in patients colonized by multidrug-resistant Gram-negative bacteria before surgery. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. 2022 Dec 22;S1198-743X(22)00632-2.
24. Apisarnthanarak A, Kondo S, Mingmalairak C, Mahawongkajit P, Juntong J, Limpavitayaporn P, et al. Outcomes of extended-spectrum beta-lactamases producing *Enterobacteriaceae* colonization among patients abdominal surgery patients. *Infect Control Hosp Epidemiol*. 2019 Nov;40(11):1290–3.
25. Golzarri MF, Silva-Sánchez J, Cornejo-Juárez P, Barrios-Camacho H, Chora-Hernández LD, Velázquez-Acosta C, et al. Colonization by fecal extended-spectrum β -lactamase-producing *Enterobacteriaceae*

- and surgical site infections in patients with cancer undergoing gastrointestinal and gynecologic surgery. *Am J Infect Control*. 2019 Aug;47(8):916–21.
26. Dubinsky-Pertsov B, Temkin E, Harbarth S, Fankhauser-Rodriguez C, Carevic B, Radovanovic I, et al. Carriage of Extended-spectrum Beta-lactamase-producing Enterobacteriaceae and the Risk of Surgical Site Infection After Colorectal Surgery: A Prospective Cohort Study. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2019 May 2;68(10):1699–704.
 27. De Pastena M, Paiella S, Azzini AM, Zaffagnini A, Scarlini L, Montagnini G, et al. Antibiotic Prophylaxis with Piperacillin-Tazobactam Reduces Post-Operative Infectious Complication after Pancreatic Surgery: An Interventional, Non-Randomized Study. *Surg Infect*. 2021 Jun;22(5):536–42.
 28. Bert F, Larroque B, Paugam-Burtz C, Dondero F, Durand F, Marcon E, et al. Pretransplant fecal carriage of extended-spectrum β -lactamase-producing Enterobacteriaceae and infection after liver transplant, France. *Emerg Infect Dis*. 2012 Jun;18(6):908–16.
 29. Bert F, Larroque B, Dondero F, Durand F, Paugam-Burtz C, Belghiti J, et al. Risk factors associated with preoperative fecal carriage of extended-spectrum β -lactamase-producing Enterobacteriaceae in liver transplant recipients. *Transpl Infect Dis Off J Transplant Soc*. 2014 Feb;16(1):84–9.
 30. Mazza E, Proserpi M, Panzeri MF, Limuti R, Nichelatti M, De Gasperi A. Carbapenem-Resistant *Klebsiella Pneumoniae* Infections Early After Liver Transplantation: A Single-Center Experience. *Transplant Proc*. 2017 May;49(4):677–81.
 31. Freire MP, Song ATW, Oshiro ICV, Andraus W, D'Albuquerque LAC, Abdala E. Surgical site infection after liver transplantation in the era of multidrug-resistant bacteria: what new risks should be considered? *Diagn Microbiol Infect Dis*. 2021 Jan;99(1):115220.
 32. Giannella M, Bartoletti M, Morelli MC, Tedeschi S, Cristini F, Tumietto F, et al. Risk factors for infection with carbapenem-resistant *Klebsiella pneumoniae* after liver transplantation: the importance of pre- and posttransplant colonization. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2015 Jun;15(6):1708–15.
 33. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant*. 2015 Jan;34(1):1–15.
 34. Kochar S, Sheard T, Sharma R, Hui A, Tolentino E, Allen G, et al. Success of an infection control program to reduce the spread of carbapenem-resistant *Klebsiella pneumoniae*. *Infect Control Hosp Epidemiol*. 2009 May;30(5):447–52.
 35. Johnson LE, D'Agata EMC, Paterson DL, Clarke L, Qureshi ZA, Potoski BA, et al. *Pseudomonas aeruginosa* bacteremia over a 10-year period: multidrug resistance and outcomes in transplant recipients. *Transpl Infect Dis Off J Transplant Soc*. 2009 Jun;11(3):227–34.
 36. Bodro M, Sabé N, Tubau F, Lladó L, Baliellas C, González-Costello J, et al. Extensively drug-resistant *Pseudomonas aeruginosa* bacteremia in solid organ transplant recipients. *Transplantation*. 2015 Mar;99(3):616–22.
 37. Bodro M, Sabé N, Tubau F, Lladó L, Baliellas C, Roca J, et al. Risk factors and outcomes of bacteremia caused by drug-resistant ESKAPE pathogens in solid-organ transplant recipients. *Transplantation*. 2013 Nov 15;96(9):843–9.

38. Tebano G, Geneve C, Tanaka S, Grall N, Atchade E, Augustin P, et al. Epidemiology and risk factors of multidrug-resistant bacteria in respiratory samples after lung transplantation. *Transpl Infect Dis Off J Transplant Soc.* 2016 Feb;18(1):22–30.
39. Enfield KB, Huq NN, Gosseling MF, Low DJ, Hazen KC, Toney DM, et al. Control of simultaneous outbreaks of carbapenemase-producing enterobacteriaceae and extensively drug-resistant *Acinetobacter baumannii* infection in an intensive care unit using interventions promoted in the Centers for Disease Control and Prevention 2012 carbapenemase-resistant Enterobacteriaceae Toolkit. *Infect Control Hosp Epidemiol.* 2014 Jul;35(7):810–7.
40. Freire MP, Pierrotti LC, Oshiro ICVS, Bonazzi PR, Oliveira LM de, Machado AS, et al. Carbapenem-resistant *Acinetobacter baumannii* acquired before liver transplantation: Impact on recipient outcomes. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc.* 2016 May;22(5):615–26.
41. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect.* 2013 Feb;14(1):73–156.
42. Logre E, Bert F, Khoy-Ear L, Janny S, Giabicani M, Grigoresco B, et al. Risk Factors and Impact of Perioperative Prophylaxis on the Risk of Extended-spectrum β -Lactamase-producing Enterobacteriaceae-related Infection Among Carriers Following Liver Transplantation. *Transplantation.* 2021 Feb 1;105(2):338–45.
43. Cardile S, Del Chierico F, Candusso M, Reddel S, Bernaschi P, Pietrobattista A, et al. Impact of Two Antibiotic Therapies on Clinical Outcome and Gut Microbiota Profile in Liver Transplant Paediatric Candidates Colonized by Carbapenem-Resistant *Klebsiella pneumoniae* CR-KP. *Front Cell Infect Microbiol.* 2021;11:730904.
44. Hadjiliadis D, Steele MP, Chaparro C, Singer LG, Waddell TK, Hutcheon MA, et al. Survival of lung transplant patients with cystic fibrosis harboring panresistant bacteria other than *Burkholderia cepacia*, compared with patients harboring sensitive bacteria. *J Heart Lung Transplant [Internet].* 2007 Aug 1 [cited 2023 Jan 2];26(8):834–8. Available from: doi.org/10.1016/j.healun.2007.05.018
45. Flume PA, Egan TM, Paradowski LJ, Detterbeck FC, Thompson JT, Yankaskas JR. Infectious complications of lung transplantation. Impact of cystic fibrosis. *Am J Respir Crit Care Med.* 1994 Jun;149(6):1601–7.
46. Paterson DL, Rihs JD, Squier C, Gayowski T, Sagnimeni A, Singh N. Lack of efficacy of mupirocin in the prevention of infections with staphylococcus aureus in liver transplant recipients and candidates. *Transplantation [Internet].* 2003 Jan 27 [cited 2023 Jan 1];75(2):194. Available from: journals.lww.com/transplantjournal/Fulltext/2003/01270/Lack_of_efficiency_of_mupirocin_in_the_prevention_of.6.aspx
47. Singh N, Squier C, Wannstedt C, Keyes L, Wagener MM, Cacciarelli TV. Impact of an Aggressive Infection Control Strategy on Endemic *Staphylococcus aureus* Infection in Liver Transplant Recipients. *Infect Control Hosp Epidemiol [Internet].* 2006 Feb [cited 2023 Jan 1];27(2):122–6. Available from: www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/article/abs/impact-of-an-aggressive-infection-control-strategy-on-endemic-staphylococcus-aureus-infection-in-liver-transplant-recipients/CBACC922F6FF51F80B6B71F9D6FAA024
48. Huttner B, Hausteiner T, Uçkay I, Renzi G, Stewardson A, Schaerr D, et al. Decolonization of intestinal carriage of extended-spectrum β -lactamase-producing Enterobacteriaceae with oral colistin and

- neomycin: a randomized, double-blind, placebo-controlled trial. *J Antimicrob Chemother* [Internet]. 2013 Oct 1 [cited 2023 Jan 3];68(10):2375–82. Available from: doi.org/10.1093/jac/dkt174
49. Jonsson AK, Larsson A, Tängdén T, Melhus Å, Lannergård A. A trial with IgY chicken antibodies to eradicate faecal carriage of *Klebsiella pneumoniae* and *Escherichia coli* producing extended-spectrum beta-lactamases. *Infect Ecol Epidemiol*. 2015;5:28224.
 50. Buehlmann M, Bruderer T, Frei R, Widmer AF. Effectiveness of a new decolonisation regimen for eradication of extended-spectrum β -lactamase-producing Enterobacteriaceae. *J Hosp Infect*. 2011 Feb;77(2):113–7.
 51. Decré D, Gachot B, Lucet JC, Arlet G, Bergogne-Bérézin E. Clinical and Bacteriologic Epidemiology of Extended-Spectrum β -Lactamase-Producing Strains of *Klebsiella pneumoniae* in a Medical Intensive Care Unit. *Clin Infect Dis* [Internet]. 1998 Oct 1 [cited 2023 Jan 3];27(4):834–44. Available from: doi.org/10.1086/514938
 52. Abecasis F, Sarginson RE, Kerr S, Taylor N, van Saene HKF. Is selective digestive decontamination useful in controlling aerobic gram-negative bacilli producing extended spectrum beta-lactamases? *Microb Drug Resist Larchmt N*. 2011 Mar;17(1):17–23.
 53. Troché G, Toly LM, Guibert M, Zazzo JF. Detection and Treatment of Antibiotic-Resistant Bacterial Carriage in a Surgical Intensive Care Unit: A 6-Year Prospective Survey. *Infect Control Hosp Epidemiol* [Internet]. 2005 Feb [cited 2023 Jan 3];26(2):161–5. Available from: www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/article/abs/detection-and-treatment-of-antibiotic-resistant-bacterial-carriage-in-a-surgical-intensive-care-unit-a-6-year-prospective-survey/8C22DB29FC89A9D0ADF1B9E332A1D87F
 54. Bar-Yoseph H, Hussein K, Braun E, Paul M. Natural history and decolonization strategies for ESBL/carbapenem-resistant Enterobacteriaceae carriage: systematic review and meta-analysis. *J Antimicrob Chemother*. 2016 Oct;71(10):2729–39.
 55. Fariñas MC, González-Rico C, Fernández-Martínez M, Fortún J, Escudero-Sanchez R, Moreno A, et al. Oral decontamination with colistin plus neomycin in solid organ transplant recipients colonized by multidrug-resistant Enterobacteriales: a multicentre, randomized, controlled, open-label, parallel-group clinical trial. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. 2021 Jun;27(6):856–63.
 56. Rattanaumpawan P, Lorsutthitham J, Ungprasert P, Angkasekwinai N, Thamlikitkul V. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria. *J Antimicrob Chemother* [Internet]. 2010 Dec 1 [cited 2023 Jan 3];65(12):2645–9. Available from: doi.org/10.1093/jac/dkq360
 57. Lin CC, Liu TC, Kuo CF, Liu CP, Lee CM. Aerosolized colistin for the treatment of multidrug-resistant *Acinetobacter baumannii* pneumonia: experience in a tertiary care hospital in northern Taiwan. *J Microbiol Immunol Infect Wei Mian Yu Gan Ran Za Zhi*. 2010 Aug;43(4):323–31.
 58. Hallal A, Cohn SM, Namias N, Habib F, Baracco G, Manning RJ, et al. Aerosolized tobramycin in the treatment of ventilator-associated pneumonia: A pilot study. *Surg Infect* [Internet]. 2007 Feb [cited 2023 Jan 3];8(1):73–81. Available from: www.scopus.com/inward/record.url?scp=34247129544&partnerID=8YFLogxK
 59. Kofteridis DP, Alexopoulou C, Valachis A, Maraki S, Dimopoulou D, Georgopoulos D, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated

- pneumonia: a matched case-control study. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2010 Dec 1;51(11):1238–44.
60. Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagas ME. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. *Crit Care [Internet]*. 2005 [cited 2023 Jan 3];9(1):R53–9. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC1065114/
 61. Liang F, Browne DJ, Gray MJ, Gartlan KH, Smith DD, Barnard RT, et al. Development of a Multiplexed Microsphere PCR for Culture-Free Detection and Gram-Typing of Bacteria in Human Blood Samples. *ACS Infect Dis*. 2018 May 11;4(5):837–44.
 62. She RC, Bender JM. Advances in Rapid Molecular Blood Culture Diagnostics: Healthcare Impact, Laboratory Implications, and Multiplex Technologies. *J Appl Lab Med [Internet]*. 2019 Jan 1 [cited 2023 Feb 10];3(4):617–30. Available from: doi.org/10.1373/jalm.2018.027409
 63. Peker N, Couto N, Sinha B, Rossen JW. Diagnosis of bloodstream infections from positive blood cultures and directly from blood samples: recent developments in molecular approaches. *Clin Microbiol Infect [Internet]*. 2018 Sep 1 [cited 2023 Feb 10];24(9):944–55. Available from: [www.clinicalmicrobiologyandinfection.com/article/S1198-743X\(18\)30419-1/fulltext](http://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(18)30419-1/fulltext)
 64. Berinson B, Both A, Berneking L, Christner M, Lütgehetmann M, Aepfelbacher M, et al. Usefulness of BioFire FilmArray BCID2 for Blood Culture Processing in Clinical Practice. *J Clin Microbiol*. 2021 Jul 19;59(8):e0054321.
 65. García-Rivera C, Parra-Grande M, Merino E, Boix V, Rodríguez JC. Concordance of the filmarray blood culture identification panel 2 and classical microbiological methods in a bacteriemia diagnostic unit. *Diagn Microbiol Infect Dis [Internet]*. 2022 Dec 1 [cited 2023 Feb 10];104(4):115787. Available from: www.sciencedirect.com/science/article/pii/S0732889322001535
 66. Monard C, Pehlivan J, Auger G, Alviset S, Tran Dinh A, Duquaire P, et al. Multicenter evaluation of a syndromic rapid multiplex PCR test for early adaptation of antimicrobial therapy in adult patients with pneumonia. *Crit Care Lond Engl*. 2020 Jul 14;24(1):434.
 67. Peiffer-Smadja N, Bouadma L, Mathy V, Allouche K, Patrier J, Reboul M, et al. Performance and impact of a multiplex PCR in ICU patients with ventilator-associated pneumonia or ventilated hospital-acquired pneumonia. *Crit Care Lond Engl*. 2020 Jun 19;24(1):366.
 68. Ginocchio CC, Garcia-Mondragon C, Mauerhofer B, Rindlisbacher C, and the EME Evaluation Program Collaborative. Multinational evaluation of the BioFire® FilmArray® Pneumonia plus Panel as compared to standard of care testing. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol*. 2021 Aug;40(8):1609–22.
 69. High J, Enne VI, Barber JA, Brealey D, Turner DA, Horne R, et al. INHALE: the impact of using FilmArray Pneumonia Panel molecular diagnostics for hospital-acquired and ventilator-associated pneumonia on antimicrobial stewardship and patient outcomes in UK Critical Care-study protocol for a multicentre randomised controlled trial. *Trials*. 2021 Oct 7;22(1):680.
 70. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children. *Clin Infect Dis [Internet]*. 2011 Feb 1 [cited 2023 Jan 3];52(3):e18–55. Available from: doi.org/10.1093/cid/ciq146

71. Brown NM, Brown EM, the Guideline Development Group. Treatment of methicillin-resistant *Staphylococcus aureus* (MRSA): updated guidelines from the UK. *J Antimicrob Chemother* [Internet]. 2021 Jun 1 [cited 2023 Jan 3];76(6):1377–8. Available from: doi.org/10.1093/jac/dkab036
72. Zhanel GG, Lam A, Schweizer F, Thomson K, Walkty A, Rubinstein E, et al. Ceftobiprole: a review of a broad-spectrum and anti-MRSA cephalosporin. *Am J Clin Dermatol*. 2008;9(4):245–54.
73. Sotgiu G, Aliberti S, Gramegna A, Mantero M, Di Pasquale M, Trogu F, et al. Efficacy and effectiveness of Ceftaroline Fosamil in patients with pneumonia: a systematic review and meta-analysis. *Respir Res* [Internet]. 2018 Oct 23 [cited 2023 Jan 3];19(1):205. Available from: doi.org/10.1186/s12931-018-0905-x
74. Balli EP, Venetis CA, Miyakis S. Systematic review and meta-analysis of linezolid versus daptomycin for treatment of vancomycin-resistant enterococcal bacteremia. *Antimicrob Agents Chemother*. 2014;58(2):734–9.
75. Whang DW, Miller LG, Partain NM, McKinnell JA. Systematic review and meta-analysis of linezolid and daptomycin for treatment of vancomycin-resistant enterococcal bloodstream infections. *Antimicrob Agents Chemother*. 2013 Oct;57(10):5013–8.
76. Britt NS, Potter EM, Patel N, Steed ME. Comparison of the Effectiveness and Safety of Linezolid and Daptomycin in Vancomycin-Resistant Enterococcal Bloodstream Infection: A National Cohort Study of Veterans Affairs Patients. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2015 Sep 15;61(6):871–8.
77. Britt NS, Potter EM, Patel N, Steed ME. Comparative Effectiveness and Safety of Standard-, Medium-, and High-Dose Daptomycin Strategies for the Treatment of Vancomycin-Resistant Enterococcal Bacteremia Among Veterans Affairs Patients. *Clin Infect Dis* [Internet]. 2017 Mar 1 [cited 2023 Jan 3];64(5):605–13. Available from: doi.org/10.1093/cid/ciw815
78. Chuang YC, Lin HY, Chen PY, Lin CY, Wang JT, Chang SC. Daptomycin versus linezolid for the treatment of vancomycin-resistant enterococcal bacteraemia: implications of daptomycin dose. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. 2016 Oct;22(10):890.e1-890.e7.
79. Edmond MB, Ober JF, Dawson JD, Weinbaum DL, Wenzel RP. Vancomycin-resistant enterococcal bacteremia: natural history and attributable mortality. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 1996 Dec;23(6):1234–9.
80. Carvalhaes CG, Sader HS, Streit JM, Castanheira M, Mendes RE. Activity of Oritavancin against Gram-Positive Pathogens Causing Bloodstream Infections in the United States over 10 Years: Focus on Drug-Resistant Enterococcal Subsets (2010-2019). *Antimicrob Agents Chemother*. 2022 Feb 15;66(2):e0166721.
81. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β -lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-P. *aeruginosa*). *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2021 Apr 8;72(7):e169–83.
82. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of AmpC β -Lactamase-Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2022 Jul 6;74(12):2089–114.

83. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. 2022 Apr;28(4):521–47.
84. Gatti M, Giannella M, Rinaldi M, Gaibani P, Viale P, Pea F. Pharmacokinetic/Pharmacodynamic Analysis of Continuous-Infusion Fosfomycin in Combination with Extended-Infusion Cefiderocol or Continuous-Infusion Ceftazidime-Avibactam in a Case Series of Difficult-to-Treat Resistant *Pseudomonas aeruginosa* Bloodstream Infections and/or Hospital-Acquired Pneumonia. *Antibiot Basel Switz*. 2022 Dec 2;11(12):1739.
85. Gatti M, Pascale R, Cojutti PG, Rinaldi M, Ambretti S, Conti M, et al. A descriptive pharmacokinetic/pharmacodynamic analysis of continuous infusion ceftazidime-avibactam in a case series of critically ill renal patients treated for documented carbapenem-resistant Gram-negative bloodstream infections and/or ventilator-associated pneumonia. *Int J Antimicrob Agents*. 2022 Dec 2;61(1):106699.
86. Gatti M, Fornaro G, Viale P, Pea F, Giannella M. Clinical efficacy of renal dosing adjustments of ceftazidime-avibactam in patients affected by carbapenem-resistant Gram-negative infections: A systematic review and meta-analysis of observational studies. *Br J Clin Pharmacol*. 2022 Nov 7;
87. Shimasaki T, Seekatz A, Bassis C, Rhee Y, Yelin RD, Fogg L, et al. Increased Relative Abundance of *Klebsiella pneumoniae* Carbapenemase-producing *Klebsiella pneumoniae* Within the Gut Microbiota Is Associated With Risk of Bloodstream Infection in Long-term Acute Care Hospital Patients. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2019 May 30;68(12):2053–9.
88. Petersen AM, Mirsepasi-Lauridsen HC, Vester-Andersen MK, Sørensen N, Kroghfelt KA, Bendtsen F. High Abundance of Proteobacteria in Ileo-Anal Pouch Anastomosis and Increased Abundance of Fusobacteria Associated with Increased Pouch Inflammation. *Antibiot Basel Switz*. 2020 May 8;9(5):237.
89. Macareño-Castro J, Solano-Salazar A, Dong LT, Mohiuddin M, Espinoza JL. Fecal microbiota transplantation for Carbapenem-Resistant Enterobacteriaceae: A systematic review. *J Infect*. 2022 Jun;84(6):749–59.
90. Mehta N, Wang T, Friedman-Moraco RJ, Carpentieri C, Mehta AK, Roupael N, et al. Fecal Microbiota Transplantation Donor Screening Updates and Research Gaps for Solid Organ Transplant Recipients. *J Clin Microbiol*. 2022 Feb 16;60(2):e0016121.
91. Tacconelli E, Mazzaferri F, de Smet AM, Bragantini D, Eggimann P, Huttner BD, et al. ESCMID-EUCLIC clinical guidelines on decolonization of multidrug-resistant Gram-negative bacteria carriers. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. 2019 Jul;25(7):807–17.