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Signature: DocuSigned by: Ahmed Babiker E055844B1150464...

Ahmed Babiker
Name

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Date

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Author Ahmed Babiker

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Approved by the Committee

DocuSigned by:
3DF70A15D4E64AF...

Michael Woodworth
Advisor

DocuSigned by:
Colleen Kraft
88D324E8F4D640F...

Colleen Kraft
Advisor

DocuSigned by:
Jesse Jacob
63403CD480614F1...

Jesse Jacob
Committee Member

DocuSigned by:
Jordan Kempker
39DC6753655C4B8...

Jordan Kempker
Committee Member

Accepted by the Laney Graduate School

Kimberly Jacob Arriola, PhD, MPH
Dean, James T. Laney School of Graduate Studies

Abstract Cover Page

The Burden and Impact of Early Post-Transplant Multidrug-resistant Organism Detection Among Renal Transplant Recipients, 2005-2021

By

Ahmed Babiker

M.B.B.S., University of Medical Sciences and Technology, 2011

Co-Advisors:

Michael H. Woodworth, M.D., M.Sc.

Colleen S. Kraft, M.D., M.Sc.

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Abstract

The Burden and Impact of Early Post-Transplant Multidrug-resistant Organism Detection Among Renal Transplant Recipients, 2005-2021

By Ahmed Babiker

Background

Understanding the impact of multi-drug resistant organism (MDRO) detection on renal transplant recipient (RTR) mortality and allograft function is paramount to mitigating morbid outcomes. We aimed to assess whether the detection of an MDRO or a comparative susceptible organism during the early post-transplant period was associated with increased mortality and allograft failure among RTRs.

Methods

We performed a retrospective cohort study of RTRs 2005 to 2021. Early post-transplant culture positivity was defined as a positive bacterial culture within 30 days of renal transplant. Incidence per 1,000 early post-transplant days at risk and prevalence of early post-transplant MDRO detection was calculated. The primary outcome was a composite of one year allograft loss or mortality following transplant. Differences between survival times were assessed using the log-rank test. Multivariable Cox proportional hazard regression modeling, competing risk analysis and a sensitivity analysis utilizing propensity score weighting was performed. A subgroup analysis of urine culture positive and RTRs transplanted between 2011-2021 cohort was performed.

Results

Among 3,507 RTRs, the prevalence of early post-transplant MDRO detection was 1.3% [95% C.I 0.31- 0.57] (44/3507) with an incidence rate per early post-transplant days at risk of 0.42 [95% C.I 0.31- 0.57] . Among RTRs eligible for survival analysis (N=3,432), 263 (7.6%) had a susceptible organism detected and 31 (0.9%) had an MDRO detected in the early post-transplant period. The composite outcome rate was higher among RTRs with an MDRO detected (12.9%, 4/31) compared to RTRs with a susceptible organism detected (6.8%, 18/263) and negative controls (4.3%, 135/3138). There was a significant difference from time of transplantation to the composite outcome when comparing negative controls, MDRO and susceptible organisms RTRs (MDROs: 20[76] *vs.* susceptible: 116 [166] *vs*. negative controls: 155[211]; log rank *p* =0.01)). Early post-transplant MDRO detection was significantly associated with the composite outcome (aHR: 3.19 [1.18, 8.63]) and allograft loss (cause-specific aHR*: 7.92 [1.01, 62.1], sub-distribution aHR 8.23 [1.17 54.2]). Similar results were seen in the sub-group and sensitivity analysis.

Conclusion

MDRO detection during the early post-transplant period was associated with increased allograft loss, suggesting the need for increased infection prevention efforts within this vulnerable population.

Cover Page

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Table of Contents

Introduction

The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) have declared antimicrobial resistance (AMR) a priority public health threat (1, 2). In 2019 alone, there were an estimated 1.27 million deaths attributable to bacterial AMR globally (3). In the US, the CDC has estimated that the 2.8 million infections by multi-drug resistant organisms (MDRO) contribute to over 35,000 deaths annually (1). These MDROs include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), Extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales and carbapenem-resistant organisms (CROs) all of which have been designated as urgent or serious threats by the CDC (1).

Given the limited, less efficacious, and more toxic, therapeutic options for patients with infections by MDRO, rates of mortality are disproportionately increased when compared to infections caused by susceptible bacteria (3-5). Colonization, the detection of an organism without signs or symptom of infection, with MDROs frequently precedes invasive clinical infection (6-8). Renal transplant recipients (RTR) represent a vulnerable population at increased risk of MDRO acquisition and colonization(9). This is especially true in the early post-transplantation period due to prolonged hospitalization, the need for invasive procedures, indwelling devices, exposure to broad-spectrum antibiotics and immunomodulatory therapy (9-12). Post-transplant infection is a major cause of mortality and has been linked to allograft loss among RTRs (4, 13, 14) .

Understanding the impact of MDRO colonization and infections on RTR patient mortality and allograft function is paramount to mitigate these deleterious outcomes. Prior studies have been limited by lack of control groups (using patients with infections caused by susceptible

organisms or patients without an infection), small sample sizes, a focus on one taxa/species of MDR infections or a single infection site (such as urinary tract) (15-19). To overcome previous limitations, we utilized a prospective cohort of over 4,000 RTRs followed from 2005 to 2021 to estimate the prevalence and incidence of early post-transplant MDRO detection among RTRs and compare outcomes (mortality and allograft failure) among RTRs with early post-transplant MDRO detection vs negative control RTRs.

Background

Renal Transplantation in the United States

Chronic kidney disease affects more than 1 in 7 adults in the US (20). Kidney transplantation is now recognized as the preferred treatment option for those with end-stage renal disease (ESRD) (21). Advances in surgical, immunosuppressive, and monitoring protocols have led to a significant improvement in outcomes including long-term graft survival (22).

Early Allograft Failure among RTRs

Despite the improvement in outcomes, renal allograft failure, defined as relisting for transplantation or resumption of renal replacement therapy, is associated with significant mortality, and economic burden (23). Many variables have been linked to early allograft loss. Recipient factors include race (likely a proxy for healthcare disparities) (24)), age at time of transplantation (25) and the presence of HLA antibodies (26). Non-recipient variables include the type of source of the kidney, as there are two types of kidney donors: living or deceased. Deceased donors are those which donate their organs either after brain death dead or cardiac death. Living kidney donation is known to offer the best graft and recipient survival (27). Post-operative contributing factors include delayed allograft function which can be induced by tissue injury through different events such as ischemia and/or reperfusion injury, and infection (28).

Impact of Urinary Tract Infections and Asymptomatic Bacteriuria (ASB) on Graft Function

While a there is a clear, established link between allograft dysfunction and viral infections such as BK virus (29) and cytomegalovirus (CMV) infection (30), the role of bacterial infection, and in particular urinary tract infections (UTIs), in loss of allograft function remains unclear (14, 31). RTRs are at an increased risk of UTI due to host, renal allograft and anatomical features, and post-transplant surgical interventions (32). UTIs represent the most

common infectious complication follow renal transplantation (32). The absence of a sphincter between the transplanted ureter and the native bladder can predispose RTRs to ascending infection and allograft pyelonephritis. Ureteral stents placed during transplantation and kidney cysts in patients with polycystic kidney disease can serve as reservoirs for bacteria and predispose patients to developing recurrent UTIs (33). It is hypothesized that bacterial invasion of the urinary tract during infection leads to an inflammatory response and cytokine activation contributing to allograft dysfunction (34, 35). Moreover, clinicians may change immunotherapy to support immune response in the setting of infection which can have deleterious impact on graft survival. Nonetheless, the literature has not uniformly demonstrated an association between UTIs and ASB , defined as $\geq 10^5$ colony-forming units (CFU)/mL in a voided urine specimen without signs or symptoms attributable to UTI, and allograft loss (14, 36) . Some studies have demonstrated no association between ASB/UTIs and allograft failure (37-41) , while some (generally of larger sample size) have demonstrated an association (41-44). Result heterogeneity may be driven by different practices, UTI or time of exposure definitions (34, 40, 41) outcome definitions (45).

The current landscape of Multidrug-resistant Organisms (MDROs)

The WHO and CDC have declared multidrug-resistant organisms (MDROs) priority global public health threats (1, 2). Compared to infections with antibiotic-susceptible bacteria, the limited therapeutic options for MDRO infections contribute to higher rates of associated patient morbidity and mortality (46). Furthermore, they represent a significant excess economic burden on our healthcare system, with $1.2 billion estimated attributable healthcare costs in 2017 in 2017 caused by extended spectrum beta-lactamase (ESBL) producing *Enterobacterales* alone (1). These MDRO include MRSA(47) all of which have been designated as urgent or serious threats by the CDC(1) for each MDRO group respectively(48). In addition, these organisms

have been specifically addressed in the American Society of Transplantation Infectious Diseases Community guidelines, underlining their importance among RTRs (9, 49, 50).

Epidemiology of MDROs in RTRs

Renal transplant patients have a unique propensity for the acquisition of high consequence MDROs, especially in the early post-transplant period (10, 12). This is primarily due to prolonged and frequent hospitalizations, the need for invasive procedures and indwelling devices, and exposure to broad-spectrum antibiotics and immunomodulatory therapy. The incidence of post-transplant colonization (51) and infections due to MDROs appears to have increased, especially those caused by Gram-negative MDROs (52). These studies have focused on either Gram-negative or Gram-positive organisms and inadequately described the cumulative burden of all MDROs. Recently, surveillance studies have suggested stabilization of some MDRO infection incidence rates (53). Understanding the MDRO burden for RTRs could inform optimization of surveillance, peri-operative antibiotic prophylaxis, empiric treatment recommendations, and inform the urgency for developing novel therapeutic and decolonization options for antimicrobial resistance (54).

Impact of MDROs on clinical outcomes in RTRs

Despite improved solid-organ transplant (SOT) outcomes from advances in surgical and immunosuppressive management, MDRO infections remain an important risk for mortality among RTRs (16, 17, 55). Published studies among RTRs to date have been limited by small sample sizes (15, 18, 56), the lack of appropriate control groups (16, 56), focus on one taxa/species of MDRO infections (17, 56) or lack of adjustment for confounding (57) and have reported poor outcomes. Paradoxically, evidence has also suggested that prior SOT is associated with decreased mortality among patients with sepsis and MDRO infections when

compared to non-transplant recipients (58-60). Attenuation of the septic inflammatory response with immunosuppression agents, access to healthcare services, low threshold for hospitalization, with surveillance for MDROs carriage and prompt initiation of appropriate antimicrobial therapy are hypothesized potential drivers of improved outcomes (61).

In conclusion early allograft failure among RTRs remains an important cause of morbidity and mortality. Furthermore, the impact of bacterial infection and colonization of the urinary tract in on allograft loss and the additive impact of MDROs over susceptible bacteria remains unclear and requires further study (31),(62) .

Methods

Study Aims

The first aim was to estimate the prevalence and incidence rate of early post-transplant MDRO detection among RTRs. The second aim was to compare outcomes (mortality and allograft failure) among RTRs with early post-transplant MDRO detection vs negative control RTRs.

Study Setting, Design and Data sources

The Emory Transplant Center performs approximately 250 adult renal transplants annually and provides ongoing care for over 4,000 renal transplant patients. The renal transplant prospective cohort dataset is a prospectively enrolled database, which contains data on RTRs pulled from Emory's electronic medical records. We performed a retrospective cohort study of RTRs enrolled into the Emory Renal Transplant database between 2005-2021.

Study Participants

Adult RTRs underdoing their first episode of renal transplantation at Emory were included. RTRs less than 18 years old and/or who had their renal transplant performed outside of Emory University Hospital or who were undergoing a repeat renal transplant were excluded. The study was approved by the Emory University Institutional Review Board.

Exposure, Outcomes and Covariates Definitions

For aim one the outcome variable was early post-transplant MDRO detection. This was defined as a positive clinical or surveillance culture (any anatomic site) with a target MDRO within 30 days of renal transplant.

For aim two, the exposure variable was early post-transplant bacterial culture positive for MDRO or corresponding antibiotic susceptible target organism (such as MRSA and methicillin-susceptible S. aureus [MSSA], respectively). Early post-transplant culture positivity was defined as a positive culture (irrespective of culture site) within 30 days of renal transplant.

Target organism selection was guided by CDC and WHO MDRO priority lists and the American Society of Transplantation Infectious Diseases Community guidelines (1, 2, 9, 49, 50). Target MDROs included MRSA, VRE, extended-spectrum cephalosporin resistant *Enterobacterales* (ESCRE) and CROs which included carbapenem-resistant *Enterobacterales* (CRE), carbapenem-resistant *Acinetobacter baumanii* complex (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). Target MDRO susceptible organisms' counterparts included MSSA, vancomycin-susceptible Enterococcus (VSE), extended-spectrum cephalosporin susceptible *Enterobacterales* (ESCSE), carbapenem-susceptible *P. aeruginosa* (CSPA) and carbapenem-susceptible *Acinetobacter baumanii* complex (CSAB). Antimicrobial susceptibility testing was performed at the Emory University Hospital microbiology laboratory as part of routine clinical care on the Vitek 2 (bioMérieux, Durham, NC, USA) and MicroScan (Beckman Coulter, Brea, CA) platforms. MDROs and comparative susceptible organisms were defined as per Clinical and Laboratory Standards Institute (CLSI) breakpoints (63).

The primary outcome was a combined composite outcome of one year- allograft loss and/or mortality following renal transplant. One-year allograft loss was defined as renal replacement therapy for more than 3 months or relisting for transplant within one year of renal transplant and one year post-transplant mortality was defined as death within one year of renal transplant.

Covariates of interest included sex, age at time of renal transplant, race, immune induction therapy, etiology of ESRD, type of renal transplant donor (living *vs.* cadaveric donor), pre-transplant positive MDRO culture status (any), dual solid organ transplant status (kidney vs. kidney/pancreas or kidney/liver), year of transplantation, CMV serostatus of donor and recipient, CMV viremia within the first-year post-transplant (CMV level > 35 IU/ml for CMV negative recipients and > 1000 IU/ml for CMV positive recipients), BK viremia within the first-year post-transplant (defined as more than >1000 copies/mL), and biopsy proven acute graft rejection. All variables included were extracted from the Electronic Medical Record (EMR).

Exclusion Criteria

RTRs were excluded from the survival analysis if they had a positive early post-transplant cultures with organisms not within the MDRO or comparative susceptible organism categories or had key susceptibility results missing (eg. vancomycin for *Enterococcus* spp.) To avoid misclassification bias RTRs who had both MDRO and comparative susceptible organism on culture in the early post-transplant period were also excluded.

Statistical Analysis

Aim one: The prevalence of early post-transplant MDRO detection was estimated using all eligible RTRs as the denominator. The incidence rate of early post-transplant MDRO detection was calculated per 1,000 early post-transplant-days at risk. At-risk time was calculated for each RTR as time between transplantation and positive early MDRO culture (event), allograft loss or death or 30 days (whichever came first). Difference in pre- and post-break point change incidence rates were assessed using Wilcoxon signed-rank test. Overall change in incidence over time was assessed using a negative binomial model with adjustment for pre- and post-breakpoint change period and model fit was assessed using log likelihood test (compared to model without breakpoint change).

Aim two: Cohort characteristics were described by overall and early-post transplant culture positivity status. Differences in baseline characteristics across exposure categories were performed using X^2 tests or Fisher's exact test for categorical variables and t-test for continuous variables or non-parametric tests (Kruskal-Wallis rank sum test) as appropriate.

To examine the impact of post-transplant MDRO detection on post-transplant outcomes we examined the hazards of primary and secondary outcomes among mutually exclusive exposure categories i- RTRs with early post-transplant MDRO detection, ii- RTRs with early post-transplant susceptible organism detection, iii- RTRs with no positive cultures. Among RTRs with multiple MDROs or susceptible organisms detected in the early post-transplant period, the earliest post-transplant organism detected was recorded.

A Kaplan–Meier survival analysis was performed, and differences between survival curves were assessed using the log-rank test. Multivariable cox proportional hazard regression modeling was performed with adjustment covariates selection informed by literature review, directed acyclic graphs and bivariate analysis. The proportional hazard assumption was assessed graphically and statistically by assessing Schoenfeld residuals and no variables violated the proportional hazards assumption. Given the competing risks of risk of death on allograft loss, a competing risk analysis was performed by fitting a cause-specific and subdistribution hazard model for both outcomes (mortality and allograft loss). The competing cumulative incidence of each outcome (mortality and allograft loss) by exposure group were compared using Gray's test. Wilcoxon tests were used to compare these measurements between the treatment groups. Adjusted hazard ratio (aHR) and corresponding 95% confidence intervals (CIs) were reported. A subgroup analyses among a subset of patients with positive

urine cultures and among patients in the post *Enterobacterales* breakpoint change period (2011-2021) was performed (64).

A sensitivity analysis was performed to adjust for the propensity of MDRO acquisition on poor outcomes. A propensity score (PS) weighted analysis was performed where a PS was generated based on the probability of being in each exposure category strata. The PS was created by performing a multinomial logistic regression model which modeled the exposure category (negative controls, susceptible, MDRO) as the outcome variable with backward selection for the final model selection. After generation of the PS, two methods of weighting, inverse probability of treatment weighting (IPTW) and matching weighting (MW), which incorporated the PS were applied to create weighted cohorts (65). PS covariate balance before and after generation of the weighted cohorts were assessed by examining the standard mean difference for variables across the exposure category. A weighted multivariable cox proportional hazard modeling was performed using the MW and IPTW cohorts.

A complete case analysis was performed as missing data across important covariates was < 5% . Statistical analysis was performed with R using Rstudio V2022.12.0.353 (R Foundation for Statistical Computing, Vienna, Austria)

Results

Between 2005 and 2021 there were 4,554 unique RTRs enrolled in the Emory Renal Transplant database, 3,507 who were >18 years old and had their renal transplant performed at Emory University Hospital (**Figure 1**).

Prevalence and Incidence of Early Post-Transplant MDRO Detection

Among eligible RTRs (N=3,507), 328 (10.5%, 369/3,507) had an early post-transplant positive culture with any organism. Eighty-three MDROs were detected among the 44 unique RTRs giving an early post-transplant MDRO detection prevalence of 1.3% [95% CI: 0.91, 1.69] (**Figure 2**). ESCRE was the most common MDRO detected (52%, 43/83) followed by MRSA (25%, 21/83), VRE (14%, 12/83), CRPA (5%, 4/83) and CRAB (4%, 3/82). MDROs were most detected in urinary tract samples (48%, 40/83), followed by blood samples (23%, 19/83), intra-abdominal sources (18%, 15/83), respiratory tract samples (4%, 3/83), other invasive sites (4%, 3/83) and superficial wounds (2%, 2/83).

The incidence of early post-transplant MDRO detection during study period was 0.42 [95% C.I 0.31- 0.57] per 1000 early post-transplant days at risk (**Figure 3**). The incidence in pre-*Enterobacterales* breakpoint change period was 0.33 [0.14, 0.71] which was similar to post-break period (incidence: 0.44, [0.31, 0.61]; p= 0.79). change. There was no association with time (year) in a negative binomial model adjusted for breakpoint change ($p > 0.05$)

Impact of Early Post-Transplant MDRO Detection on RTR Outcomes

Among eligible RTRs (N=3,507), seventy-five (2%, 75/3,507) were excluded from survival analysis. Fifty-nine RTRs (2%, 74/3,307) had an early-post transplant positive culture with non-target organisms considered not of interest, six RTRs (6, 6/3,507) had a positive culture with a target organism but had key missing susceptibility data missing and eleven RTRs (11/3,507) had both an MDRO and comparative susceptible organism detected in the early post-transplant period.

Cohort Characteristics

Among RTRs who met survival analysis inclusion criteria (n=3,432), 3,138 (91%, 2,939/3,233) had no positive early post-transplant cultures and were designated as negative controls, 259 (8%, 258/3,432) had a comparative susceptible organism detected (MSSA: 2% [6/263], VSE: 25% [67/263], ESCSE: 25% [152/263], CSPA: 10% [26/263]) and 31 (1%, 31/3,434) and had an MDRO detected (MRSA: 19% [6/31], VRE: 14% [3/31], ESCRE: 61% [19/31], CRAB 3% [1/31]) in the early post-transplant period (**Figure 1, Table 2**).

Compared to negative control RTRs, RTRs with a positive early post-transplant culture were older (median [intra-quartile range (IQR)] age for MDRO: 55 [18] *vs*. susceptible 53[20] *vs.* negative controls: 50[20]; p <0.001), had a higher proportion of females (55%[17/31] *vs.* 62% [162/263] *vs.* 41% [1,274/3,138]; p= <0.001), more DM as the primary etiology of their ESRD (32% [10/31] *vs*. 38% [99/263] *vs.* 30% [945/3,138]; p= 0.04), received a deceased donor kidney (81% [25/31] *vs.* 76% [200/263] *vs.* 67% [2,107/3,138]; p = 0.003), experienced more BK viremia (39% [12/31] *vs.* 23% [61/263] *vs.* 20% [627/3,138]; p = 0.02) within the first year post-transplant and had a longer transplant admission length of stay (4[3] *vs*. 4[3] *vs.* 7[11], p <0.001) . The remaining demographic and transplant-related characteristics are summarized in **Table 1.**

Among RTRs with a positive early-transplant culture the median [IQR] days between transplant and positive culture was 13 [13] days and was similar across RTRs with MDRO and susceptible organisms (10 [19] *vs.* 13 [13] days, p = 0.40) detected. The most common organisms detected were *Enterobacterales spp.* detected among 62% (183/294) of RTRs followed by *Enterococcus spp.* which detected among 24% (72/294) of RTRs. The urinary tract (80%, 234/294) was the most common site of early post-transplant positive cultures followed by a blood and/or endovascular sources (11%, 31/294). Trimethoprim-sulfamethoxazole resistance was similar among MDRO and susceptible organisms in which trimethoprim-

sulfamethoxazole antimicrobial susceptibility testing is appropriate (59% [16/27] *vs.* 66 [120/181]; *p*= 0.50) **(Table 2).**

Survival Analysis

One hundred and forty-nine (5%, 157/3,432) RTRs experienced the primary composite outcome of one-year mortality and/or allograft failure. A higher proportion of RTRs in the MDRO positive group experienced the primary composite outcome compared to RTRs in the susceptible organism and negative controls groups (MDRO: 13%, [4/31], susceptible: 7%, [18/263]), negative controls: 4%, [135/3,138]; *p*= 0.02). A higher proportion of RTRs in the MDRO positive group had one-year allograft failure compared to RTRs in the susceptible organism and negative controls groups (14% [4/31] *vs.* 4% [9/259] *vs*. 2% [54/2,939]; *p* = 0.01). One-year mortality was similar across the exposure categories (3% [1/31] *vs.* 4% *vs.* [11/263] *vs.* 3% [86/3,138]) (**Table 3**). The median [IQR] days from transplant to primary composite outcome was 152[211] days. Kaplan–Meier analysis revealed a significant difference between time from transplantation to the composite outcome when comparing negative controls, MDRO and susceptible organisms RTRs (MDROs: 20[76] *vs.* susceptible: 116 [166] *vs*. negative controls: 155[211]; log rank *p* =0.01) (**Figure 4**).

The unadjusted hazards ratio (HR) of experiencing the primary composite outcome was increased among RTRs with early post-transplant MDRO detection (HR: 3.19 ([95% CI, 1.18, 9.6], *p*= 0.02) and early post-transplant susceptible (HR: 1.62 ([95% CI, 0.99, 2.65], *p*= 0.05) compared to negative controls (**Table 4**). The adjusted hazards ratio (aHR) of experiencing the primary composite outcome was increased among RTRs with early post-transplant MDRO detection (aHR: 3.59 ([95% CI, 1.32, 9.77], *p*= 0.01) and early post-transplant susceptible organism detection (aHR 1.58 ([95% CI, 0.96, 2.60], *p*= 0.07) compared to negative controls, adjusting for age, sex, year of transplant, one year post-transplant BK viremia, one year post-

transplant CMV viremia, deceased donor status, diabetes as the primary etiology of ESRD and category of induction therapy. This was not statistically significant in the susceptible group (**Table 4)**.

Similar results were seen among RTRs with early post-transplant MDRO detection in the post breakpoint change subgroup (aHR: 3.71 [95% CI, [1.17, 11.8]; *p*= 0.03)), but not among the urine positive subgroup (aHR: 1.50 ([95% CI, 0.21, 10.8]; *p*= 0.70)) (**Table 5**). Age at transplant, sex, category of induction regimen, type of donor, BK viremia within one year of transplant, transplant year and sex were all associated with the MDRO or comparative susceptible organism detection in the early post-transplant period and were including in the PS generation. PS weighting resulted in better covariate balance among the MW cohort compared to IPTW cohort (**Figure 5**). A similar trend was seen in the sensitivity analysis of RTRs with early post-transplant MDRO detection in MW cohort (aHR: 3.73 ([95% CI, 1.34, 10.4]; *p*= 0.01) and PTW cohort (aHR: 3.05 ([95% CI, 0.97, 9.58]; *p*= 0.60).

Competing Risk Analysis

Given the competing risk of mortality on allograft loss we examined performed a competing risk analysis to examine the impact of early post-transplant MDRO detection on allograft loss. Across the exposure variable strata, the cumulative incidence of one-year allograft loss was significantly different across the exposure group (*p* =0.04) (**Figure 6**). When accounting for death as a competing risk, an increased adjusted cause-specific hazards (aHR 7.92 [1.01, 62.1]; *p* = 0.049) and subdistribution hazards (aHR 7.92 [1.17, 53.6]; *p*= 0.03) of one-year allograft loss was observed among RTRs with an MDRO detected on early post-transplant culture compared to negative control RTRs when adjusting for age, sex, year of transplant, one year post-transplant BK viremia, one year post-transplant CMV viremia , deceased donor status, diabetes as the primary etiology of ESRD and category of induction

therapy. This finding was not seen among RTRs with an early-post transplant susceptible organism detected (cause-specific aHR 0.85 [0.11, 6.62], subdistribution aHR: 0.82 [1.17, 5.74]; *p*= 0.9) (**Table 6)**.

Similar results were seen among RTRs with early post-transplant MDRO detection the post breakpoint change subgroup (cause-specific aHR: 11.3 [95% CI, [1.45, 88.3]; *p*= 0.03)), and urine positive subgroup (cause-specific aHR: 13.0 ([95% CI, 1.69, 99.7]; *p*= 0.02)) (**Table 7**). Similar results were seen among RTRs with early post-transplant MDRO detection in MW cohort (cause-specific aHR: 8.99 ([95% CI, 1.17, 68.9]; *p*= 0.02), but not among the IPTW cohort (cause-specific aHR: 3.55 ([95% CI, 1.49, 10.8]; *p*= 0.30) (**Table 7**).

Discussion

We found the incidence and prevalence of early post-transplant MDRO detection to be low, but MDRO detection during the early post-transplant period was significantly associated with an increased hazards of experiencing the composite outcome of one-year mortality and/or allograft loss and of death censored allograft loss adjusting for important variables when compared to negative control RTRs. These findings were consistent across the subgroup and PS weighted sensitivity analysis giving more confidence in the relevance of these findings. Our retrospective cohort study of over 3,500 RTRs over two decades represents one of the largest studies to estimate the burden of MDRO detection during this critical early post-transplant period and examine its association with key outcomes.

As originally described by Fishman and Rubin, the first 30 days in the post-transplant period represent a time where RTRs are most vulnerable for infections by nosocomial MDROs (66-68). We found MDRO culture positivity during this period predominated by uropathogenic bacteria

(ESCR-*E. coli*, VRE) with low rate of CROs. Our findings are similar to the epidemiology described in other large cohort studies (67, 69) and reflect the practice of frequent urine sampling (32) and the low rates of CROs reported in population surveillance within the area (70). Consistent with prior literature, our patients with an MDRO were older, female, diabetic, received a kidney from a deceased donor and had a longer transplant length of stay (25, 71). While our prevalence and incidence were of MDRO detection was low this represents the tip of the iceberg, as clinical culture positivity underestimates rates of MDRO colonization compared to active surveillance (72). Illustrating this point is a single center study of 200 deceased donor RTRs which found close to a quarter of RTRs to be colonized with an ESBL *Enterobacterales* when screened on admission (73). Further prospective active surveillance studies to determine the rates of MDRO colonization among RTRs are needed.

We found that early post-transplant MDRO detection resulted in an increased hazards of experiencing the composite outcome of one-year death or allograft loss. A similar signal was seen among RTRs with a susceptible organism detected. Although prior studies have previously demonstrated poor outcomes in RTRs recipients with MDRO infections (5), our study adds to this literature by examining the specific impact of MDROs detection among a large cohort of 3,432 RTRs during the critical early-post transplant period, a period characterized by healthcare exposure and risk for MDRO acquisition (67). Our cohort was primarily comprised of RTRs with positive urinary tract cultures, and among this subgroup we found an increased hazards of death-censored allograft loss. Bacterial invasion of the urinary tract of RTRs during infections or colonization is hypothesized to lead to an inflammatory response and cytokine activation contributing to allograft dysfunction (23). The association between UTIs and particularly ASB with allograft loss remains unclear (14). Moreover, most prior studies only included patients with ASB/UTIs in the post-early transplant (after 30 days) period or had a wide inclusion period (32, 74). The lack of association in the susceptible group suggests the additive impact of AMR on

RTR outcomes (3, 5). This may be due to increased use of nephrotoxic treatments and reduction in immunosuppression among RTRs with MDRO *vs*. susceptible organisms detected, rather than increased virulence. As has been suggested by the American Society of Transplantation's Infectious Diseases Community of Practice, multicenter studies using standardized definitions to parse the impact of ASB and UTI on graft function and to guide surveillance strategies and management are required (32). In such studies, stratification based on susceptibility profile or adjusting for inappropriate empiric therapy will be helpful to assess impact of resistance on outcomes(75).

While association does not necessarily imply causality, our findings support increased stewardship and infection prevention-based interventions to decrease MDRO acquisition in ESRD and RTRs. These include both system and patient level interventions such as limiting the duration of urinary catheters and stents, avoiding broad-spectrum nephrotoxic agents when possible and vigilance in standard infection prevention practices (48, 60, 76). Pre-transplant MDRO infection/colonization has been associated with high rates of early post-transplant MDRO invasive infection (4, 77, 78). If our findings are replicated in prospective cohorts using standardized definitions, the next possible step would be using active surveillance of RTRs prior to transplantation and decolonization using novel techniques such microbiome therapeutics or bacterial consortia (54, 79). We recently demonstrated safety and efficacy of fecal microbiota transplantation (FMT) in a phase 1 randomized, controlled trial of FMT administered for MDRO decolonization among RTRs (NCT02922816). Moreover, in a post-hoc analysis FMT-treated participants had longer time to recurrent MDRO infection compared to matched patients our RTR cohort who met FMT eligibility criteria but were not treated with FMT further supporting the benefit of such intervention. (Woodworth et al. under review)

While our study builds on the limitations of prior studies in terms of sample size, the expanded inclusion of multiple MDROs time period analyzed, some key limitations exist. Firstly, we were unable to use raw MIC data for our classification of MDROs which may lead to misclassification bias due to changes in MDRO definitions over time. To account for this and for clinical practice changes over time we included transplant year as an adjustment variable our sensitivity analysis and in the PS creation and we performed a subgroup analysis on the post breakpoint change cohort with findings remaining similar. Second, our study is a retrospective observational study and our MDRO positive group was small, and thus subject to residual confounding. While we attempted to account for confounding by multivariable adjustment and a sensitivity analysis using PS weighting, important potential confounders such as timing of ureteral stent removal, antibiotic and nephrotoxic drug exposure, and intra-operative variables such as cold times were not available the dataset. Despite this, our results remained significant across the MW cohort which was used as it is reported to have improved mean squared error compared to IPTW in scenarios with a rare outcome, unequally sized treatment groups, or poor covariate overlap as it down-weights the data in regions of poor overlap (80, 81). Finally, like prior studies (60, 82), our case definition was based on culture positivity in the absence of symptoms or clinical indicators of infection, as we believe culture positivity (colonization) represents an important dysbiotic phenotype associated with poor outcomes and subsequent invasive infections (54, 77, 78, 83). Finally, since center level characteristics and are associated with RTR outcomes, our findings in a single center may not be generalizable to other centers and require further validation in multicenter studies (84).

Overall, our findings underscore how the acquisition or presence of MDROs in this early-post transplant period while infrequent, has a significant impact on allograft function and underlines the need for continued antibiotic and device stewardship and infection prevention efforts in this vulnerable population.

References

1. CDC. Antibiotic Resistance Threats in the United States. Atlanta, GA: U.S. Department of Health and Human Services, CDC, 2019.
2. WHO. Global priority list of antibiotic-resistant bacteria to guide research, discover, and development of new antibiotics World Health Organization, 2017.
3. Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 2022;399(10325):629-55.
4. 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):800-9.
5. Anesi JA, Lautenbach E, Thom KA, et al. Clinical Outcomes and Risk Factors for Carbapenem-resistant *Enterobacterales* Bloodstream Infection in Solid Organ Transplant Recipients. *Transplantation* 2023;107(1):254-63.
6. Isendahl J, Giske CG, Hammar U, et al. Temporal Dynamics and Risk Factors for Bloodstream Infection With Extended-spectrum β-Lactamase-producing Bacteria in Previously-colonized Individuals: National Population-based Cohort Study. *Clin Infect Dis* 2019;68(4):641-9.
7. Howard-Anderson JR, Bower CW, Smith G, et al. Carbapenem-resistant *Enterobacterales* bacteriuria and subsequent bacteremia: A population-based study. *Infect Control Hosp Epidemiol* 2021;42(8):962-7.
8. Hong Nguyen M, Shields RK, Chen L, et al. Molecular Epidemiology, Natural History, and Long-Term Outcomes of Multidrug-Resistant Enterobacterales Colonization and Infections Among Solid Organ Transplant Recipients. *Clinical Infectious Diseases* 2021;74(3):395-406.
9. Pouch SM, Patel G, Practice tAIDCo. Multidrug-resistant Gram-negative bacterial infections in solid organ transplant recipients—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical Transplantation* 2019;33(9):e13594.
10. Rodriguez-Bano J, Picon E, Gijon P, et al. Risk factors and prognosis of nosocomial bloodstream infections caused by extended-spectrum-beta-lactamase-producing Escherichia coli. *J Clin Microbiol* 2010;48(5):1726-31.
11. Pouch SM, Patel G. Multidrug-resistant Gram-negative bacterial infections in solid organ transplant recipients-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019;33(9):e13594.
12. Fishman JA. Infection in Solid-Organ Transplant Recipients. *New England Journal of Medicine* 2007;357(25):2601-14.
13. Almond PS, Matas A, Gillingham K, et al. Risk factors for chronic rejection in renal allograft recipients. *Transplantation* 1993;55(4):752-6; discussion 6-7.
14. Hollyer I, Ison MG. The challenge of urinary tract infections in renal transplant recipients. *Transpl Infect Dis* 2018;20(2):e12828.
15. Taglietti F, Di Bella S, Galati V, et al. Carbapenemase-producing Klebsiella pneumoniae-related mortality among solid organ-transplanted patients: do we know enough? *Transplant infectious disease : an official journal of the Transplantation Society* 2013;15(4):E164-5.

16. Qiao B, Wu J, Wan Q, et al. Factors influencing mortality in abdominal solid organ transplant recipients with multidrug-resistant gram-negative bacteremia. *BMC infectious diseases* 2017;17(1):171.
17. Moreno A, Cervera C, Gavalda J, et al. Bloodstream infections among transplant recipients: results of a nationwide surveillance in Spain. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2007;7(11):2579-86.
18. Venditti M, Falcone M, Micozzi A, et al. Staphylococcus aureus bacteremia in patients with hematologic malignancies: a retrospective case-control study. *Haematologica* 2003;88(8):923-30.
19. Yuan X, Liu T, Wu D, et al. Epidemiology, susceptibility, and risk factors for acquisition of MDR/XDR Gram-negative bacteria among kidney transplant recipients with urinary tract infections. *Infect Drug Resist* 2018;11:707-15.
20. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States. 2021. (Accessed).
21. Abecassis M, Bartlett ST, Collins AJ, et al. Kidney transplantation as primary therapy for end-stage renal disease: a National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQITM) conference. *Clin J Am Soc Nephrol* 2008;3(2):471-80.
22. Loupy A, Lefaucheur C, Vernerey D, et al. Complement-binding anti-HLA antibodies and kidney-allograft survival. *N Engl J Med* 2013;369(13):1215-26.
23. Kaplan B, Meier-Kriesche HU. Death after graft loss: an important late study endpoint in kidney transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2002;2(10):970-4.
24. Higgins RS, Fishman JA. Disparities in solid organ transplantation for ethnic minorities: facts and solutions. *Am J Transplant* 2006;6(11):2556-62.
25. Summers DM, Johnson RJ, Hudson A, et al. Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study. *Lancet* 2013;381(9868):727-34.
26. Terasaki PI, Ozawa M. Predicting kidney graft failure by HLA antibodies: a prospective trial. *Am J Transplant* 2004;4(3):438-43.
27. Treat EG, Miller ET, Kwan L, et al. Outcomes of shipped live donor kidney transplants compared with traditional living donor kidney transplants. *Transpl Int* 2014;27(11):1175-82.
28. Quiroga I, McShane P, Koo DD, et al. Major effects of delayed graft function and cold ischaemia time on renal allograft survival. *Nephrol Dial Transplant* 2006;21(6):1689-96.
29. Hirsch HH, Randhawa PS, Practice AIDCo. BK polyomavirus in solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical Transplantation* 2019;33(9):e13528.
30. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical Transplantation* 2019;33(9):e13512.
31. Martin-Gandul C, Mueller NJ, Pascual M, et al. The Impact of Infection on Chronic Allograft Dysfunction and Allograft Survival After Solid Organ Transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2015;15(12):3024-40.
32. Goldman JD, Julian K. Urinary tract infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical Transplantation* 2019;33(9):e13507.

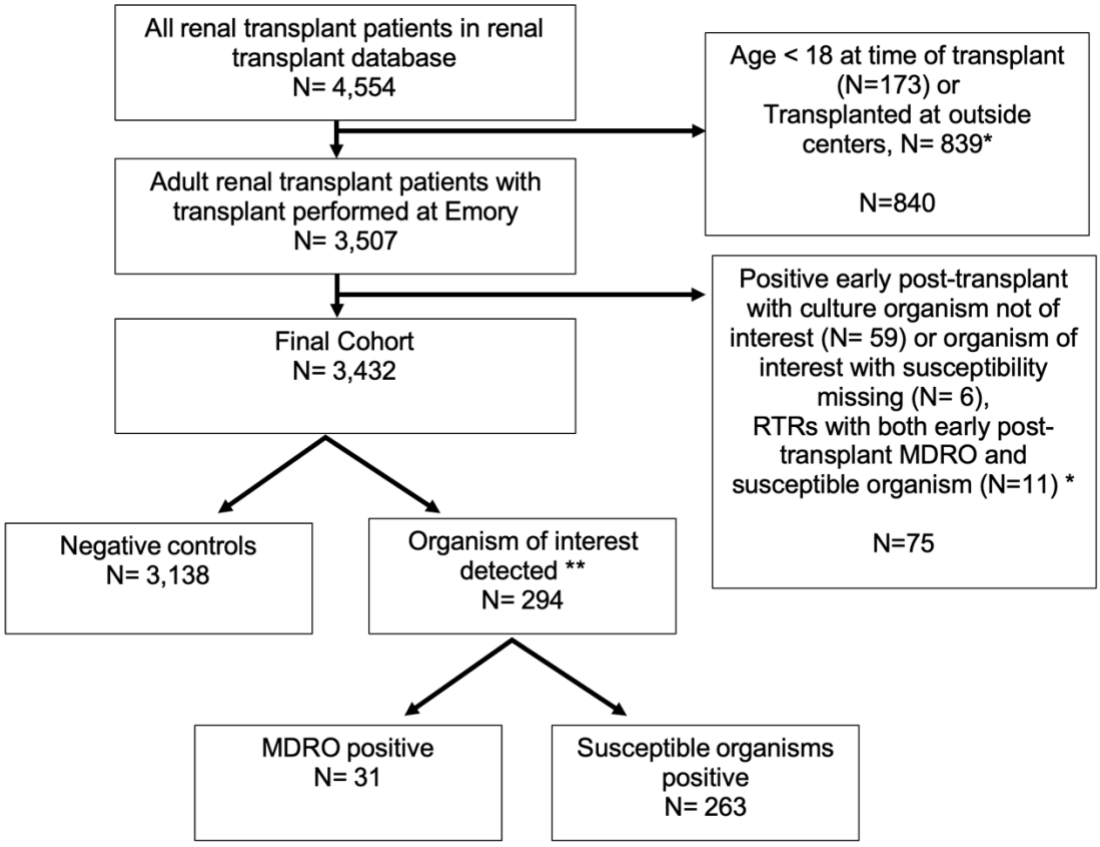
33. Liu S, Luo G, Sun B, et al. Early Removal of Double-J Stents Decreases Urinary Tract Infections in Living Donor Renal Transplantation: A Prospective, Randomized Clinical Trial. *Transplantation Proceedings* 2017;49(2):297-302.
34. Bodro M, Sanclemente G, Lipperheide I, et al. Impact of urinary tract infections on short-term kidney graft outcome. *Clinical Microbiology and Infection* 2015;21(12):1104.e1-.e8.
35. Ciszek M, Paczek L, Bartłomiejczyk I, et al. Urine cytokines profile in renal transplant patients with asymptomatic bacteriuria. *Transplantation* 2006;81(12):1653-7.
36. Nicolle LE, Gupta K, Bradley SF, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of Americaa. *Clinical Infectious Diseases* 2019;68(10):e83-e110.
37. Papasotiriou M, Savvidaki E, Kalliakmani P, et al. Predisposing factors to the development of urinary tract infections in renal transplant recipients and the impact on the long-term graft function. *Ren Fail* 2011;33(4):405-10.
38. Camargo LF, Esteves ABA, Ulisses LRS, et al. Urinary Tract Infection in Renal Transplant Recipients: Incidence, Risk Factors, and Impact on Graft Function. *Transplantation Proceedings* 2014;46(6):1757-9.
39. Adamska Z, Karczewski M, Cichańska L, et al. Bacterial Infections in Renal Transplant Recipients. *Transplant Proc* 2015;47(6):1808-12.
40. Rice JC, Peng T, Kuo Yf, et al. Renal Allograft Injury Is Associated with Urinary Tract Infection Caused by Escherichia coli Bearing Adherence Factors. *American Journal of Transplantation* 2006;6(10):2375-83.
41. Pellé G, Vimont S, Levy PP, et al. Acute Pyelonephritis Represents a Risk Factor Impairing Long-Term Kidney Graft Function. *American Journal of Transplantation* 2007;7(4):899-907.
42. Abbott KC, Swanson SJ, Richter ER, et al. Late urinary tract infection after renal transplantation in the United States. *Am J Kidney Dis* 2004;44(2):353-62.
43. Giral M, Pascuariello G, Karam G, et al. Acute graft pyelonephritis and long-term kidney allograft outcome. *Kidney Int* 2002;61(5):1880-6.
44. Naik AS, Dharnidharka VR, Schnitzler MA, et al. Clinical and economic consequences of first-year urinary tract infections, sepsis, and pneumonia in contemporary kidney transplantation practice. *Transpl Int* 2016;29(2):241-52.
45. Lim JH, Cho JH, Lee JH, et al. Risk factors for recurrent urinary tract infection in kidney transplant recipients. *Transplant Proc* 2013;45(4):1584-9.
46. Kadri SS, Lai YL, Ricotta EE, et al. External Validation of Difficult-to-Treat Resistance Prevalence and Mortality Risk in Gram-Negative Bloodstream Infection using Electronic Health Record Data from 140 US Hospitals. 2019.
47. Schlaberg R, Chiu CY, Miller S, et al. Validation of Metagenomic Next-Generation Sequencing Tests for Universal Pathogen Detection. *Archives of Pathology & Laboratory Medicine* 2017;141(6):776-86.
48. Babiker A, Clarke L, Doi Y, et al. Fosfomycin for treatment of multidrug-resistant pathogens causing urinary tract infection: A real-world perspective and review of the literature. *Diagn Microbiol Infect Dis* 2019;95(3):114856.
49. Nellore A, Huprikar S, the AST ID Community of Practice. Vancomycin-resistant Enterococcus in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical Transplantation* 2019;33(9):e13549.
50. Pereira MR, Rana MM, the AST ID Community of Practice. Methicillin-resistant *Staphylococcus aureus* in solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical Transplantation* 2019;33(9):e13611.

51. Ziakas PD, Pliakos EE, Zervou FN, et al. MRSA and VRE colonization in solid organ transplantation: a meta-analysis of published studies. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2014;14(8):1887-94.
52. Oriol I, Sabe N, Simonetti AF, et al. Changing trends in the aetiology, treatment and outcomes of bloodstream infection occurring in the first year after solid organ transplantation: a single-centre prospective cohort study. *Transplant international : official journal of the European Society for Organ Transplantation* 2017;30(9):903-13.
53. Diekema DJ, Hsueh P-R, Mendes RE, et al. The Microbiology of Bloodstream Infection: 20-Year Trends from the SENTRY Antimicrobial Surveillance Program. *Antimicrobial agents and chemotherapy* 2019;63(7):e00355-19.
54. Woodworth MH, Hayden MK, Young VB, et al. The Role of Fecal Microbiota Transplantation in Reducing Intestinal Colonization With Antibiotic-Resistant Organisms: The Current Landscape and Future Directions. *Open Forum Infect Dis* 2019;6(7).
55. Chuang P, Parikh CR, Langone A. Urinary tract infections after renal transplantation: a retrospective review at two US transplant centers. *Clinical Transplantation* 2005;19(2):230-5.
56. Rodrigues dos Santos BG, Amaral ES, Fernandes PFCBC, et al. Urinary Tract Infections and Surgical Site Infections due to Carbapenem-Resistant Enterobacteriaceae in Renal Transplant. *Transplantation Proceedings* 2016;48(6):2050-5.
57. Linares L, Cervera C, Cofán F, et al. Epidemiology and Outcomes of Multiple Antibiotic–Resistant Bacterial Infection in Renal Transplantation. *Transplantation Proceedings* 2007;39(7):2222-4.
58. Donnelly JP, Locke JE, MacLennan PA, et al. Inpatient Mortality Among Solid Organ Transplant Recipients Hospitalized for Sepsis and Severe Sepsis. *Clinical Infectious Diseases* 2016;63(2):186-94.
59. Kalil AC, Syed A, Rupp ME, et al. Is bacteremic sepsis associated with higher mortality in transplant recipients than in nontransplant patients? A matched case-control propensity-adjusted study. *Clin Infect Dis* 2015;60(2):216-22.
60. Babiker A, Clarke LG, Saul M, et al. Changing Epidemiology and Decreased Mortality Associated With Carbapenem-resistant Gram-negative Bacteria, 2000-2017. *Clin Infect Dis* 2021;73(11):e4521-e30.
61. Zilberberg MD, Nathanson BH, Sulham K, et al. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis. *BMC infectious diseases* 2017;17(1):279.
62. Ariza-Heredia EJ, Beam EN, Lesnick TG, et al. Impact of urinary tract infection on allograft function after kidney transplantation. *Clinical transplantation* 2014;28(6):683-90.
63. Clinical and Laboratory Standards Institute. M100-S27 Psfast, 27th informational supplement. Wayne, PA: Clinical and Laboratory Standards Institute; 2017. Clinical and Laboratory Standards Institute. M100-S27, Performance standards for antimicrobial susceptibility testing, 27th informational supplement. Wayne, PA: Clinical and Laboratory Standards Institute; 2017. 2017.
64. Wang P, Hu F, Xiong Z, et al. Susceptibility of extended-spectrum-beta-lactamase-producing *Enterobacteriaceae* according to the new CLSI breakpoints. *J Clin Microbiol* 2011;49(9):3127-31.
65. Li L, Greene T. A weighting analogue to pair matching in propensity score analysis. *Int J Biostat* 2013;9(2):215-34.
66. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998;338(24):1741-51.

67. San Juan R, Aguado JM, Lumbreras C, et al. Incidence, Clinical Characteristics and Risk Factors of Late Infection in Solid Organ Transplant Recipients: Data from the RESITRA Study Group. *American Journal of Transplantation* 2007;7(4):964-71.
68. Lanini S, Costa AN, Puro V, et al. Incidence of carbapenem-resistant gram negatives in Italian transplant recipients: a nationwide surveillance study. *PLoS One* 2015;10(4):e0123706.
69. Sommerer C, Schröter I, Gruneberg K, et al. Incidences of Infectious Events in a Renal Transplant Cohort of the German Center of Infectious Diseases (DZIF). *Open Forum Infect Dis* 2022;9(7):ofac243.
70. Babiker A, Bower C, Lutgring JD, et al. Clinical and Genomic Epidemiology of mcr-9-Carrying Carbapenem-Resistant *Enterobacterales* Isolates in Metropolitan Atlanta, 2012 to 2017. *Microbiol Spectr* 2022;10(4):e0252221.
71. Dharnidharka VR, Agodoa LY, Abbott KC. Risk factors for hospitalization for bacterial or viral infection in renal transplant recipients--an analysis of USRDS data. *Am J Transplant* 2007;7(3):653-61.
72. Smith RM, Lautenbach E, Omulo S, et al. Human Colonization With Multidrug-Resistant Organisms: Getting to the Bottom of Antibiotic Resistance. *Open Forum Infect Dis* 2021;8(11):ofab531.
73. Bertrand D, Pallet N, Sartorius A, et al. Clinical and microbial impact of screening kidney allograft preservative solution for bacterial contamination with high-sensitivity methods. *Transplant International* 2013;26(8):795-9.
74. Origüen J, López-Medrano F, Fernández-Ruiz M, et al. Should Asymptomatic Bacteriuria Be Systematically Treated in Kidney Transplant Recipients? Results From a Randomized Controlled Trial. *Am J Transplant* 2016;16(10):2943-53.
75. Kadri SS, Lai YL, Warner S, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. *The Lancet Infectious Diseases* 2021;21(2):241-51.
76. So M, Yang DY, Bell C, et al. Solid organ transplant patients: are there opportunities for antimicrobial stewardship? *Clin Transplant* 2016;30(6):659-68.
77. Macesic N, Gomez-Simmonds A, Sullivan SB, et al. Genomic Surveillance Reveals Diversity of Multidrug-Resistant Organism Colonization and Infection: A Prospective Cohort Study in Liver Transplant Recipients. *Clin Infect Dis* 2018;67(6):905-12.
78. Taimur S, Pouch SM, Zubizarreta N, et al. Impact of pre-transplant carbapenem-resistant Enterobacterales colonization and/or infection on solid organ transplant outcomes. *Clinical Transplantation* 2021;35(4):e14239.
79. Piewngam P, Khongthong S, Roekngam N, et al. Probiotic for pathogen-specific *Staphylococcus aureus* decolonisation in Thailand: a phase 2, double-blind, randomised, placebo-controlled trial. *The Lancet Microbe* 2023;4(2):e75-e83.
80. Yoshida K, Hernández-Díaz S, Solomon DH, et al. Matching Weights to Simultaneously Compare Three Treatment Groups: Comparison to Three-way Matching. *Epidemiology* 2017;28(3):387-95.
81. Mao H, Li L, Greene T. Propensity score weighting analysis and treatment effect discovery. *Stat Methods Med Res* 2019;28(8):2439-54.
82. Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-Resistant Bacterial Infections in U.S. Hospitalized Patients, 2012-2017. *N Engl J Med* 2020;382(14):1309-19.
83. Isendahl J, Giske CG, Hammar U, et al. Temporal Dynamics and Risk Factors for Bloodstream Infection With Extended-spectrum β-Lactamase–producing Bacteria in Previously-colonized Individuals: National Population-based Cohort Study. *Clinical Infectious Diseases* 2018;68(4):641-9.

84. Tsampalieros A, Knoll GA, Fergusson N, et al. Center Variation and the Effect of Center and Provider Characteristics on Clinical Outcomes in Kidney Transplantation: A Systematic Review of the Evidence. *Can J Kidney Health Dis* 2017;4:2054358117735523.

Figure 1. Study Flow diagram



* Groups not mutually exclusive

Figure 2. Waffle plot of all RTRS (N=3,507) stratified by early post-transplant culture status, 2005-2021

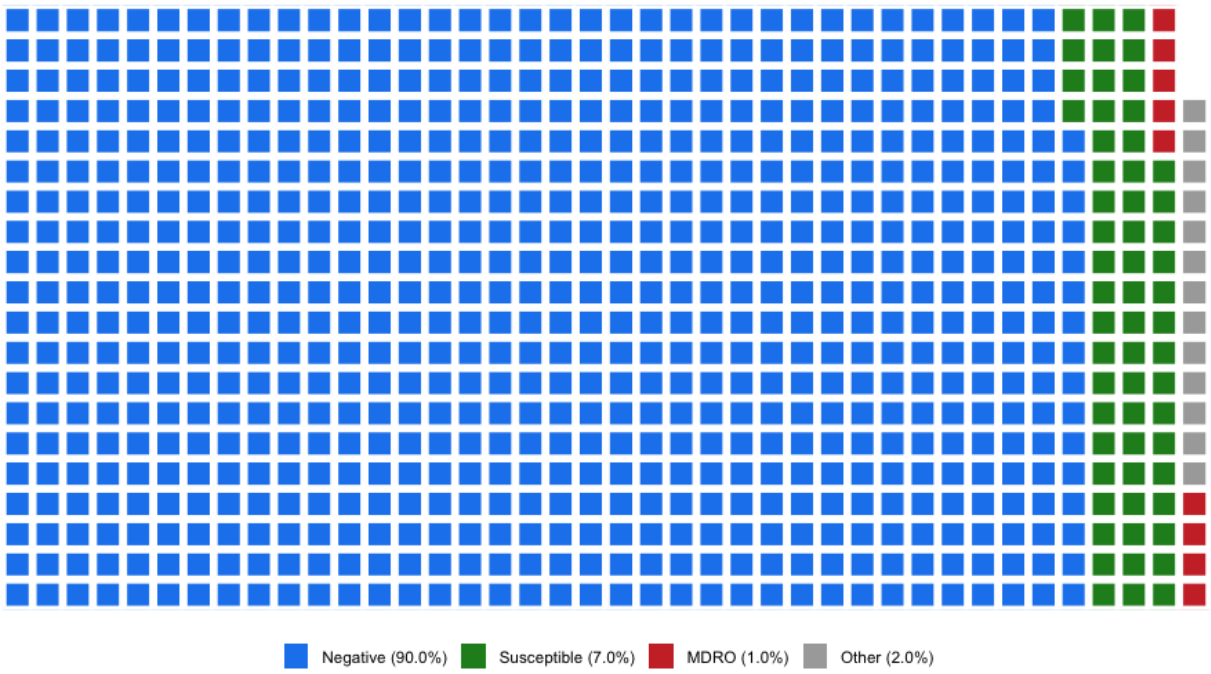


Figure 2 legend. Waffle plot of all RTRS (N=3,507) stratified by early post-transplant culture status into those with no early-post transplant culture positivity (blue), those with early-post transplant culture positive with a target MDRO (red), a comparative susceptible organism (blue) or a non-target organism (grey).

Figure 3. Incidence of MDRO detection per 1000 early post-transplant days, 2005-2021

Figure 3 legend. Incidence of MDRO detection per 1000 early post-transplant days at risk in the pre- (left panel) and post- (right panel) Enterobacterales breakpoint change period. 95% confidence interval represented by shaded areas and line of best fit (black) added using binomial regression. *P-value* for binomial regression model examining association of incidence with time (year) adjusting for breakpoint change period.

Figure 4. Kaplan–Meier analysis of composite outcome of Renal Transplant Recipients by Early Post Transplant Positive Culture status, 2005-2021 (N= 3,432)

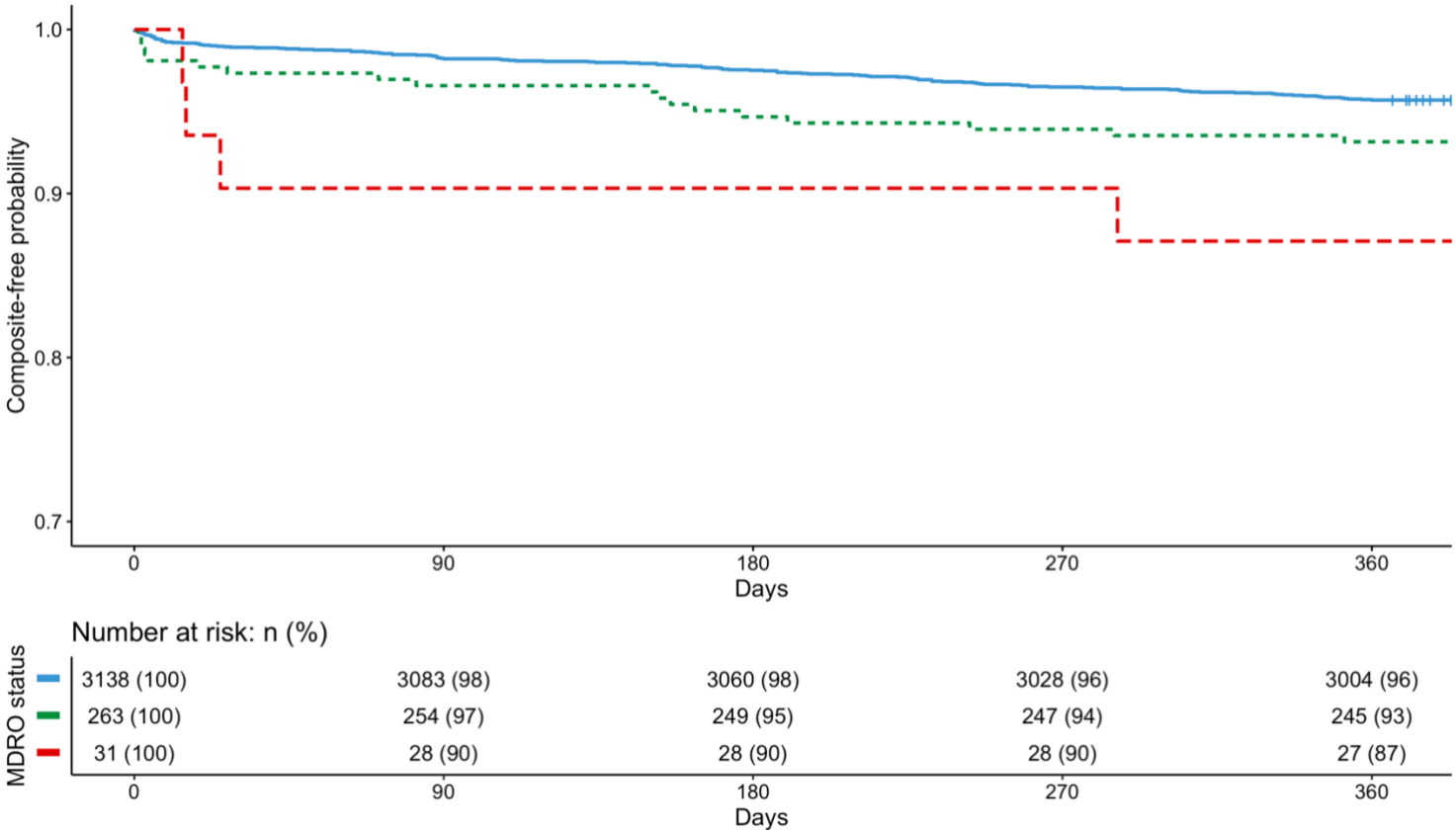


Figure 4 Legend. Kaplan–Meier analysis of composite outcome comparing renal transplant recipients with an MDRO detected on early post-transplant culture (red) a susceptible organism detected on post-transplant culture (green) and negative controls (blue) (**B**). Time is measured from transplant until event. Log-rank *p*-value =0.01.

Figure 5. Cumulative incidence curves for one-year mortality (solid line) and one-year allograft loss of Renal Transplant Recipients by Early Post Transplant Positive Culture status, 2005-2021 (N= 3,432)

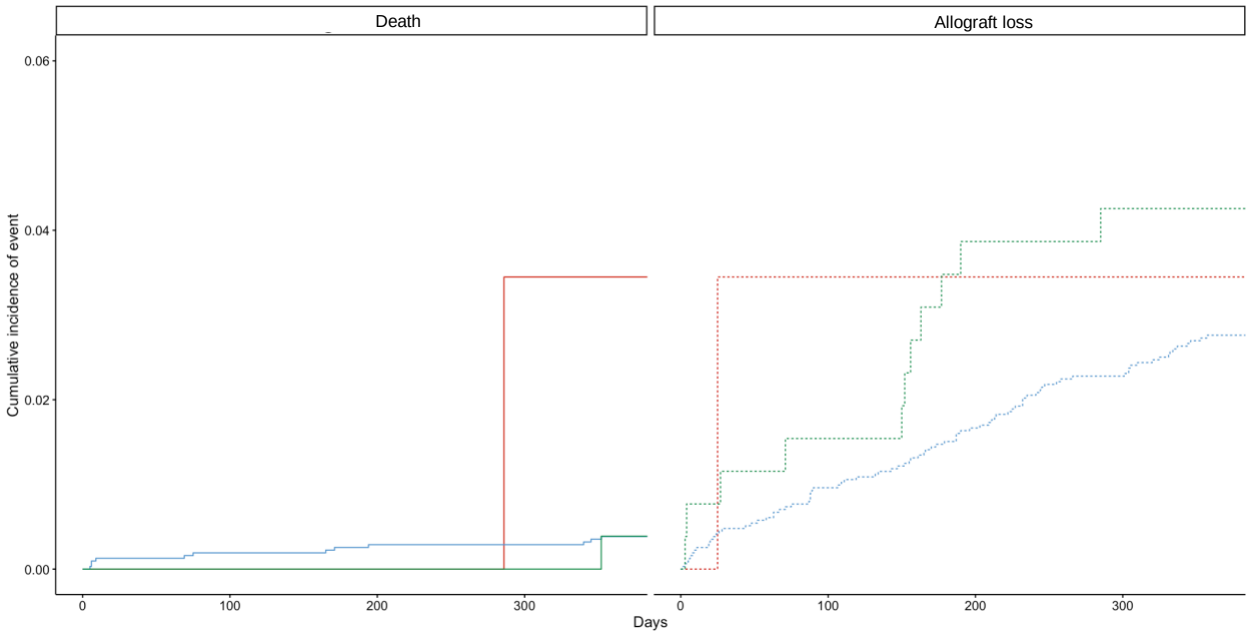


Figure 5 Legend. Cumulative incidence curves for one-year mortality (left panel, dashed line) and one-year allograft loss (right panel, solid line) comparing renal transplant recipients with an MDRO detected on early post-transplant culture (red), a susceptible organism detected on post-transplant culture (green) and negative controls (blue). Time is measured from transplant until event.

Figure 6. Standardized mean differences for key covariates across weighting methods.

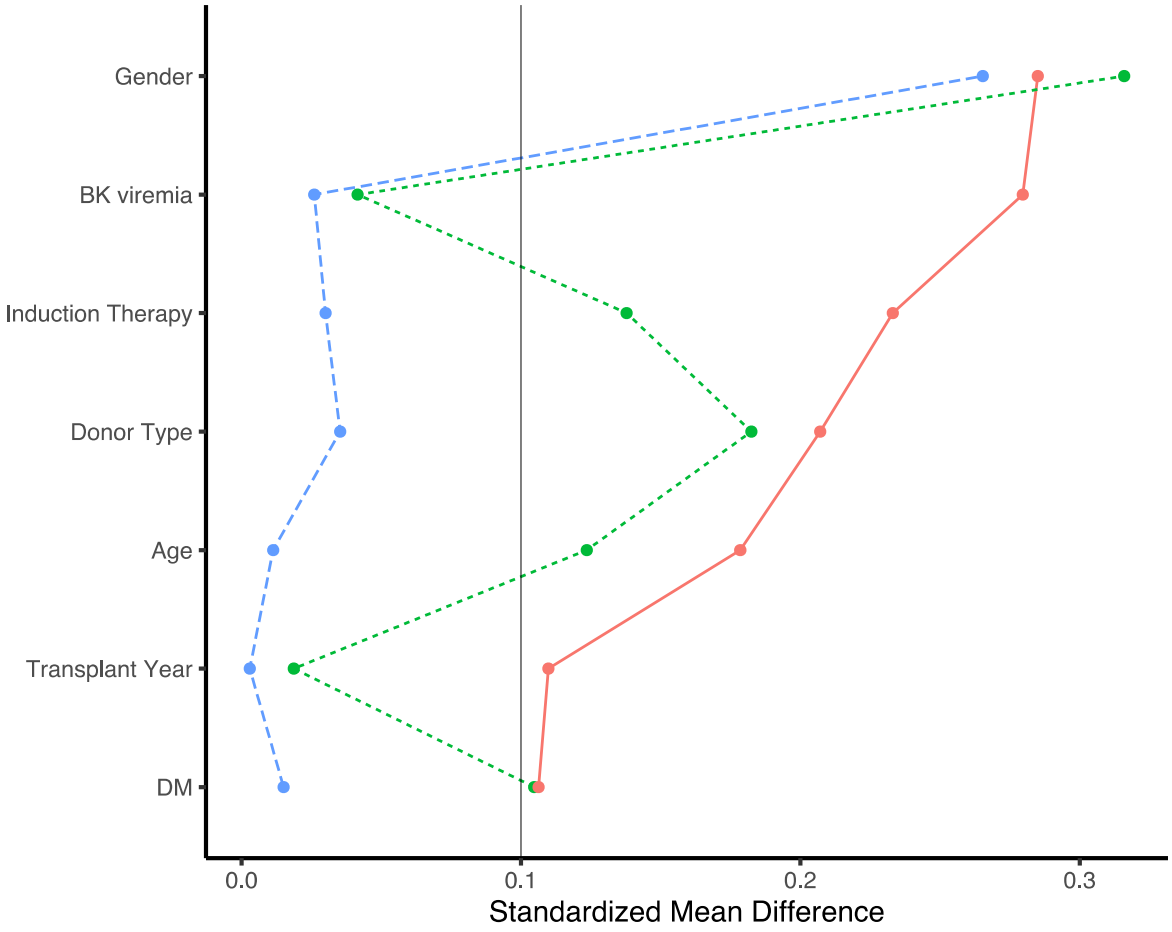


Figure 6 Legend. Standardized mean differences for key covariates which included the propensity score generation averaged across three exposure categories in the unmatched (red, solid line), IPTW (green, dotted line) and matching weights (blue, dashed line), cohorts. Matching weights achieved better covariate balance than IPTW

Table 1. Baseline Characteristics of Renal Transplant Recipients by Early Post Transplant Positive Culture status, 2005-2021 (N= 3,432)

Variables	Study Population, N= 3,432	Negative Controls, N= 3,138	Early Post Transplant Positive Culture, N= 294	
			Susceptible organisms, N= 263	MDRO, N = 31
Age, median [IQR]	51 [20]	50 [20]	53 [20]	55 [18]
Sex, N (%)				
Female	1,453 (42)	1,274 (41)	162 (62)	17 (55)
Race, N (%)				
Black	1,749 (51)	1,607 (51)	128 (49)	14 (45)
White	1,395 (41)	1,271 (41)	109 (41)	15 (48)
Biracial	13 (0.4)	12 (0.4)	1(0.4)	0 (0)
Other	252 (8)	226 (8)	4 (11)	22 (9)
Unknown	134 (4)	122 (4)	11 (4)	1 (3)
Primary ESRD etiology, N (%)				
Diabetes Mellitus	1,054 (31)	945 (30)	99 (38)	10 (32)
Hypertension	858 (25)	796 (25)	49 (19)	13 (42)
Glomerular Disease	665 (21)	611 (21)	4 (11)	50 (19)
Polycystic Kidney Disease	308 (9.0)	293 (9.3)	13 (5)	2 (7)
Other	494 (14)	443 (14)	48 (18)	3 (10)
Transplant Type, N (%)				
Kidney	3,201 (93)	2,934 (93)	240 (91)	27 (87)
Kidney-Pancreas	229 (6.7)	202 (6)	23 (9)	4 (13)
Kidney-Liver	2 (<0.01)	2 (<0.01)	0 (0)	0 (0)
Transplant Year, N (%)				
2005-2009	674 (20)	620 (20)	50 (19)	4 (13)
2010-2015	1,188 (35)	1,056 (34)	118 (45)	14 (45)
2016-2020	1,570 (46)	1,462 (47)	95 (36)	13 (42)
Donor Type, N (%)				
deceased	2,332 (68)	2,107 (67)	200 (76)	25 (81)
living	1,100 (32)	1,031 (33)	63 (24)	6 (19)
Years on dialysis, median [IQR]	4.4 [5.1]	4.4 [5.1]	4.7 [5.0]	7.0 [6.5]
Missing, N (%)	1,021 (29)	933	80	8
Immune Induction Protocol, N (%)				
Basiliximab	2,466 (72)	2,256 (72)	188 (71)	22 (71)
Thymoglobulin	605 (18)	541 (17)	56 (21)	8 (26)
Other	361 (11)	341 (11)	19 (7)	1 (3)
CMV status, N (%)				
D-/R-	402 (12)	376 (12)	260 (9)	3 (10)
D-/R+ or D+/R+	2,454 (72)	2,228 (72)	201 (77)	25 (83)
D+/R-	529 (16)	491 (16)	36 (14)	2 (7)
Missing	47 (1)	43 (1)	3 (1)	1 (3)

CMV Viremia within first year post-transplant *	461 (13)	418 (13)	38 (14)	5 (16)
BK viremia within first year post-transplant **	656 (19)	588 (19)	56 (21)	12 (39)
Rejection within first year post-transplant	441 (13)	399 (13)	38 (14)	4 (13)
MDRO detected pre-transplant	67(2)	58(2)	7(3)	2(7)
Transplant admission LOS, median [IQR]	4.0 [3.0]	4.0 [3.0]	5.0 [4.0]	7.0 [1.0]
Missing , N(%)	1	1	0	0

*Defined as a CMV level > 35 IU/ml for R- and > 1000 IU/ml for R+
**Defined as more than >1000 copies/mL

Abbreviations: CMV: cytomegalovirus, D: donor, ESRD: end-stage renal disease, IQR: interquartile range LOS: length of stay, MDRO: multidrug resistant organism, R: recipient

Table 2: Microbiological Characteristics of Renal Transplant Recipients with Positive Early Post Transplant Cultures, 2005-2021 (N=294)

Variables	Overall, N = 294	Susceptible organisms, N= 263	MDRO, N = 31
Species/Taxa, N (%)^			
Staphylococcus aureus	12 (4)	6 (2)	6 (19)
*Enterococcus spp**	72 (24)	67 (25)	5 (16)
*Enterobacterales***	183 (62)	164 (62)	19 (61)
Pseudomonas aeruginosa	26 (9)	26 (10)	0 (0)
Acinetobacter baumannii	1 (0.3)	0 (0)	1 (3)
Trimethoprim-sulfamethoxazole Resistance	136 (46)		
Anatomic source , N(%)			
Urinary tract	234 (80)	214 (81)	20 (65)
Blood/Endovascular	31 (11)	25 (10)	6 (19)
Respiratory	9 (3.1)	9 (3)	0 (0)
Superficial Wound	3 (1.0)	3 (1)	0 (0)
Intra-abdominal	9 (3.1)	5 (2)	4 (13)
Superficial wound	3 (1)	3 (1)	0 (0)
Other Invasive Site	7 (2)	6 (2)	1 (3)
Stool	1 (0.3)	1 (0.4)	0 (0)
Time between transplant and positive culture, median[IQR]	13 [13]	13 [13]	10 [10]

^ If an RTR had multiple MDROs or susceptible organism detected in the early post-transplant only the first organism was recorded.
* Enterococcus spp group includes: *Enterococcus faecalis* (n= 65), *Enterococcus faecium* (n=7)
** Enterobacterales group includes: *Citrobacter freundii* complex (n= 8), *Enterobacter cloacae* complex (n=7), *Enterobacter spp.* (n=2)*, Escherichia coli* (n=111), *Hafnia alvei* (n=1), *Klebsiella* aerogenes (n=3), *Klebsiella oxytoca* (n=9), *Klebsiella pneumoniae (*n=28), *Proteus mirabilis* (n=8), *Providencia rettgeri* (n=1), *Serratia marcescens* (n=5). None were carbapenem resistant.

Table 3: Outcomes of Renal Transplant Recipients Stratified by Early Post Transplant Positive Culture Status, 2005-2021 (N= 3,432)

Variables	Study Population, N= 3,432	Negative Controls, N= 3,138	Early Post Transplant Positive Culture, N=294	
			Susceptible organisms, N= 263	MDRO, N = 31
One-year post-transplant mortality, N (%)	98 (2.9)	86 (2.7)	11 (4.2)	1 (3.2)
One-year post-transplant graft failure, N (%)	75 (2.2)	63 (2.0)	9 (3.4)	3 (9.7)
Composite Outcome, N (%)	157 (4.6)	135 (4.3)	18 (6.8)	4 (13)

Abbreviations: MDRO: multidrug-resistant organism

Table 4. Results of Cox Proportional Hazards Regression Model for Primary Outcome by Early Post-transplant Culture Positivity Status (N= 3,432)

	Composite outcome HR			
	HR (95%CI)	*P*-value	aHR (95%CI)*	*P*-value
Negative controls	Ref	-	Ref	-
Susceptible	1.62 (0.99, 2.65)	0.05	1.58 (0.96, 2.59)	0.07
MDRO	3.19 (1.18, 8.63)	0.02	3.62 (1.33, 9.84)	0.01

Abbreviations: aHR: adjusted hazards ratio, HR: hazards ratio, MDRO: multidrug-resistant organism

*Adjusted for age, sex, year of transplant, one-year post-transplant BK viremia, one-year post-transplant, CMV viremia, deceased donor status, diabetes as the primary etiology of ESRD and category of induction therapy

Table 5. Results of Sensitivity and Subgroup Analysis of Cox Proportional Hazards of Composite Outcome among RTRs

Cohort		Composite outcome HR			
		HR (95%CI)	*P*-value	aHR (95%CI)*^	*P*-value
MW cohort	Negative controls	Ref	-	Ref	-
	Susceptible organism	1.57 (0.92, 2.67)	0.10	1.63 (0.94, 2.83)	0.08
	MDRO	3.40 (1.34, 9.78)	0.01	3.73 (1.34, 10.4)	0.01
IPTW cohort	Negative controls	Ref	-	Ref	-
	Susceptible organism detected	1.68 (0.97, 2.90)	0.06	1.74 (0.94, 2.93)	0.08
	MDRO	2.95 (0.92, 7.02)	0.06	3.05 (0.97, 9.58)	0.06
Urine subgroup (N= 3,372)	Negative controls (N=3,138)	Ref	-		-
	Susceptible organism (N=199)	0.76 (0.35, 1.61)	0.5	0.76 (0.35, 1.63)	0.50
	MDRO (N=22)	1.15 (0.16, 8.20)	0.9	1.50 (0.21, 10.8)	0.70
Post Breakpoint subgroup (N=2,585)	Negative controls (N=2,364)	Ref	-		
	Susceptible organism (n=199)	1.79 (1.02, 3.14)	0.04	1.76 (1.00, 3.11)	0.05
	MDRO (n=22)	3.60 (1.14, 11.4)	0.03	3.72 (1.17, 11.8)	0.03

Abbreviations: aHR: adjusted hazards ratio, HR: hazards ratio, MDRO: multidrug-resistant organism

*Adjusted for age, sex, year of transplant, one-year post-transplant BK viremia, one-year post-transplant, CMV viremia, deceased donor status, diabetes as the primary etiology of ESRD and category of induction therapy for subgroup analysis.
^ Adjusted for age, sex year of transplant, one-year post-transplant BK viremia, one-year post-transplant, CMV viremia, diabetes as the primary etiology of ESRD and category of induction therapy

Table 6. Competing Risk Analysis Results Stratified by Stratified by Early Post Transplant Positive Culture Status (N= 3,432)

	Cause Specific One-year Mortality			**Sub-distribution** One-year Mortality		
	HR (95%CI)	*aHR*(95%CI)*	*P*-value **	*HR (95%CI)*	*aHR*(95%CI)*	*P*-value **
Negative controls	Ref	Ref	-	Ref	Ref	-
Susceptible organism	1.56 (0.83, 2.92)	1.44 (0.77, 2.72)	0.3	1.44 (0.75, 2.77)	1.45 (0.76, 2.77)	0.3
MDRO	1.56 (0.18, 9.08)	1.53 (0.21, 11.0)	0.7	1.26 (0.17, 9.26)	1.53 (0.20, 11.7)	>0.9
	Cause Specific One year Allograft Loss			**Sub-distribution** One year Allograft Loss		
	HR (95%CI)	*aHR*(95%CI)*	*P*-value	*HR (95%CI)*	*aHR*(95%CI)*	*P*-value
Negative controls	Ref	Ref	-	Ref	Ref	
Susceptible organism	1.02 (0.13, 7.82)	0.85 (0.11, 6.62)	0.9	1.02 (0.13, 7.79	0.82 (0.12, 5.74)	0.9
MDRO	9.41 (1.16 68.8)	7.92 (1.01, 62.1)	0.049	8.95 (1.18, 67.9)	8.23 (1.17, 54.2)	0.03

Abbreviations: aHR: adjusted hazards ratio, HR: hazards ratio, MDRO: multidrug-resistant organism

*Adjusted for age, sex, year of transplant, one-year post-transplant BK viremia, one-year post-transplant, CMV viremia, deceased donor status, diabetes as the primary etiology of ESRD and category of induction therapy
** *p*-value of adjusted model

Table 7. **Cause specific Hazards of Allograft loss among subgroup and sensitivity analysis cohorts.**

Cohort		Cause Specific One year Allograft Loss		
		HR (95%CI)	*aHR*^(95%CI)*	*P*-value **
MW cohort	Negative controls	Ref	Ref	-
	Susceptible organism	1.04 (0.13, 8.15)	1.17 (0.14, 9.63)	0.9
	MDRO	8.99 (1.17, 68.9)	8.53 (1.46, 50.0)	0.02
IPTW cohort	Negative controls	Ref	Ref	-
	Susceptible organism	0.44 (0.06, 3.40)	0.45 (0.06, 3.53)	0.4
	MDRO	3.55 (0.45, 27.9)	2.94 (0.46, 18.8)	0.3
Urine subgroup (N= 3,372)	Negative controls (N=3,138)	Ref	Ref	-
	Susceptible organism (N=199)	1.21 (0.16, 9.34)	1.03 (0.13, 8.04)	>0.9
	MDRO detected (N=22)	13.0 (1.69, 99.7)	12.4 (1.53, 98.0)	0.02
Post Breakpoint subgroup (N=2,585)	Negative controls (N=2,364)	Ref	Ref	-
	Susceptible organism (n=199)	0.00 (0.00, ∞)	0.00 (0.00, ∞)	>0.9
	MDRO detected (n=22)	11.3 (1.45, 88.3)	12.6 (1.52, 104)	0.02

Abbreviations: aHR: adjusted hazards ratio, HR: hazards ratio, MDRO: multidrug-resistant organism

*Adjusted for age, sex, year of transplant, one-year post-transplant BK viremia, one-year post-transplant, CMV viremia, deceased donor status, diabetes as the primary etiology of ESRD and category of induction therapy for subgroup analysis.
^ Adjusted for age, sex, year of transplant, one-year post-transplant BK viremia, one-year post-transplant, CMV viremia, diabetes as the primary etiology of ESRD and category of induction therapy
** *p*-value of adjusted model