Antimicrobial Resistance in Organ Transplant Recipients

Editorial comments:

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.

Author's answer: Thank you for the edits, we have reviewed the manuscript and made changes, marked in yellow, according with your comments. Please let us know if additional requirements are needed.

Antimicrobial Resistance in Organ Transplant Recipients

Maddalena Giannella[1,2], Matteo Rinaldi[1,2], Pierluigi Viale[1,2]

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

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

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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 peri-operative 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 ≥ 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 ≥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 cefoxitin (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 ≥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	Risk factors	Outcome	
		(incidence/ prevalence)		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≥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 *P. aeruginosa*	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

*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 *in vitro* 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 ≤8 mg/L, consider carbapenem combination regimen

Abbr: ESBL extended spectrum beta-lactamase, CRE carbapenem-resistant Enterobacterales, DTR-PA diffult-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/sulfametoxazole, 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.

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