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Treatment of Multidrug Resistant Gram-Negative Bacilli after Solid Organ Transplant: Outcomes and Complications

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Abstract

Infections caused by multi-drug resistant gram-negative bacilli cause significant morbidity and mortality in solid organ transplant recipients. We present a single center retrospective analysis of all solid organ transplant recipients from January 1, 2007 to April 15, 2017 treated for infections caused by multi-drug resistant gram-negative bacilli. This study examined the effects of specific antibiotics on nephrotoxicity, neurotoxicity, 30-day mortality, and length of stay in the hospital and intensive care unit. A total of 225 infections were identified among 143 patients. Carbapenem-resistant organisms were present in 121 (51.1%) infections. Neurotoxicity was associated with polymyxin use with an 8% increase in odds of neurotoxicity per day of exposure (*P*=0.03). There was no relationship between nephrotoxicity and any individual antibiotic class. Increased hospital length-of-stay occurred among patients exposed to aminoglycosides (β-statistic= 0.48 (0.23); p= 0.04), while there was no relationship between antibiotic class and intensive care unit (ICU) length-of-stay. Mortality at 30 days occurred in 37 infections (16%). Carbapenem exposure was associated with decreased 30-day mortality (OR 0.93; 95%CI 0.90-0.98; P=0.02). No other antibiotic class had a significant impact on 30-day mortality. Carbapenems appear to be a safe

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and effective treatment for solid-organ transplant recipients with infections caused by multi-drug resistant gram-negative bacilli.

Introduction

Bacterial infections are the most common infectious complication after solid organ transplant (SOT)[1]. Infection with gram-negative bacilli (GNB) is common, with gram-negative bloodstream infection (BSI) occurring in up to 30% of SOT recipients in the first 6 months after transplant.[2,3] Multi-drug resistant (MDR) gram-negative bacilli have become increasingly common in the past several decades. MDR *Pseudomonas*, carbapenem-resistant *Acinetobacter baumannii* (CRAB), extended-spectrum beta-lactamase (ESBL)-producing and carbapenem-resistant *Enterobacteriaceae* (CRE) account for the majority of these pathogens.[4] Risk factors for multi-drug resistance in the general population include antibiotic exposure, intensive care unit (ICU) admissions, mechanical ventilation, and medical instrumentation, all of which are an integral part of the solid organ transplant process.[5] Among gram-negative infections in SOT recipients, multi-drug resistance is common, occurring in over 40% of GNB infections in both liver and kidney transplant recipients.[2,6-8] Infection with ESBL producing organisms at any site occurs in 5-7% of all liver transplant recipients[8] and an increased risk of several MDR *Enterobacter*, *Klebsiella*, and *Acinetobacter* has been reported in the SOT population.[6,9-11] Although UTIs caused by MDRO are associated with increased mortality in this population,[12] these MDRO infections tend to be less severe than infections from other sources.[13] Among SOT patients with bacteremia, kidney transplant recipients have lower mortality than recipients of any other solid organ.[14,15]

Most studies have demonstrated that infections with MDR bacteria are associated with poor outcomes in both the general and SOT population. Among solid-organ recipients with gram-negative BSI, MDR pathogens are associated increased mortality compared to antibiotic susceptible organisms (35-40% vs. 15%).[2,16,17] Increased experience with these MDR organisms (MDROs) may result in improved outcomes. A recent multi-center retrospective study showed that most patients with carbapenem-resistant bacterial infections had a 72% survival rate; mortality was higher (42%) in patients who developed infections greater than 1 year post-transplant.[18]

Despite the growing burden of MDR pathogens in the transplant population, the optimal treatment strategy for these infections remains unknown. Carbapenems are the cornerstone of treatment for ESBL-producing organisms. Cefepime and fluoroquinolones may also be effective, and fosfomycin may be used for urinary tract infections.[8,19,20] Options for treatment of carbapenem-resistant organisms are limited. Novel combination β-lactam/β-lactamase inhibitors including ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, and imipenem-relebactam, have changed the landscape for treating carbapenem resistant infections (CRIs) in recent years.[21-23] However, these agents remain costly and are not routinely carried on many hospital formularies, limiting widespread use.[24] Carbapenems may be effective for bacteria with lower mean inhibitory concentrations (MIC),[19,25,26] but treatment of CRIs often requires use of polymyxins or

aminoglycosides, agents frequently associated with neurotoxicity and nephrotoxicity..[24] Improved mortality has been demonstrated with simultaneous use of two agentswhile delayed initiation of effective antimicrobial therapy is associated with higher mortality for both ESBL and carbapenem resistant infections (CRI).[4,19,20,27] However, our understanding of treatment outcomes is based on small studies, with few case series addressing outcomes in SOT recipients.[10,27] While mortality is a frequent endpoint, there has been little evaluation of the impact of antimicrobial therapy on other outcomes. We performed a retrospective chart review to assess the impact on both morbidity and mortality associated with antimicrobial therapy for MDR gram-negative infections among solid organ transplant recipients at a single transplant center.

Materials and Methods

2.1 Study Design and patients

The Institutional Review Board of Northwestern University approved this study (study number STU00205081) prior to conducting any research. We performed a single-center, retrospective analysis to determine the antimicrobial therapy used to treat MDR gram negative infections among patients aged 18-89 who received a solid organ transplant at our institution from January 1, 2007 to April 15, 2017. Cultures from SOT recipients which were positive for an ESBL-producing organism or which had resistance to meropenem, imipenem, or ertapenem were identified. An organism was defined as an ESBL-producer when there was resistance to third-generation cephalosporins and susceptibility to a second-generation cephalosporin. A clinical infection was defined as a positive culture obtained from a SOT recipient who received antimicrobial therapy within 48 hours prior to or within 7 days after the time the culture was collected, and was deemed to be a clinically significant event by the treating TID attending physician Cultures with the same organism collected within 7 days of one another were considered one infection. Retrospective chart review was used to determine the primary site of infection in instances where multiple cultures from different media were positive for the same pathogen. The date of the infection event was defined as the date that the first positive culture was collected.

2.2 Exposure

We identified all systemic anti-microbial therapies used to treat MDR gram-negative organisms that were initiated within 48 hours prior to and 7 days after an infection event. Antibiotics used to treat or prevent an infection caused by an organism other than an MDR gram-negative bacillus were excluded. Antibiotics initiated beyond 7 days were included if they were used as an adjunct or alternatives to prior treatment. The length of exposure (days) for each antibiotic was determined. Antibiotics were grouped by class for statistical analysis.

2.2 Covariates

Comprehensive data were collected on demographic and clinical characteristics including effect modifiers and confounders for both exposure and outcomes. Information regarding the anatomical site of each culture as well as the site of transplant were collected.

2.3 Outcomes

Study outcomes included: 1) Nephrotoxicity, defined as the need to initiate renal replacement therapy (RRT) within 90 days of infection in a patient who had not received RRT within the previous 90 days; 2) Neurotoxicity, defined as a change in mental status prompting neurology consult and no other well-documented cause; 3) Mortality at 30-days from the time of culture collection 4) Adverse drug reaction, defined as the addition of an antibiotic to the patients allergy list in the electronic medical record after use; 5) Hospital length of stay (for inpatients only); and 6) Intensive care unit (ICU) length of stay (for inpatients only).

2.4 Statistical Analysis

Descriptive statistics were used to define proportions and averages. Pearson's chi-squared test was used to compare dichotomous variables. Univariate GEE regression models were used to define odds ratio of key outcomes of interest.

Results

3.1 Infection characteristics

During the study period, SOT recipients had 740 cultures positive for relevant pathogens (see Figure 1). Three hundred fifty-four cultures resulted in treatment and represent a total of 225 infections among 143 patients. Eighty-two patients had at least one previous infection. One patient, who had one positive culture and one infection was transferred to another center 48 hours after the culture was collected and was lost to follow-up and was excluded from analysis.

Infections occurred at a mean of 193 days after transplant (see Table 1). Urinary and respiratory tract infections were the most common, and about half occurred at the site of transplant. Most (92%) of infections occurred in patients who were hospitalized, and the majority (58%) of infections were associated with an ICU admission. Nearly half of all pathogens were carbapenem resistant. *E. coli, K. pneumoniae* and *P. aeruginosa* were the most common pathogens. (See Table 1, supplementary materials).

3.2 Antibiotic Use

Most infections were treated with either a carbapenem (26.7%), a cephalosporin (24.9%), or a penicillin/β-lactamase inhibitor (19.6%) (See Table 2). Less than ha(41.8%) of infection events were empirically treated with antibiotics that were appropriate for the isolated pathogen(s). For definitive therapy, carbapenems were most common (42.2%). Nine infections (4.0%) were treated with a novel cephalosporin/β-lactamase, including either ceftazidime-avibactam or ceftolozane-tazobactam.

3.3 Nephrotoxicity

About a quarter (52, 23.1%) of infections occurred in patients were already on renal replacement therapy prior to the infection. Of the 173 infections in RRT-naïve patients, 32 (18.5%) developed new-onset RRT within 90 days of treatment for the infection. No patients receiving fosfomycin required new RRT. Other antibiotic exposure did not have

a statistically significant effect on need for RRT (See Table 3). Infections among patients admitted to the ICU were more likely to require new RRT (OR 6.30, 95%CI 2.13-18.67), while infections at the site of transplant were less likely to require new RRT (OR 0.36, 95%CI 0.16-0.79) (See Table 4).

3.4 Neurotoxicity

Twelve (5.4%) infections were associated with neurotoxicity. Polymicrobial infections were more likely to result in neurotoxicty compared with monomicrobial infection (OR 4.91; 95%CI 1.49-16.2). Polymyxins were the only class of antibiotics associated with a statistically significant increase in neurotoxicity, with an expected 8% increase in the odds of neurotoxicity per day of exposure to polymyxins. Cephalosporins, carbapenems, and aminoglycosides were also associated with neurotoxicity, but this increase did not reach statistical significance.

3.5 Other adverse drug reaction

Three adverse drug reactions were observed after exposure to antibiotics. One patient developed hives after exposure to a cephalosporin during treatment for a polymicrobial respiratory tract infection. Two other patients developed unknown reactions (listed as “allergy” in the electronic medical record) to antibiotics (one to aztreonam and the other to ciprofloxacin) after receiving treatment for a urinary tract infection.

3.6 30-day mortality

Thirty-seven of 225 infections (16%) resulted in mortality within 30 days of culture collection.) Carbapenems were the only class of antibiotics to have a significant effect on mortality (OR 0.93, 95%CI 0.90-0.98), with a 6% reduction in 30-day mortality per each day of carbapenem exposure (See Table 3), there was no mortality benefit for patients infected with carbapenem-resistant organisms (OR 0.8, 95% CI: 0.3 −2.0; p = 0.65). Increased 30-day mortality occurred among infections in patients requiring ICU admission (OR 30.7, 95% CI 4.59-205.3, P <0.001) and infections in which definitive therapy required multiple agents (OR 5.36, 95%CI 2.55-11.27). Infections at the site of transplant (OR 0.24, 95%CI 0.10-0.54) and infections with carbapenem-sensitive organisms (OR 0.35, 95%CI 0.16-0.75, P=0.007) were associated with lower 30-day mortality. There was a trend toward lower mortality among urinary tract infections (OR 0.50 95% CI 0.09-2.77), but no site of infection demonstrated a statistically significant risk of mortality (see Table 4). Empiric therapy with in-vitro activity did not confer any mortality benefit for either carbapenem sensitive (OR 1.09, 95% CI 0.33-3.61) or carbapenem resistant (OR 1.24, 95% CI 0.52-3.01) infections.

3.7 Hospital length of stay

Most infections (206, 91.6%) developed in patients who were hospitalized for > 1 midnight (See Table 1). Patients treated with aminoglycosides had an increased LOS (β statistics=0.48, STE 0.23, P=0.04) (See Table 3). No other antibiotic class had an impact on length of stay. Additional factors associated with increased length of stay included extra-urinary infections, *E. cloacae, P. aeruginosa* (See Table 2, supplementary materials).

Infections at the site of transplant were associated with shorter hospital LOS (β statistic= −5.45 (0.16); P <0.001)

3.8 ICU length of stay

Of the 206 infections occurring in hospitalized patients, 129 (62.6%) infections occurred in patients who required admission to an ICU (See Table 1). No antibiotic class had an impact on ICU length of stay (See Table 3). Length of ICU stay was increased among bloodstream and respiratory infections, and infections with *E. cloacae* and *P. aeruginosa* (See Table 2, supplementary materials). Decreased length of stay was observed in infections at the site of transplant (β statistic= −0.93 (0.28); P <0.001).

Discussion

To our knowledge, this study of 225 MDR GNB infections is the largest study of MDR gram-negative infections in the SOT recipients, and the first to describe the effects of specific treatments in this population. The results of this study confirm the high morbidity and mortality observed in prior studies. Infections with carbapenem sensitive, ESBL-producing pathogens had lower 30-day mortality than infections with carbapenem-resistant pathogens. Abdominal, bloodstream, and respiratory infections were also associated with increased length of hospital and ICU stay, consistent with findings in previous studies of MDR gram-negative infections in SOT recipients.[17,20,26,28] We observed that infection at the site of transplant was associated with improved outcomes in all studied areas, though the majority (69.7%) of these infections occurred in kidney transplant recipients with urinary tract infections, which were independently associated with decreased morbidity and mortality.

In this study, carbapenem exposure was associated with reduced 30-day mortality without an increase in neurotoxicity, nephrotoxicity, hospital LOS or ICU LOS. This observed benefit of carbapenems is consistent with a recent study demonstrating a mortality benefit of meropenem over piperacillin/tazobactam for ceftriaxone-resistant gram-negative infections.[32] Several novel combination β-lactam/β-lactamase inhibitor combinations have recently emerged as treatments for infections caused by MDR gram-negative bacilli. Ceftazidime-avibactam, imipenem-cilastin-relebactam, and meropenem-vaborbactam have activity against carbapenemase producing organisms, and ceftazidime-avibactam and meropenem-vaborbactam have demonstrated to have superior safety and efficacy compared to older agents when used to treat infections with carbapenem-resistant *Enterobacteriaceae.*[35,36] Ceftolozane-tazobactam withstands expulsion by efflux pumps and has efficacy when used to treat MDR *Pseudomonas* infections.[37] However, these agents lack activity against some carbapenemases, including metallo-β-lactamases, and none of these agents is effective for treating carbapenem-resistant *Acinetobacter baumannii* (CRAB). [38] Furthermore, these agents are often not readily available on many hospital formularies.[39] Only nine infections in this study were treated with either ceftazidime-avibactam or ceftolozane-tazobactam, as many infections analyzed in this study occurred before the availability of any of these novel agents. Due to the rarity of their use in this study, we are unable to provide any meaningful outcomes data. Given the limitations of these novel

agents described above, the antimicrobial therapy used in this study is still relevant in the management of CRIs.

Studies in the general population have shown significant advantages in using combination therapy over monotherapy in the treatment of *Klebsiella Pneumoniae* carbapenemase (KPC) infections.[26,40,41] Monotherapy, particularly in the treatment of respiratory infections, has been associated with significantly more treatment failures and a two-fold increase in mortality rates than combination therapy.[40,41] Decreased mortality has been observed in some studies with carbapenem containing regimens, particularly with an MIC ≤ 8mg/L, though carbapenem monotherapy is associated with higher mortality.[26,42] In this study, use of multiple agents was associated with an increase in 30-day mortality compared to monotherapy. This finding may reflect providers decision to use additional antibiotics in patients who were already critically ill, rather than a deleterious effect of the additional therapy. We did not observe a reduction in 30 day mortality among with appropriate empiric antimicrobial therapy among either carbapenem sensitive nor carbapenem resistant infections, which was unexpected based on demonstrable improvement in mortality with early administration of appropriate antibiotics in MDR gram-negative infections from other centers.[43,44] However, this analysis only considered the in-vitro efficacy of the initial antibiotics(s) administered, and did not consider time to appropriate antibiotic administration, which may have precluded detection of a benefit of early appropriate antibiotics.

Antibiotic toxicity is a significant concern in treatment of MDR infections. Polymyxins and aminoglycosides have been associated with acute kidney injury in 50% and 10-20% of exposed recipients, respectively.[45,46] In our study, 64 (28.4%) infections were treated with an aminoglycoside and 38(16.9%) were treated with polymyxin at some point during therapy. No specific antibiotic group was associated with a significant need for new RRT. Neurotoxicity was a rare event but occurred most frequently among patients exposed to polymyxins. The lack of nephrotoxicity observed in this study does not necessarily imply that these agents are safer than previously thought, as this study only captured renal toxicity significant enough to result in renal replacement therapy. However, the need for renal replacement therapy is clinically significant outcome with direct influence of patients' quality of life, especially in recipients of kidney transplants who have may have a strong desire to avoid returning to dialysis.[47]

This study provides a large sample size of solid organ transplant recipients with diverse microbiological and clinical characteristics, though there are several limitations. Exposure to various antibiotics was not random and instead based on clinician assessment of the patient at the time of illness. Thus, severity of illness may have served as an important unmeasured co-founder, increasing a patient's likelihood of exposure to more potent agents as well as serving as a risk factor for treatment-independent nephrotoxicity, neurotoxicity, and mortality. The excellent outcomes observed with fosfomycin therapy likely reflect the relatively mild nature of infections for which it was used to treat. Many patients received multiple classes of antibiotics during any given infection, clouding the effect of any individual class on antibiotic. Despite our large sample size, it may not have been sufficient to detect an effect of therapy class on neurotoxicity and adverse drug reactions,

two rare but important outcomes. Additionally, we required a neurology consultation as part of our definition of neurotoxicity. Signs and symptoms of neurotoxicity are not uniformly recorded in the chart and most patients with clinically significant neurotoxicity would have a neurology consult to evaluate the cause and direct treatment at our center. The requirement for a neurology consult may result in missing less significant toxicity. Outcomes were measured by infection rather than unique patient outcomes, as many patients in this study had more than one relevant infection. There is inherent interdependence of two different infections in the same patient, such that a patient who dies from a first infection cannot die from a second infection. However, we chose to analyze by infection rather than unique patients to capture as many clinically relevant events as possible. We attempted to minimize the event interdependence by using short-interval follow-up outcomes, such as using 30-day mortality as an end point rather than 90-day mortality. We evaluated the impact of a plethora of relevant variables other than antibiotic class, but did not account for the individual contribution of each of these variables on measured outcomes, limiting the applicability of some aspects of this study.

Overall, this study confirms prior studies and demonstrates that MDRO in SOT recipients can be treated in the majority of patients. Carbapenems appear to be safe and effective agents for treating MDR gram-negative infections in this population, though further studies are needed to determine to optimal regimens and the benefit of carbapenems in the treatment pathogens with *in vitro* carbapenem resistance. .Novel β-lactam/β-lactamase inhibitors are emerging and show promise for susceptible organisms,[21,35] but these agents are not able to overcome all mechanisms of antibiotic resistance, and access to these agents limits their routine widespread use Future investigations should include these novel agents and focus on patients with carbapenem-resistant organisms and infections outside the urinary tract

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations:

BLBLI	β-lactam/β-lactamase inhibitors
BSI	bloodstream infection
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CRE	carbapenem-resistant *Enterobacteriaceae*
CRI	carbapenem-resistant infections
CRKP	carbapenem-resistant *Klebsiella Pneumoniae*
CSKP	carbapenem-sensitive *Klebsiella Pneumoniae*
CLSI	Clinical and Laboratory Standards Institute
ESBL	extended-spectrum beta-lactamase

GNB	gram-negative bacilli
ICU	intensive care unit
KPC	*Klebsiella Pneumoniae* carbapenemase
LOS	infections length of stay
MIC	mean inhibitory concentrations
MDR	multi-drug resistant
MDRO	multi-drug resistant organisms
SOT	solid organ transplant
RRT	renal replacement therapy
TID	transplant infectious diseases
UTI	urinary tract infection

References

1. Snydman DR. Epidemiology of infections after solid-organ transplantation. Clin Infect Dis. 2001;33 Suppl 1:S5–8. [PubMed: 11389515]
2. Shi SH, Kong HS, Xu J, et al. Multidrug resistant gram-negative bacilli as predominant bacteremic pathogens in liver transplant recipients. Transpl Infect Dis. 2009;11(5):405–412. [PubMed: 19638006]
3. Al-Hasan MN, Razonable RR, Eckel-Passow JE, Baddour LM. Incidence rate and outcome of Gram-negative bloodstream infection in solid organ transplant recipients. Am J Transplant. 2009;9(4):835–843. [PubMed: 19344469]
4. Cervera C, van Delden C, Gavaldà J, et al. Multidrug-resistant bacteria in solid organ transplant recipients. Clin Microbiol Infect. 2014;20 Suppl 7:49–73.
5. Kaye KS, Pogue JM. Infections Caused by Resistant Gram-Negative Bacteria: Epidemiology and Management. Pharmacotherapy. 2015;35(10):949–962. [PubMed: 26497481]
6. Linares L, Cervera C, Cofán F, et al. Risk factors for infection with extended-spectrum and AmpC beta-lactamase-producing gram-negative rods in renal transplantation. Am J Transplant. 2008;8(5):1000–1005. [PubMed: 18727176]
7. Shi SH, Kong HS, Jia CK, et al. Risk factors for pneumonia caused by multidrug-resistant Gram-negative bacilli among liver recipients. Clin Transplant. 2010;24(6):758–765. [PubMed: 20047611]
8. Santoro-Lopes G, de Gouvêa EF. Multidrug-resistant bacterial infections after liver transplantation: an ever-growing challenge. World J Gastroenterol. 2014;20(20):6201–6210. [PubMed: 24876740]
9. Camargo LF, Marra AR, Pignatari AC, et al. Nosocomial bloodstream infections in a nationwide study: comparison between solid organ transplant patients and the general population. Transpl Infect Dis. 2015;17(2):308–313. [PubMed: 25726707]
10. Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D, et al. Infection with Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae in solid organ transplantation. Transpl Infect Dis. 2012;14(2):198–205. [PubMed: 22093103]
11. van Delden C, Blumberg EA, Practice AIDCo. Multidrug resistant gram-negative bacteria in solid organ transplant recipients. Am J Transplant. 2009;9 Suppl 4:S27–34. [PubMed: 20070690]
12. Säemann M, Hörl WH. Urinary tract infection in renal transplant recipients. Eur J Clin Invest. 2008;38 Suppl 2:58–65. [PubMed: 18826483]
13. Jeganathan N, Yau S, Ahuja N, et al. The characteristics and impact of source of infection on sepsis-related ICU outcomes. J Crit Care. 2017;41:170–176. [PubMed: 28564621]

14. Oriol I, Sabé N, Melilli E, et al. Factors influencing mortality in solid organ transplant recipients with bloodstream infection. Clin Microbiol Infect. 2015;21(12):1104.e1109–1114.
15. Kritikos A, Manuel O. Bloodstream infections after solid-organ transplantation. Virulence. 2016;7(3):329–340. [PubMed: 26766415]
16. Bodro M, Sabé N, Tubau F, et al. Risk factors and outcomes of bacteremia caused by drug-resistant ESKAPE pathogens in solid-organ transplant recipients. Transplantation. 2013;96(9):843–849. [PubMed: 23883973]
17. Qiao B, Wu J, Wan Q, Zhang S, Ye Q. Factors influencing mortality in abdominal solid organ transplant recipients with multidrug-resistant gram-negative bacteremia. BMC Infect Dis. 2017;17(1):171. [PubMed: 28241746]
18. Huprikar S C L, Camera L, Nellore A, Madan R, Garcia-Diaz J, Jacobs S, Lee D, Trindade W, Alangaden G, La R, Theodoropoulos N, Miceli M, Santoro-Lopes G, Banach D, Simon D, Patel G. Outcomes Associated with Carbapenem-Resistant Enterobacteriaceae Infection After Solid Organ Transplantation in a Multicenter Study. Am J Transplant. 2016;16 (suppl 3).
19. Morrill HJ, Pogue JM, Kaye KS, LaPlante KL. Treatment Options for Carbapenem-Resistant Enterobacteriaceae Infections. Open Forum Infect Dis. 2015;2(2):ofv050. [PubMed: 26125030]
20. van Duin D, van Delden C, Practice AIDCo. Multidrug-resistant gram-negative bacteria infections in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:31–41.
21. van Duin D, Bonomo RA. Ceftazidime/Avibactam and Ceftolozane/Tazobactam: Second-generation β-Lactam/β-Lactamase Inhibitor Combinations. Clin Infect Dis. 2016;63(2):234–241. [PubMed: 27098166]
22. Zhanel GG, Lawrence CK, Adam H, et al. Imipenem-Relebactam and Meropenem-Vaborbactam: Two Novel Carbapenem-β-Lactamase Inhibitor Combinations. Drugs. 2018;78(1):65–98. [PubMed: 29230684]
23. Zhanel GG, Golden AR, Zelenitsky S, et al. Cefiderocol: A Siderophore Cephalosporin with Activity Against Carbapenem-Resistant and Multidrug-Resistant Gram-Negative Bacilli. Drugs. 2019;79(3):271–289. [PubMed: 30712199]
24. Nielsen TB, Brass EP, Gilbert DN, Bartlett JG, Spellberg B. Sustainable Discovery and Development of Antibiotics - Is a Nonprofit Approach the Future? N Engl J Med. 2019;381(6):503–505. [PubMed: 31216396]
25. Tumbarello M, Trecarichi EM, De Rosa FG, et al. Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study. J Antimicrob Chemother. 2015;70(7):2133–2143. [PubMed: 25900159]
26. Aguado JM, Silva JT, Fernández-Ruiz M, et al. Management of multidrug resistant Gram-negative bacilli infections in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations. Transplant Rev (Orlando). 2018;32(1):36–57. [PubMed: 28811074]
27. Winters HA, Parbhoo RK, Schafer JJ, Goff DA. Extended-spectrum beta-lactamase-producing bacterial infections in adult solid organ transplant recipients. Ann Pharmacother. 2011;45(3):309–316. [PubMed: 21386016]
28. Kalpoe JS, Sonnenberg E, Factor SH, et al. Mortality associated with carbapenem-resistant Klebsiella pneumoniae infections in liver transplant recipients. Liver Transpl. 2012;18(4):468–474. [PubMed: 22467548]
29. Tamma PD, Han JH, Rock C, et al. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. Clin Infect Dis. 2015;60(9):1319–1325. [PubMed: 25586681]
30. Ng TM, Khong WX, Harris PN, et al. Empiric Piperacillin-Tazobactam versus Carbapenems in the Treatment of Bacteraemia Due to Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae. PLoS One. 2016;11(4):e0153696. [PubMed: 27104951]
31. Rodríguez-Baño J, Navarro MD, Retamar P, Picón E, Pascual Á, Group E-SB-LREdIePIGdEdIH. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing Escherichia coli: a post hoc analysis of prospective cohorts. Clin Infect Dis. 2012;54(2):167–174. [PubMed: 22057701]
32. Harris PNA, Tambyah PA, Lye DC, et al. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and

Ceftriaxone Resistance: A Randomized Clinical Trial. JAMA. 2018;320(10):984–994. [PubMed: 30208454]

33. Simkins J, Muggia V, Cohen HW, Minamoto GY. Carbapenem-resistant Klebsiella pneumoniae infections in kidney transplant recipients: a case-control study. Transpl Infect Dis. 2014;16(5):775–782. [PubMed: 25092500]
34. Pouch SM, Kubin CJ, Satlin MJ, et al. Epidemiology and outcomes of carbapenem-resistant Klebsiella pneumoniae bacteriuria in kidney transplant recipients. Transpl Infect Dis. 2015;17(6):800–809. [PubMed: 26341757]
35. van Duin D, Lok JJ, Earley M, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis. 2018;66(2):163–171. [PubMed: 29020404]
36. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infect Dis Ther. 2018;7(4):439–455. [PubMed: 30270406]
37. Zhanel GG, Chung P, Adam H, et al. Ceftolozane/tazobactam: a novel cephalosporin/β-lactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli. Drugs. 2014;74(1):31–51. [PubMed: 24352909]
38. Wong D, van Duin D. Novel Beta-Lactamase Inhibitors: Unlocking Their Potential in Therapy. Drugs. 2017;77(6):615–628. [PubMed: 28303449]
39. Bradley N, Lee Y. Practical Implications of New Antibiotic Agents for the Treatment of Carbapenem-Resistant Enterobacteriaceae. Microbiol Insights. 2019;12:1178636119840367. [PubMed: 30992668]
40. Lee GC, Burgess DS. Treatment of Klebsiella pneumoniae carbapenemase (KPC) infections: a review of published case series and case reports. Ann Clin Microbiol Antimicrob. 2012;11:32. [PubMed: 23234297]
41. Qureshi ZA, Paterson DL, Potoski BA, et al. Treatment outcome of bacteremia due to KPC-producing Klebsiella pneumoniae: superiority of combination antimicrobial regimens. Antimicrob Agents Chemother. 2012;56(4):2108–2113. [PubMed: 22252816]
42. Daikos GL, Tsaousi S, Tzouvelekis LS, et al. Carbapenemase-producing Klebsiella pneumoniae bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother. 2014;58(4):2322–2328. [PubMed: 24514083]
43. Falcone M, Bassetti M, Tiseo G, et al. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing Klebsiella pneumoniae. Crit Care. 2020;24(1):29. [PubMed: 32000834]
44. Kohler PP, Volling C, Green K, Uleryk EM, Shah PS, McGeer A. Carbapenem Resistance, Initial Antibiotic Therapy, and Mortality in Klebsiella pneumoniae Bacteremia: A Systematic Review and Meta-Analysis. Infect Control Hosp Epidemiol. 2017;38(11):1319–1328. [PubMed: 28950924]
45. Pike M, Saltiel E. Colistin- and polymyxin-induced nephrotoxicity: focus on literature utilizing the RIFLE classification scheme of acute kidney injury. J Pharm Pract. 2014;27(6):554–561. [PubMed: 25237156]
46. Moore RD, Smith CR, Lipsky JJ, Mellits ED, Lietman PS. Risk factors for nephrotoxicity in patients treated with aminoglycosides. Ann Intern Med. 1984;100(3):352–357. [PubMed: 6364908]
47. Tucker EL, Smith AR, Daskin MS, et al. Life and expectations post-kidney transplant: a qualitative analysis of patient responses. BMC Nephrol. 2019;20(1):175. [PubMed: 31096942]

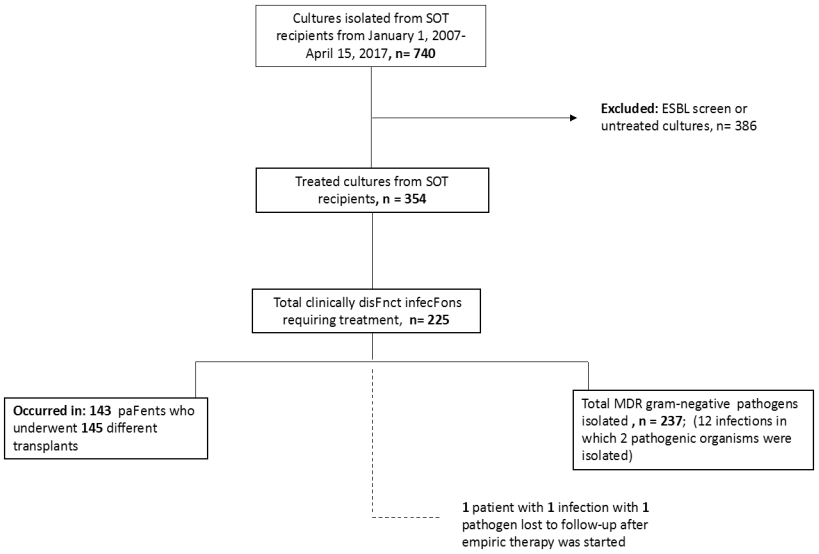

Figure 1: Inclusion criteria*

* Cultures were untreated if they were felt to represent colonization rather than a clinically significant infection by the transplant infectious diseases attending physician.

Table 1:

Demographics and Infection characteristics

	N (%)[†]
Total infections	225
Total patients	143
Total patients with ≥ 1 year follow-up	142 (99.3)
Survival at 30 days after first infection	122 (85.9)
Survival at 1 year after first infection	94 (66.2)
Survival at 1 year after transplant	110 (77.5)
Total pathogens	237
Mean Age, years (STD)	57.7 (11.7)
Female (%)	102 (45.3)
Mean duration between transplant and infection, days (STD)	193 (383.1)
Organ received[≠] (%)	
Heart	16 (7.1)
Kidney	69 (30.7)
Liver	68 (30.2)
Lung	7 (3.1)
Multi-organ	65 (28.9)
Primary infection site (%)	
Intra-abdominal	21 (9.3)
Biliary	7 (3.1)
Blood	26 (11.6)
Catheter	2 (0.9)
Respiratory	55 (24.4)
Urine	100 (44.4)
Other site	14 (6.2)
Multifocal infection	53 (23.5)
Infection at site of transplant (%)	109 (48.4)
Intra-abdominal[§]	18 (16.5)
Biliary[§]	7 (6.4)
Respiratory[§]	4 (3.7)
Urine[§]	76 (69.7)
Other[§]	3 (2.7)
Carbapenem-resistant pathogen	113 (50.2)
Polymicrobial infection	54 (24.0)
Renal replacement therapy prior to infection	52 (23.1)
Infection requiring hospitalization	207 (92.0)
Infection requiring ICU admission	130 (57.8)
Pathogen (s) sensitive to empiric therapy	94 (41.8)

	N (%)[†]
Final therapy different from empiric therapy	152 (67.6)
Multiple agents used for definitive therapy	61 (27.1)
Antibiotics completed as outpatient	18 (8.0)

Abbreviations: Intensive care unit (ICU)

[†] Except when specified, (%) refers to percent of total infections (N=225)

[‡] Refers to most recent organ transplanted prior to infection for patients who underwent >1 transplant

[§] Refers to percent of infections at site of transplant (N=109)

Table 2:

Antibiotic use[†]

Antimicrobial Class	Empiric Antibiotic Therapy (%)	Definitive Therapy (%)	Additional Therapy (%)	Total Exposed (%)
Aminoglycoside	5 (2.2)	31 (13.8)	30 (13.3)	64 (28.4)
Aztreonam	17 (7.6)	6 (2.7)	0 (0.0)	17 (7.6)
Cephalosporin	56 (24.9)	27 (12.0)	8 (3.6)	73 (32.4)
Cephalosporin/β-lactamase inhibitor	3 (1.8)	9 (4.0)	0 (0.0)	9 (4.0)
Carbapenem	60 (26.7)	94 (41.8)	25 (11.1)	135 (60.0)
Fluoroquinolone	18 (8.0)	31 (13.8)	8 (3.6)	47 (20.9)
Fosfomycin	15 (6.7)	26 (11.6)	1 (0.4)	30 (13.3)
Other	12 (5.3)	32 (14.2)	8 (3.6)	43 (19.1)
Penicillin/β-lactamase inhibitor	44 (19.6)	18 (8.0)	9 (4.0)	62 (27.6)
Polymyxin	6 (2.7)	31 (13.8)	5 (2.2)	38 (16.9)

[†]Total number and percent of infections (n=225) in which each class of antibiotics was use. Total exposure refers to the total number of infections for which antibiotic class was used.

Table 3:

Antibiotic-related outcomes

	Outcomes (OR, 95% CI)‡			Length of Stay (Beta estimate (STE); p-value)	
	New RRT (n=32)	Neurotoxicity (n=12)	30-day mortality (n=37)	Hospital LOS	ICU LOS
Cephalosporin	1.02 (0.97-1.06)	1.02 (0.97-1.065)	1.01 (0.97-1.04)	−0.11 (0.43); *P*=0.81	0.09 (0.76); *P*=0.90
Aztreonam	1.13 (0.92-1.40)	0.82 (0.32-2.11)	1.00 (0.75-1.34)	0.21(0.322); *P*=0.52	0.22 (0.56); *P*=0.69
Carbapenem	0.98 (0.95-1.01)	1.02 (0.97-1.05)	0.93 (0.90-0.98)*	−0.32 (0.26); *P*=0.21	−0.45 (0.45); *P*=0.31
Penicillin/β-lactamase inhibitor	1.03 (0.95-1.12)	0.92 (0.73-1.16)	0.95 (0.83-1.09)	0.40 (0.41); *P*=0.33)	0.24 (0.71); *P*=0.73
Fluoroquinolone	0.94 (0.85-1.05)	0.93 (0.75-1.14)	1.00 (0.92-1.08)	−0.07 (0.44); *P*=0.88	−0.59(0.776); *P*=0.44
Polymyxin	1.07 (0.99-1.16)	1.08 (1.01-1.17)*	0.99 (0.91-1.08)	0.61 (0.54); *P*=0.26	0.61 (0.95); *P*=0.52
Aminoglycoside	0.97 (0.88-1.06)	1.06 (0.99-1.14)	1.01 (0.97-1.05)	0.48 (0.23); *P*=0.04*	0.63 (0.41); *P*=0.12
Other	0.99 (0.94-1.06)	0.81 (0.70-0.95)*	0.89 (0.73-1.08)	0.33 (0.43); *P*=0.44	0.21 (0.76); *P*=0.78
Fosfomycin	0.00 (0.00-0.00)*	0.00 (0.00-0.00)*	0.82 (0.45-1.47)	−0.08 (1.21); *P*=0.95	0.38 (2.11); *P*=0.87

Abbreviations: RRT (renal replacement therapy), LOS (length of stay)

†Analysis for combination cephalosporin/β-lactamase inhibitors could not be done due to low overall use

‡Odds of outcome per day of exposure class of antibiotics

Table 4:

Therapy independent outcomes

	New RRT (n=32) †	Neurotoxicity (n=12) †	30-day mortality (n=37)
Infection at site of transplant (vs. non-transplant site)	0.36 (0.16-0.79)*	0.20 (0.03-0.77)*	0.24 (0.10-0.54)*
Carbapenem sensitive	0.97 (0.46-2.07)	0.98 (0.31-3.14)	0.35 (0.16-0.75)*
Admitted to ICU (vs. no ICU admission)	6.30 (2.13-18.67)*	3.26 (0.69-15.9))	30.7 (4.59-205.3)*
Definitive therapy with multiple agents (vs. single agent)	1.49 (0.67-3.30)	2.89 (0.83-10.1)	5.36 (2.55-11.27)*
Secondary organism	2.14 (0.97-4.73)	4.91 (1.49-16.2)*	2.00 (0.55-7.23)
Appropriate empiric antibiotic therapy	_	_	0.93 (0.45-1.91)
Carbapenem sensitive	_	_	1.09 (0.33-3.61)
Carbapenem resistant	_	_	1.24 (0.52-3.01)
Primary infection site (vs. abdominal fluid)			
Abdominal Fluid	_	_	-
Bile	_	_	1.58 (0.12-20.7)
Blood	_	_	3.69 (0.68-20.2)
IV catheter	_	_	9.5 (0.41-217.6)
Respiratory	_	_	4.62 (0.97-22.0)
Urine	_	_	0.50 (0.09-2.77)
Other	_	_	2.59 (0.37-18.0)

† New RRT and neurotoxicity were too rare to analyze by site of infection.

Abbreviations: RRT (renal replacement therapy), ICU (intensive care unit)