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Special Article

Multidrug-Resistant Gram-Negative Bacteria Infections in Solid Organ Transplantation

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Abbreviations: BCSA, *Burkholderia cepacia* selective agar; BOS, bronchiolitis obliterans; CF, cystic fibrosis; CLSI, Clinical and Laboratory Standards Institute; CR, carbapenem resistant; CRAB, carbapenem-resistant *Acinetobacter*; CRE, carbapenem resistant *Enterobacteriaceae*; ESBL, extended-spectrum beta-lactamase; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, Food and Drug Administration; ICU, intensive care unit; IV, intravenous; MCBT, multiple combination bactericidal antibiotic testing; MDR, multidrug resistant; MIC, minimum inhibitory concentration; OFPBL, oxidation-fermentation, polymyxin B, lactose; OR, odds ratio; PC, *Pseudomonas cepacia*; PR, pan-resistant; SBP, spontaneous bacterial peritonitis; SOT, solid organ transplant; TMP/SMX-R, trimethoprim sulfamethoxazole resistant; UNOS, United Network of Organ Sharing; UTI, urinary tract infection; VIA, vancomycin, imipenem, amphotericin B.

Epidemiology

The prevalence of multidrug resistance (MDR) in Gram-negative bacteria isolated from clinical samples continues to increase globally (1,2). Several reports indicate a similar continued trend toward increased resistance in Gram-negative bacteria isolated from transplant patients (3–6). Clinically important MDR bacteria that have been reported in transplant recipients include nonlactose fermenters such as *Pseudomonas* species, *Burkholderia* species and *Stenotrophomas* species, as well as carbapenem-resistant (CR) *Acinetobacter* species, and MDR *Enterobacteriaceae*, with CR *Enterobacteriaceae* (CRE) being of particular concern. For the purposes of this paper, MDR is defined as nonsusceptibility to at least one agent in three or more antibiotic classes (7). Pan-resistance (PR) is defined as nonsusceptibility to all licensed, routinely available antibacterials. The impact of infection with MDR or PR bacteria on transplant recipient survival has become an important concern as several reports indicate significantly decreased survival of patients infected with such bacteria (8–12).

MDR Enterobacteriaceae and CR Acinetobacter (CRAB)

In several cohorts of transplant recipients, dramatic increases in percentages of *Enterobacteriaceae,* which are ciprofloxacin-resistant or produce extended-spectrum beta-lactamase (ESBL) or AmpC have been reported. Rates of ESBL producing *Enterobacteriaceae* ranged from 8% to 77% in these studies (3,4,13–15). In kidney transplant recipients, ESBL-producing *Enterobacteriaceae* were found to be associated with recurrent urinary tract infection (UTI); the incidence of ESBL producing *Enterobacteriaceae* increased from 13%, 38% to 45% for first, second, and third UTI episodes, respectively (15).

Prevalence data for CRE and CRAB in transplant populations are limited and highly variable by region. Most case series are from higher endemic areas for these MDR bacteria, resulting in relatively higher percentages of resistant bacteria reported, ranging from 18% to 50% (16–18). One year after transplantation, infection with CR *Klebsiella pneumoniae* was a predictor of time-to-death in 175 liver transplant recipients, (HR 4.9, 95%CI 1.5–15.6) (16). Mortality at 30 days was 42% in 12 transplant recipients infected with CR *K. pneumoniae*, with most deaths directly attributable to infection (17).

MDR Pseudomonas, Stenotrophomonas, Achromobacter and Burkholderia

Lung transplant recipients: MDR or PR *Pseudomonas aeruginosa* colonize the respiratory tract of especially cystic fibrosis (CF)-lung transplant recipients in up to 52% prior to transplantation, with posttransplantation colonization rates reaching 75% (19–21). *P. aeruginosa* also remains the most frequent microorganism identified during pneumonia after lung transplantation, being responsible in 25% (22). Despite early reports suggesting reduced survival, more recent studies suggest similar survival of CF-lung transplant recipients independently of pretransplant colonization by MDR or PR *P. aeruginosa*, with an overall survival similar to general results in the United Network of Organ Sharing (UNOS) registry (20,21,23). Pretransplant colonization with MDR or PR *P. aeruginosa* is therefore not

considered an absolute contraindication for lung transplantation in the "International Guidelines for the Selection of Lung Transplant Candidates". It is suggested to include colonization by such bacteria in a comprehensive evaluation including all other comorbidities to determine whether their combination increases the risk of transplantation above a safe threshold (24) (II-2). *P. aeruginosa* has also been suggested to participate in the pathogenesis of bronchiolitis obliterans (BOS), a major limiting factor for long-term survival after lung transplantation (19,23,25).

Colonization by *Burkolderia* species is less frequent, affecting 6–9% of lung transplant recipients, and colonization by PR *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans* remains rare (26,27). Of the 17 genotypically distinct species forming the *Burkholderia cepacia* complex, *Burkholderia cenocepacia* (genomovar III) and *Burkholderia multivorans* (genomovar II) account for 85% of isolates in both the United States and France (27,28). Resistance is common with 86% of *B. cenocepacia* being MDR, including 43% PR isolates and 78% of non-*B. cenocepacia* isolates being MDR including 56% PR isolates (29).

Posttransplant survival among patients colonized by *Burkholderia* depends on the species. Colonization by *B. multivorans* is associated neither with a higher mortality risk nor with reduced survival (27,29–31), and patients colonized with these bacteria should therefore not be denied access to lung transplantation (II-2). In contrast several studies have shown reduced 1-year survival from 90% to less than 30% for patients colonized by PR *B. cenocepacia* (26,27,29,31). The International Guidelines updated in 2006 did not consider colonization by PR *B. cenocepacia* to be an absolute contraindication for transplantation, but suggested particular care to be taken in the identification of species and repeated antibiotic susceptibility testing (24). However, because of a deemed unacceptably high risk of fatal outcome, some more recent reports recommend to discontinue listing such patients for lung transplantation (29,31) (III). Whether an aggressive multidisciplinary management including reduced immunosuppression, improved nutrition and long-term antibiotic treatment might improve survival of these patients remains questionable (27,32). In the light of the present data we recommend that patients colonized by *B. cepacia* complex are referred to reference centers and that the different species and antibiotic susceptibilities are precisely determined using appropriate reference laboratories (II-2). Those patients colonized by PR *B. cenocepacia* should be evaluated for lung transplant with extreme caution due to the documented increased risk of morbidity and mortality (II-2). Adequate information should be provided to patients and relatives concerning the high risk of poor outcome (II-2).

Other solid organ transplant recipients: In nonlung transplant recipients *P. aeruginosa* is also a major pathogen. *P. aeruginosa* is responsible for up to 14% of all bloodstream infections in kidney, 6.5% in liver and 5% in pancreas transplant recipients in the Spanish RESITRA cohort (8). In these patients *P. aeruginosa* remains essentially an early nosocomial pathogen, being responsible for up to 23% of Gram-negative bacteremia within 1-month posttransplantation, but only for 3% of episodes after 12 months (3,33). Strikingly, as compared to nontransplant patients, MDR isolates among *P. aeruginosa* bloodstream infections are more frequent in transplant recipients reaching 43% in Pittsburgh and even 52% in China (11,34). *P. aeruginosa* is also a frequent cause of nosocomial pneumonia in both kidney and liver transplant recipients, with an incidence of MDR isolates in this setting between 50% and 65% (10,35). In renal transplant recipients, *P. aeruginosa* is also a frequent cause of UTI, being responsible for up to 10% of cases and frequently MDR (36,37).

Risk Factors

Specific risk factors for antibiotic resistance in transplant patients have not been systematically studied in large-scale multicenter analyses. General risk factors for acquisition of MDR bacteria are increasingly recognized to be shared among pathogens, and include prior antimicrobials, devices, longer length of hospital stay, and increased severity of underlying illness (38). As transplant recipients often have several of these risk factors, it is not surprising that organ transplantation has been reported as a risk factor for MDR Gram-negative bacteria with odds ratios ranging from 3.2 to 3.7 (34,39,40). An alarming trend toward increased prevalence of MDR bacteria in long-term care facilities has been noted in several studies (41–43). Therefore, the decision to discharge a transplant recipient to an extended care facility may have a substantial impact on their risk of acquiring MDR bacteria.

MDR Enterobacteriaceae and MDR Acinetobacter

Similar to the nontransplant population, risk factors for solid organ transplant (SOT) recipients to acquire MDR *Enterobacteriaceae* and *Acinetobacter* including previous use of antibiotics, prolonged intensive care unit (ICU) stay, and renal failure with or without dialysis, have been derived from single transplant center studies (6,13,44–46). Additional transplant-specific risk factors, which have been reported include combined kidney–pancreas transplantation as compared to isolated kidney transplant recipients, posttransplant dialysis or urinary obstruction and renal transplant versus other organs (13,44). In the pediatric transplant population, younger age and the placement of central venous catheters are additional risk factors (47). No studies specifically link antimicrobial prophylaxis for spontaneous bacterial peritonitis (SBP) to posttransplant MDR infections. However, prior antibiotic use is a consistent risk factor, and studies in patients with liver cirrhosis show that SBP prophylaxis is associated with increased rates of both

Table 1: Diagnosis

Organism	Recommendation	Level
All	Obtain cultures from appropriate sites	I
	Suspect MDR bacteria in the following:	
	Lack of clinical response	
	Presence of risk factors for MDR bacteria	
	Prior isolation of MDR bacteria	
Enterobacteriaceae		
ESBL-producing	Use current CLSI or EUCAST breakpoints for cephalosporins	II-1
	Alternative: ESBL screening by double disk diffusion assay or by broth dilution testing with and without a β-lactamase inhibitor	
Carbapenem-resistant	Use current CLSI or EUCAST breakpoints for carbapenems	II-1
	Alternative: carbapenemase screening by modified Hodge testing	
MDR *Acinetobacter*	Use varying assays based on specific antibiotic tested	II-1
	Test each carbapenem individually	
MDR *P. aeruginosa*	MacConkey agar	I
	Cetrimide agar	
	Etest or standardized disk diffusion tests	
MDR *B. cepacia* complex	BCSA, OFPBL or PC agar	I
	Use MCBT only in selected cases	II-3
MDR *A. xylosoxidans*	Etest or standardized disk diffusion tests	I
MDR *S. maltophilia*	MacConkey agar or VIA agar	I
	DNase confirmatory media or biochemical or molecular identification.	
	Etest or standardized disk diffusion tests	

BCSA = *Burkholderia cepacia* selective agar; CLSI = Clinical and Laboratory Standards Institute; ESBL = extended spectrum beta-lactamase; EUCAST = European Committee on Antimicrobial Susceptibility Testing; MCBT = Multiple combination bactericidal antibiotic testing; OFPBL = oxidation-fermentation, polymyxin B = bacitracin, lactose; PC = *Pseudomonas cepacia*; VIA = vancomycin, imipenem, amphotericin B.

ESBL-producing bacteria, as well as increased quinolone resistance (48,49).

MDR Pseudomonas, Stenotrophomonas, Achromobacter and Burkholderia

As for other MDR isolates, the main risk factor for acquisition of MDR *P. aeruginosa* is exposure to repeated and/or prolonged courses of antibiotic treatments. Selection of *P. aeruginosa* isolates with increased resistance toward the antimicrobial that have been previously used has been documented in the nontransplant population, with persisting resistance toward imipenem and ciprofloxacin despite their discontinuation (50,51). For both *P. aeruginosa* and *B. cepacia* complex, patient-to-patient transmission occurs mainly via the direct or indirect contact or droplet routes (52). Importantly transmission of the epidemic *P. aeruginosa* Liverpool strain has been linked to social networks among patients (52). Posttransplant acquisition in non-CF lung transplant recipients of both *P. aeruginosa* and *B. cepacia* complex has not been well documented. For both *S. maltophilia* and *A. xylosidans* there is also evidence of patient-to-patient transmission. For MDR *P. aeruginosa* blood-stream infections in nonlung transplant recipients, independent risk factors include admission to ICU in the previous year (Odds Ratio [OR]: 5.14), antibiotic treatments in the last 30 days (OR: 5.62) and hospital acquisition (OR 3.81) (34).

Diagnosis

When resistant bacteria are isolated from a patient, the clinical significance of the organism must be evaluated by assessing the source of the culture and the method of collection (II-2). Early involvement of an infectious disease specialist may aid in distinguishing colonization from infection and to help guide therapy. Identification of MDR Gram-negative bacteria may be complicated and it is important that isolates be evaluated in microbiology laboratories experienced in the recognition of these bacteria. If unusual susceptibility patterns are noted on routine screening of Gram-negative bacteria, further testing may be warranted. If the laboratory is not experienced in this testing, referral to a reference laboratory may be indicated (III) (Table 1).

MDR Enterobacteriaceae

Following the initiative of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the Clinical and Laboratory Standards Institute (CLSI) revised their interpretive criteria for cephalosporins in 2010 (53,54). If these new criteria are employed, further ESBL screening is no longer recommended for all isolates. However, as per CLSI, confirmatory testing may still be useful for epidemiological or infection control purposes (54). Differences between nonsusceptibility breakpoints between EUCAST and CLSI can

lead to differences in detection of ESBL-producing *Enterobacteriaceae* for instance for ceftazidime (55). In case new cephalosporin interpretive criteria have not been adopted by the clinical microbiology laboratory, ESBL screening will still need to be performed by either a double disk diffusion assay or by broth dilution testing with and without a β-lactamase inhibitor (54) (II-1). Some laboratories use the ESBL E-test strip, although there are no CLSI guidelines for interpretation. New CLSI breakpoints for carbapenem susceptibility in *Enterobacteriaceae* were also established. These are substantially lower than the previous breakpoints, for instance for ertapenem the breakpoint for susceptibility has been lowered from ≤2 to ≤0.5 μg/mL (54). However, the Food and Drug Administration (FDA) breakpoints have not yet been changed. This has resulted in a complicated situation for clinical microbiologists, who may be reluctant to use the new CLSI breakpoints. If the current CLSI carbapenem breakpoints are not yet adopted by the clinical microbiology laboratory, CLSI recommends screening for carbapenemase production by modified Hodge testing (54).

MDR Acinetobacter Baumannii

Identifying resistance in *Acinetobacter baumanii* is complicated and there may be poor concordance between disc susceptibility testing and microbroth dilution methods (56,57). The accuracy of breakpoints for susceptibility testing with regards to clinical outcomes may be variable. Consequently different assays may be required for different antibiotic classes (II-1). Because susceptibility to specific carbapenems may vary, each carbapenem should be tested individually.

MDR Pseudomonas, Stenotrophomanas, Achromobacter and Burholderia

Identification of MDR bacteria from CF respiratory tract secretions may be complicated by their mucoid and polymicrobial nature and the slow growth of some bacteria. Selective media and specific identification procedures are recommended for the isolation of *P. aeruginosa* (MacConkey agar, cetrimide), *B. cepacia* complex (OFPBL agar, PC agar, BCSA), *S. maltophilia* (MacConkey agar, VIA agar, DNase agar confirmatory media or biochemical or molecular identification) and *A. xylosoxidans* (MacConkey agar, biochemical identification assay) (58–61) (I). Identification of species of the *B. cepacia* complex, indicated because of differing clinical outcomes with infections caused by certain members of this class, may require molecular testing. Antibiotic resistance is common and susceptibility testing should be repeated at regular time intervals while patients are on the waiting list to allow adequate antimicrobial therapy at the time of transplant surgery. Automated susceptibility testing may be unreliable and either Etest or standardized disk diffusion tests should be used (62) (I). Multiple combination bactericidal antibiotic testing (MCBT) initially appeared a promising tool to design treatment combinations for CF patients infected by *B. cepacia* complex. However, the only controlled clinical trial testing MCBT to treat exacerbations in CF patients failed to show any improvement as compared to standard culture and sensitivity techniques (63). In the absence of clinical data supporting an advantage of *in vitro* synergy testing, MCBT cannot be routinely recommended, but might be useful in specific cases (64) (II-3).

Prevention

Various MDR Gram-negative bacteria are associated with different settings—for example MDR or PR *P. aeruginosa* and *B. cepacia* typically emerge in CF patients due to repeated antibiotic exposure over many years—and consequently preventive strategies for different bacteria vary (25–27,52). However, important areas of overlap in preventive efforts can be identified. Most importantly, prevention should include a reduction in antibiotic exposure before and after transplantation wherever it is safe to do so (6,13,38,65). All unnecessary exposure to antibiotics should be avoided, the length of antibiotic treatments should be kept as short as possible, and the spectrum of coverage as narrow as possible (III). Except for lungs, per transplant prophylactic antibiotics should not be used beyond 48 hours posttransplantation (III). Exposure to interventions and indwelling devices should similarly be restricted. Length of endotracheal intubation should be reduced, invasive devises and central venous and urinary catheters should be removed as soon as possible (10,38,65) (III).

MDR Enterobacteriaceae and Acinetobacter

While ESBL producing bacteria are also seen in increasing frequency in community-acquired infections, CRE and MDR *Acinetobacter* remain mostly associated with nosocomial infections. Traditionally, infection control efforts have focused on the hospital setting. However, increasing evidence supports that long-term acute and chronic care facilities serve as a reservoir for MDR bacteria (42). Therefore, increased efforts to limit long-term care exposure for transplant recipients and efforts to improve infection control in these settings are indicated.

A number of hospital outbreaks have been reported of infections with MDR *Enterobacteriaceae*, including CRE (45,66–69). Consequently, appropriate laboratory techniques coupled to responses from healthcare providers should lead to environmental control measures and antimicrobial strategies to limit spread (I). This should include contact isolation, defined as the use of gowns and gloves and patient placement in private rooms with dedicated bathroom facilities or cohorting of patients with others who are colonized or infected with the same organism (II-2). As with all patients, strict hand hygiene measures before and after contact with the patient or patient contaminated surfaces are critical to limiting the spread of MDR bacteria (II-2). Since there is the potential for prolonged

carriage of these bacteria in the intestinal tract, even following treatment, these patients should be identified and either isolated or cohorted upon readmission to the hospital or transfer to other facilities. Currently there is no recommendation for screening of asymptomatic patients as there are no data regarding the sensitivity or benefits of this screening. Because hospital-wide as well as community antimicrobial prescribing practices will impact the resistance patterns observed in transplant recipients, it is important to restrict antibacterial use to those patients in whom bacterial infection has been documented or strongly suspected (II-3). Donor-derived infections with MDR *Enterobacteriaceae* present a unique opportunity for prevention. Twelve recipients have been reported, of whom five experienced clinical donor-derived infection resulting in death in two patients, renal graft loss in two other patients and in one patient resolution of infection after prolonged combination treatment (70–73). If donor colonization or infection with CRE is known prior to transplantation, a risk-benefit evaluation should be made, taking into account the organ to be transplanted and the source of the positive donor cultures. Selective decontamination of the digestive tract has not been proven to be of benefit in transplant recipients or candidates, and cannot be recommended at this time for prevention of infections with MDR *Enterobacteriaceae* or MDR *Acinetobacter* (III).

MDR Pseudomonas, Stenotrophomonas, Achromobacter and Burkholderia

Efforts should be made to minimize the risk of pretransplant acquisition of MDR or PR bacteria in CF-lung transplant recipients. These should include parsimonious use of antibiotics and as much as possible nonantimicrobial management strategies to control CF exacerbations (III). The widespread transmission of epidemic clones of *P. aeruginosa* also underlines the importance of avoiding socialization among CF patients (52). The "3 foot rule" advocated as the minimal distance between CF patients has recently been suggested not to be sufficient, as infectious particles in small size droplets might remain in the air for several minutes to hours (52). Whether aerosolized colistin can promote emergence of antibiotic susceptible *P. aeruginosa* in pretransplant CF patients colonized by MDR *P. aeruginosa* needs confirmation (74). On the other hand aerosolized colistin might favor colonization by intrinsic colistin resistant *B. cepacia* complex. Home-use nebulizers have been identified as potential primary source of *B. cepacia* and *S. maltophilia* in CF patients. Clearly, strict nebulizer hygienic practices should be endorsed to avoid such acquisition routes (III). Some centers recommend sinus surgery (endoscopic frontosphenoethmoidectomy) to reduce bacterial seeding from the paranasal sinuses, acting as reservoirs for *P. aeruginosa* and *B. cepacia* complex, to the transplanted lungs. Whether this approach reduces the incidence of tracheobronchitis and the risk of bronchiolitis obliterans (BOS) remains controversial (75,76). Consequently, this approach cannot be routinely recommended at this time (II-3). Combined continuous sinonasal and bronchial colistin inhalation has been recently suggested to prevent pulmonary postlung transplant recolonization by *P. aeruginosa* (77).

Colonized lung transplant recipients are also a potential reservoir for transmission to other transplant patients. Contact isolation measures should therefore be considered for transplant recipients harboring MDR and/or PR bacteria (III). Cohorting of patients with MDR *P. aeruginosa* is so far not recommended. In contrast, because of the dramatic rise in serious posttransplant complications, separation of patients colonized with *B. cenocepacia* from those patients free of this pathogen seems justified (III). As previously noted, hand hygiene measures are critical to control the spread of these resistant bacteria (II-2). Additionally the previously noted caveats regarding maintaining the appropriate level of patient care despite isolation should also be considered. Recently, donor-derived infections with MDR *P. aeruginosa* have been reported (78,79). Obviously, all efforts should be made to identify organ donors with MDR *P. aeruginosa* infections in order to give preemptive antibiotics to the recipients (II-3).

Treatment

Source control–removal of infected devices, drainage of collections—is the most important predictor of a good outcome for many infectious syndromes (40,80). Therefore, adequate source control as allowed by clinical circumstances should be the first priority in all patients infected with MDR Gram-negative bacteria (II-2). Antimicrobial treatment should be selected on the basis of *in vitro* susceptibility, predicted levels at the site of infection, cost, method of administration and side effect profile. Empiric therapy for suspected Gram-negative bacterial infections in transplant recipients should be guided by the type of infection (nosocomial vs. community acquired), the local resistance patterns, known MDR Gram-negative colonizers for the specific patient, and the severity of the infection (III). Data to support recommendations regarding duration of antibiotic courses are lacking. In general, guidelines for specific infectious syndromes such as pneumonia or bloodstream infection may be followed. However, duration of treatment in transplant recipients infected with MDR Gram-negative bacteria should be individualized and guided by response to treatment and degree of source control, as well as by side effects of therapy (III) (Table 2).

MDR Enterobacteriaceae

For MDR *Enterobacteriaceae* that retain susceptibility to carbapenems, these are generally the drug class of choice. In selected infections with ESBL producing bacteria, cefepime and piperacillin/tazobactam may still be used upon documentation of *in vitro* susceptibility. However, the use of cefepime in such conditions should be restricted to

Table 2: Treatment recommendations

Organism	Recommendation	Level
All	Source control should be aggressively pursued Early transplant infectious disease consultation	I
ESBL-producing *Enterobacteriaceae*	Carbapenems Alternative: cefepime or piperacillin/tazobactam (if susceptible and low inoculum infection)	I III
Carbapenem-resistant *Enterobacteriaceae*	Systemic infections: Individualized combination regimen with two or more of the following: Colistin Tigecycline Aminoglycosides (if susceptible) High-dose, prolonged infusion carbapenems Uncomplicated UTI: Oral fosfomycin (if susceptible) IV aminoglycosides (if susceptible)	II-3
MDR *Acinetobacter*	Carbapenems (except ertapenem) if susceptible If carbapenem resistant consider combination therapy with: Colistin Ampicillin/sulbactam if sulbactam susceptible Tigecycline (if susceptible and no bloodstream or urinary infection) Rifampicin	II-3
MDR *P. aeruginosa*	Individualized combination regimen with two or more of the following: Antipseudomonal beta-lactam (consider high doses of prolonged or continous infusion) Aminoglycoside Ciprofloxacin Adjunctive aerosolized colistin or tobramycin	II-2
PR *P. aeruginosa*	Individualized combination regimen with three or more of the following: IV colistin Doripenem or another anti-pseudomonal beta-lactam (consider high doses of prolonged or continuous infusion) Aminoglycosides Fosfomycin Rifampicin Adjunctive aerosolized colistin or tobramycin	II-2
MDR *B. cepacia* complex	High dose TMP/SMX Alternatives if susceptible: Meropenem Ciprofloxacin	II-2
TMP/SMX-R or PR *B. cepacia* complex	Combination therapy with: Meropenem Aminoglycoside Ceftazidime (or trimethoprim sulfamethoxazole)	II-2
MDR *A. xylosoxidans*	Combination therapy: Piperacillin/tazobactam Carbapenems (except ertapenem) TMP/SMX	III
MDR *S. maltophilia*	High dose TMP/SMX Alternatives: Ticarcilline/clavulanate Moxifloxacine Doxycycline Tigecyline Consider combination therapy	II-2

IV = intravenous; MDR = multidrug resistant; PR = pan-resistant; TMP/SMX-R = trimethoprim/sulfamethoxazole resistant.

infections with a low bacterial inoculum (i.e. for a UTI but not for a pneumonia) (III). CRE present a greater therapeutic challenge, as CRE generally retain *in vitro* susceptibility only to colistin, tigecycline and fosfomycin, and display variable *in vitro* susceptibility to selected aminoglycosides. Side effects of colistin include nephrotoxicity and neurotoxicity. Tigecycline is an alternative choice, with a more attractive side effect profile. Its most common side effect is nausea, which may be quite severe. Tigecycline should not be used for UTI (81,82) (II-3). Also, low serum levels raise concern for its use as monotherapy for bloodstream infections (III). The FDA issued a warning regarding increased mortality risk associated with tigecycline in 2010. The outcomes of four meta-analyses trying to assess this risk have been conflicting (83–86). However, a small but significant increased mortality risk is likely to be associated with the use of tigecycline, most likely secondary to decreased efficacy. However, it should be noted that these studies did not specifically address the treatment of CR bacteria.

In the United States, fosfomycin is currently available only in oral form, and can be quite useful in the treatment of UTI in patients without renal failure caused by MDR *Enterobacteriaceae* (fosfomycin is not active against *Acinetobacter*). However, emergence of resistance has been reported (87). For UTI with CR bacteria susceptible to aminoglycosides, these are the agents with the highest response rate (82,88). However, their use is limited by nephrotoxicity as well as ototoxicity.

Limited data suggest that if the carbapenem MIC is $\leq$4 mg/L, high-dose carbapenems given by prolonged infusion may be beneficial in a combination regimen for the treatment of CRE (89). In addition, results from a murine model and *in vitro* data hint at potential efficacy of double-carbapenem therapy (90). There is a general lack of prospective data comparing treatment modalities not only in transplant recipients but also in the nontransplant population. Whether combination therapy improves outcomes has been insufficiently studied as well. In nontransplant populations, retrospective studies in CRE bloodstream infections have shown a survival benefit associated with combination therapy (91–94). The combination of meropenem, tigecycline and colistin was associated with lower mortality in one study (OR for 30-day mortality 0.27, $p = 0.009$) (92).

MDR Acinetobacter Baumannii

Carbapenem susceptible isolates should be treated with a carbapenem (except ertapenem) (II-3). CR *Acinetobacter* may remain susceptible *in vitro* to the sulbactam component of ampicillin/sulbactam. If this is documented, ampicillin–sulbactam may be used for treatment. Many isolates however are susceptible to colistin only (95). If susceptibility is documented, aminoglycosides may also be of use in the treatment. The use of tigecyline is limited by widespread resistance and reports of treatment failure (96–98). Although rifampin has been used in combination therapy where multiresistance may be anticipated, the risk of drug interactions with calcineurin inhibitors and mTOR inhibitors should limit its use (III).

MDR Pseudomonas, Stenotrophomonas, Achromobacter and Burkholderia

Transplant recipient specific studies concerning the treatment of MDR *P. aeruginosa*, *B. cepacia* complex, *Stenotrophomonas* and *Achromobacter* infections are lacking.

Optimal treatment for non-MDR *P. aeruginosa* infections remains controversial. In the nontransplant population it appears that initiation of therapy with a combination therapy (usually a beta-lactam combined with an aminoglycoside) for a limited time (3–5 days), followed by a beta-lactam monotherapy, might improve survival and limit the nephrotoxicity of aminoglycosides (99) (II-2). This is even more important after transplantation when renal failure and /or coadministration of other nephrotoxic drugs are common. In contrast, for MDR/PR *P. aeruginosa* infections in lung transplant recipients most experts recommend combination therapies including two or three different classes (beta-lactam + aminoglycoside $\pm$ fluoroquinolone) of antibiotics for 10–14 days (23,27,29,100) (II-2). In nonlung SOT patients, shorter treatment durations (7–10 days) might be possible depending on the infection site (III). In all cases the duration of therapy, as well as the timing of downgrading towards monotherapy, should always been guided by the clinical evolution and a careful reevaluation of the balance between reduced risk of recurrence versus selection of further resistance and drug dependent side effects associated with prolonged antibiotic therapy (III). Novel combination regimens may include colistin, doripenem, aminoglycosides, fosfomycine and rifampicin, however, most of the evidence is provided so far by *in vitro* studies and clinical experience is limited to small case series (64,100–102). In order to optimize pharmacokinetics, prolonged as well as continuous high-dose beta-lactam infusion therapy might be advantageous, as suggested for piperacillin–tazobactam, ceftazidime, meropenem and doripenem (102,103) (II-2). Evidence that adjunctive aerosolized colistin might be beneficial in combination with systemic antibiotics (colistin or beta-lactam) for the treatment of MDR *P. aeruginosa* infections has emerged in several studies, with success rates up to 88% (104,105) (II-3).

For *B. cepacia* complex infections, the drug of choice remains high dose trimethoprim sulfamethoxazole, and if susceptible meropenem or ciprofloxacin (II-2). Triple combination therapies including meropenem, aminoglycoside, and ceftazidime or trimethoprim sulfamethoxazole are recommended for MDR/PR *B. cepacia* infections (II-2). The clinical significance of *A. xylosoxidans* in transplant recipient remains uncertain. Treatment should be restricted to chronically colonized/infected patients with clinical decline (III). *A. xylosoxidans* is often resistant

to beta-lactams including cephalosporins and carbapenems, aminoglycosides, quinolones and trimethoprim-sulfamethoxazole (106). Treatment should be based on susceptibility testing and combination therapies including piperacillin–tazobactam, carbapenems and/or trimethoprim sulfamethoxazole should be favored. *S. maltophilia* infections should be treated with high dose trimethoprim sulfamethoxazole (II-2). Alternative antibiotics include ticarcillin–clavulanate, moxifloxacin and doxycline, as well as combination therapies including trimethoprim sulfamethoxazole and tigecycline (107,108).

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Disclosure

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