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Multidrug-Resistant Bacterial Donor-Derived Infections in Solid Organ Transplantation

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Abstract Although rare, donor-derived infections (DDIs) caused by multidrug-resistant (MDR) bacteria can have devastating consequences for organ transplant recipients. Recognition of MDR bacterial DDIs can be challenging, as MDR bacteria are prevalent in most hospitals and distinguishing their transmission through transplantation from other, more typical routes of acquisition are difficult. New technologies such as whole genome sequencing have recently proven to be a powerful advance in the investigation of MDR bacterial DDIs. Once recognized, the optimal treatment of MDR bacterial DDIs is not clear. Herein, we review the clinical manifestations, outcomes, and management of MDR bacterial DDIs, and identify areas of uncertainty toward which the transplant community should direct further research efforts.

Keywords Donor-derived infections · Multidrug-resistant bacteria · Solid organ transplant

Introduction

Despite advances in surgical technique, immunosuppression, and chemoprophylaxis, infection is a common cause of morbidity and mortality in solid organ transplant (SOT) recipients. Infection following organ transplantation may be a consequence of complications of the surgical procedure, reactivation of latent infection, acquisition of new infection, or transmission through the donor organ. While donor-derived infections (DDIs) are the least common cause of infection following SOT, they can have significant and even devastating results [1–3]. The transplant community has made considerable efforts to identify episodes of DDI in order to understand their origin and to develop strategies to prevent such episodes and diminish their impact.

Uniform definitions for DDIs have been established by an international group of experts [4•]. DDIs fall into two general categories: expected and unexpected. Using familiar scenarios of viral pathogens in organ transplantation as examples, expected DDIs include latent or chronic infections for which donors are routinely screened, and for which disease transmission can be mitigated with the use of chemoprophylactic agents (e.g., cytomegalovirus [CMV] and hepatitis B virus), preemptive screening and treatment of the recipient (e.g., CMV), or organ donation to an appropriate seropositive recipient (e.g., hepatitis C virus [HCV]). Unexpected DDIs include infections for which screening is either not routinely performed or readily available and for which chemoprophylaxis is not routinely employed. Recent high-profile reports of unexpected viral DDIs describe transmission of human immunodeficiency virus (HIV) and hepatitis C (HCV) [2], lymphocytic choriomeningitis virus (LCMV) [3], rabies [5], and West Nile virus [6], among others.

Like other DDIs, transmission of bacteria from the donor to the recipient can be characterized as either expected or unexpected. In an expected bacterial DDI, a documented bacterial infection is recognized and treated in the donor prior to organ procurement, and, ideally, this information is properly communicated to the recipient's transplant care team, so that targeted therapy can be given to the recipient post-transplantation, if indicated. An expected bacterial DDI may arise when targeted prophylactic therapy fails or is not provided. In an

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unexpected bacterial DDI, there may be undiagnosed bacterial infection in the donor at the time of organ procurement or bacterial contamination of the organ or perfusate that is only recognized after transmission of infection to the recipient(s). Surgical antibacterial prophylaxis assuredly prevents many cases of bacterial DDI; however, transmission of multidrug-resistant (MDR) bacteria may not be prevented through the use of routine perioperative antibiotic prophylaxis for transplant surgery.

In this review, we summarize published reports of MDR bacterial DDIs. We utilize the standardized definition of MDR, previously defined by international consensus, as non-susceptibility to at least one agent in three or more antimicrobial categories [7•]. We pay particular attention to proven cases (per consensus definition [4•]) of MDR bacterial DDI that have been published in the past 2 years. We also discuss lessons learned from these cases, including the importance of prompt and accurate communication of donor culture results, as well as unanswered questions regarding the optimal diagnosis and management of MDR bacterial DDIs.

Review of Multidrug-Resistant Gram-Negative Bacterial Donor-Derived Infections

Between 2009 and 2015, there were eight published investigations of MDR Gram-negative bacterial DDIs, which included ten clusters of proven transmission from infected donor to recipient and four clusters in which infected donors did not transmit infection to the recipients. These reports and their outcomes are summarized in Table 1. The most recent reports, published in 2014 and 2015, are discussed in detail below.

In July 2014, an Italian group published a report of transmission of OXA-48-producing carbapenem-resistant *Klebsiella pneumoniae* (CRKP) from a bacteremic donor to two organ recipients, a liver and a kidney recipient [14]. The donor was a 52-year-old with a history of pulmonary tuberculosis and respiratory colonization with carbapenem-resistant *Acinetobacter baumannii* (CRAB), who died secondary to head trauma. The donor did not have a history of carbapenem-resistant *Enterobacteriaceae* colonization or infection and blood and urine cultures collected from the donor on the day of organ procurement were sterile; however, CRKP was isolated from the kidney preservation fluid at the transplantation center. The first recipient, who received a kidney from this donor, was a 43-year-old with HIV and chronic HCV infection. The recipient became febrile 6 days post-transplant and was found to have CRKP bacteremia and surgical site infection, ultimately required allograft explantation, and subsequently was lost to follow-up. The second recipient, who received the liver from this donor, was a 63-year-old with hepatocellular carcinoma and cirrhosis due to HCV. This recipient became febrile 4 days post-transplant and was found to have CRKP in blood cultures, surgical wound specimens, and abdominal drainage fluid. The patient was successfully treated; however, CRKP was isolated from biliary aspirates obtained via endoscopic retrograde cholangiopancreatography (ERCP) 2 months later; the recipient was not treated with

Table 1 Summary of clusters of multidrug-resistant Gram-negative donor-derived infection

Location	Year	Bacteria	Category of transmission risk	Source of donor culture	Number of transplant centers involved	Number infected/ number at risk	Death/ allograft loss + death
Italy [1]	2009	CRPA	Expected	Endotracheal aspirate	1	2/2	2/2
USA [8]	2009	ESBL *E. coli*	Unexpected	Urine, perfusate	2	2/2	0/2
USA [9, 10]	2012	MDR PA	Unexpected	Peritoneal fluid, blood, sputum	2	4/4	2/2
Brazil [11]	2012	CRAB	Unexpected	BAL	1	1/1	1/1
Israel [12]	2012	CRKP	Unexpected	Sputum, BAL	1	1/5	1/1
USA [13]	2012	KPC-producing CRKP	Expected	CSF, perfusate	3	1/4	0/0
Italy [14]	2014	OXA-48-producing CRKP	Unexpected	Perfusate	2	2/2	0/1
Italy [15••]	2015	CRKP	Unexpected	Blood	Not reported	2/4	0/0
Italy [15••]	2015	CRKP	Unexpected	Blood, urine, BAL	Not reported	1/2	0/0
Italy [15••]	2015	CRKP	Unexpected	Urine	Not reported	1/2	1/1
Italy [15••]	2015	CRAB	Unexpected	Blood, BAL	Not reported	0/2	0/0
Italy [15••]	2015	CRAB	Unexpected	Blood	Not reported	0/1	0/0
Italy [15••]	2015	CRAB	Unexpected	Blood	Not reported	0/1	0/0
Italy [15••]	2015	CRKP and CRAB	Unexpected	Blood	Not reported	0/1	0/0

CRPA carbapenem-resistant *Pseudomonas aeruginosa*, *ESBL* extended-spectrum beta-lactamase, *MDR* multidrug-resistant; *PA* Pseudomonas aeruginosa, *CRAB* carbapenem-resistant *Acinetobacter baumannii*, *CRKP* carbapenem-resistant *Klebsiella pneumoniae*, *KPC Klebsiella pneumoniae* carbapenemase, *BAL* bronchoalveolar lavage fluid, *CSF* cerebrospinal fluid

antibiotics at this time. KP was not isolated on biliary aspirate obtained via ERCP 6 months post-transplant.

Isolates from the kidney recipient (blood), liver recipient (blood and biliary aspirate), and kidney preservation fluid were identical by pulsed field gel electrophoresis (PFGE) and all belonged to multilocus sequence type 16. Resistance profiles were similar in all isolates, and all isolates carried $bla_{\text{OXA-48}}$ carbapenemase, $bla_{\text{CTX-M-15}}$ extended-spectrum beta-lactamase, and $bla_{\text{TEM-1}}$ broad-spectrum beta-lactamase genes [14].

More recently, in the largest published report of MDR bacterial DDIs to date, unexpected transmission of CRKP to four organ transplant recipients in Italy was described [15••]. The authors retrospectively reviewed all extra-intestinal cultures collected from deceased donors at a single institution over a 2-year period and identified 18 donors with carbapenem-resistant Gram-negative (CRGN) infection or colonization (either CRKP or CRAB) at the time of organ procurement. For the purposes of this review, we will only discuss the seven donors with unrecognized CRGN infection at the time of organ procurement. Thirteen recipients were at risk for transmission of CRGN bacteria from these infected donors; eleven were deemed to be at high risk of transmission (i.e., they received organs from a donor with bacteremia or infection of the transplanted organ) and two were deemed to be at low risk of transmission (i.e., they received organs from a donor with infection of a non-transplanted organ and without bacteremia).

Four recipients, all of whom were at high risk for transmission, had confirmed transmission; all four DDIs were due to CRKP. A right liver recipient developed a skin and soft tissue infection (SSTI) and a lung recipient developed airway colonization with CRKP without overt infection after receiving organs from a donor with CRKP bacteremia; both patients survived and the recipients of the left liver and pancreatic islet cells from the same donor did not develop infection. A liver recipient from a donor with CRKP in the blood, urine, and bronchoalveolar lavage (BAL) fluid developed SSTI and survived, while the kidney recipient from the same donor did not develop infection. A kidney recipient from a donor with CRKP in the urine developed SSTI, bloodstream infection, and a urinary tract infection and ultimately expired, while the liver recipient from the same donor did not develop infection.

In this second report, there were four clusters in which CRGN-infected donors did not transmit infection to any of their organ recipients. In the first cluster, two kidney recipients from a donor with CRAB in the blood and BAL fluid did not develop infection. In the second and third clusters, liver recipients from two separate donors with CRAB in the blood also did not develop infection. Finally, in the fourth cluster, a kidney recipient from a donor with CRKP and CRAB bacteremia did not develop infection. In all, in this report, four of 13 (31 %) recipients of organs from donors with CRGN bacterial infection had documented transmission of the MDR organism.

To summarize all published cases of MDR gram negative DDIs (Table 1), there was a 52 % attack rate with 17 of 33 at-risk recipients becoming infected. Outcomes were quite poor; 41 % of infected recipients died and 59 % of infected recipients either died or suffered allograft loss. Highlighting the importance of rapid communication in these cases, several clusters involved more than one transplant center and in eight of the 14 reported clusters, the MDR Gram-negative donor infection was unexpected.

Review of Multidrug-Resistant Gram-Positive Bacterial Donor-Derived Infections

A total of four reports of proven MDR Gram-positive DDIs have been published and are summarized in Table 2. Two of these reports were published within the past year and will be discussed in detail below.

In the first case [18•], the donor was a 40-year-old woman who presented with drug overdose, multifocal embolic strokes, and methicillin-resistant *Staphylococcus aureus* (MRSA) mitral valve endocarditis. Blood cultures grew MRSA on hospital days 1 through 6 and an echocardiogram revealed multiple large mobile vegetations on the mitral valve. She was treated with vancomycin from hospital day 3 until organ donation on hospital day 7. Blood cultures from hospital day 7 remained negative. The liver was harvested from the

Table 2 Summary of clusters of multidrug-resistant Gram-positive donor-derived infection

Location	Year	Bacteria	Category of transmission risk	Source of donor culture	Number of transplant centers involved	Number infected/ number at risk	Death/allograft loss + death
Spain [16]	1997	MRSA	Unexpected	Blood	1	1/1	1/1
Canada [17]	1999	MRSA	Unexpected	Endotracheal aspirate	2	3/4	0/0
USA [18•]	2014	MRSA	Expected	Blood	1	1/1	0/0
USA [19•]	2014	MRSA	Expected	Blood	Not reported	2/4	0/0

MRSA methicillin-resistant *Staphylococcus aureus*

donor and all other organs were declined. The liver recipient was a 64-year-old man with cirrhosis due to HCV and hepatocellular carcinoma. Pre-transplant recipient blood, urine, and ascitic fluid cultures were negative and he had no history of MRSA colonization or infection. Organ transplantation was uncomplicated and the patient received vancomycin and ertapenem for perioperative prophylaxis. Blood cultures were collected from the recipient 6 h postoperatively and grew MRSA with a susceptibility pattern identical to donor isolates. Vancomycin was continued for 4 weeks and subsequent blood cultures were negative. Genotyping revealed that both donor and recipient MRSA isolates were *spa* type 1, t008 (CC-8), SCC*mec* type IV, and carried the Panton-Valentine leukocidin (PVL) genes *lukSF-PV*. However, these data did not provide conclusive evidence that the recipient's infection was of donor origin, as the genotypes of the isolates were compatible with the epidemic community-associated MRSA strain USA300. To further investigate relatedness, a donor and a recipient isolate underwent whole genome sequencing, which demonstrated that the isolates were genetically identical.

In the second case [19•], the donor was a male with a history of intravenous drug use who presented with fever, confusion, and somnolence, and was found to have a large right parietal intracranial hemorrhage, MRSA bacteremia, and a 1-cm mitral valve vegetation, consistent with endocarditis. He rapidly deteriorated and was declared brain dead within 24 h of presentation. He was treated with vancomycin and subsequent blood cultures were without growth. The lungs, kidneys, pancreas, and liver were harvested and transplanted into four recipients.

The recipient of the bilateral lung transplant had no prior history of MRSA colonization or infection. Vancomycin was started at the time of transplantation. Intraoperative lung biopsy cultures grew MRSA as did surveillance blood cultures collected 6 days post-transplantation. This patient continued to have growth of MRSA on surveillance BAL cultures and remained on vancomycin for 9 weeks, until achieving negative cultures at 99 days post-transplantation. The patient was readmitted 6 months post-transplantation with increased dyspnea, right-sided pleural effusion, and right-sided multifocal consolidation. BAL culture again grew MRSA, and the patient was treated with 4 weeks of vancomycin with resolution of symptoms.

The liver recipient was receiving daptomycin for lower extremity cellulitis at the time of transplantation. Blood cultures collected 3 h after transplantation grew MRSA, so the patient was continued on daptomycin for 14 days. Subsequent blood cultures were negative. Two months later, the patient developed MRSA bacteremia without evidence of hepatic abscess on imaging and no valvular vegetation seen on a transthoracic echocardiogram. The patient received a 6 week course of vancomycin with resolution of symptoms and subsequent negative blood cultures.

Finally, the left kidney and pancreas recipient and right kidney recipient received five doses of vancomycin post-transplantation and had negative surveillance blood cultures and no signs or symptoms of MRSA infection.

MRSA isolates from the lung and liver recipients were indistinguishable by PFGE. The recipient isolates and MRSA DNA extracted from the donor mitral valve were *spa* type t008 (CC-8), *mec* type IVa, and PVL positive, consistent with USA300 MRSA. Whole genome comparison demonstrated that the donor and recipient isolates were identical except for one single nucleotide polymorphism.

To summarize all published cases of MDR Gram-positive DDIs (Table 2), there was a 70 % attack rate with seven of ten at-risk recipients becoming infected. One of the seven infected recipients died (14 %). In two of the four reported clusters, the MDR bacterial DDI was unexpected.

The Importance of Communication in Recognition and Management of Multidrug-Resistant Bacterial Donor-Derived Infections

In cases in which MDR bacterial infection is recognized in the donor, effective communication to the recipient institution is imperative, so that knowledgeable and trained medical personnel can be involved in the management of the recipient at an early stage, rapid and appropriate therapy can be provided, and infection in the recipient can be averted [20••].

A few particular reports in this review highlight these points. Ariza-Heredia et al. describe a donor with *Klebsiella pneumoniae* carbapemenase (KPC)-producing KP meningitis who was treated with appropriate combination therapy for 9 days prior to his death but remained culture-positive up to 2 days prior to his death [13]. Liver, kidneys, heart, and vein grafts were procured from this infected donor and transplanted into four recipients, all of whose institutions were aware of the donor infectious disease history prior to organ procurement. This allowed appropriate preventative strategies, including appropriate antimicrobial treatment, to be in place prior to organ transplantation. As such, only one of four recipients developed infection with the same bacteria as was cultured in the donor, and the infected recipient was treated successfully without resulting allograft loss or death. This report highlights the importance of timely and accurate communication of donor culture results to the recipients' institutions. However, it also emphasizes that recipients of organs from donors with MDR bacterial infections may still develop DDIs despite aggressive post-transplant preemptive treatment.

The Mularoni et al. [15••] report also highlights the importance of prompt, appropriate, and complete therapy for MDR bacterial DDIs. Four of 13 recipients of organs from donors infected with CRGN bacteria developed MDR bacterial DDI. Two of these recipients received inappropriate antibiotics but

survived, one recipient received an appropriate but incomplete duration of antibiotics and survived, and one recipient had delayed initiation of appropriate antibiotics and succumbed to the infection. Nine recipients did not develop MDR bacterial DDI, and the majority of them (78 %) received prompt (started in the first 6 days), appropriate, and complete antibiotic therapy. Targeted antibiotic treatment was not used in two recipients considered to be at low risk for DDI. In one case, the procurement fluid of a recipient of pancreatic islet cells grew CRKP; however, targeted antimicrobial prophylaxis was not given, as the final islet cell preparation cultures were sterile after antibiotic decontamination. In the other case, a liver recipient did not receive directed antimicrobial prophylaxis but was felt to be at low risk because the donor culture was from a non-transplanted organ (CRKP in urine). These examples demonstrate the effectiveness of appropriate therapy in preventing transmission of MDR bacterial DDIs.

Limitations in the Literature on Multidrug-Resistant Bacterial Donor-Derived Infections

DDIs are estimated to complicate approximately 0.2 % of all deceased organ donor transplants [21]. It is likely that bacterial DDIs are under-recognized and under-reported, as infections in the recipient that are caused by common nosocomial pathogens, including MDR pathogens such as MRSA, vancomycin-resistant *Enterococcus* (VRE), and MDR gram negatives, may not be suspected to be donor-derived. For example, there are only four published reports of DDI caused by MRSA [16, 17, 18•, 19•] and no reports of DDI caused by VRE. MRSA and VRE infections in the recipient may be thought to be hospital-acquired rather than donor-derived, and even if suspected, given the clonality and endemnicity of both VRE and MRSA in the USA, proving acquisition from the donor requires advanced molecular techniques such as whole genome sequencing [18•, 19•]. In addition, distinguishing donor-derivation from hospital acquisition of MDR Gram negatives could be difficult in regions in which strains such as KPC-producing KP sequence type 258 or CTX-M-15 extended-spectrum beta-lactamase-producing *E. coli* (ST131) are endemic [22, 23]. The situation is complicated further by the fact that resistance genes in enteric Gram negatives are often plasmid encoded, thus requiring more advanced genetic technologies to track transmission of drug resistance genes across populations or theoretically from donor to recipient [24, 25].

One must also recognize the potential for publication bias in the literature on MDR bacterial DDIs. In our review of the literature, only one report included clusters in which MDR infection in the donor was not transmitted to recipients [15••]. Therefore, while there may be under-recognition of MDR bacterial DDI clinically, there may also be bias to report MDR bacterial DDI rather than susceptible infections in the literature, which makes its true incidence difficult to estimate. Importantly, optimal management strategies for potential and confirmed MDR bacterial DDIs are not well-defined and are based on limited data [26].

Discussion

Although DDIs are the least common cause of infection following SOT, and MDR bacterial DDIs even less common, the impact of these infections on graft function and survival can be profound. The prevalence of MDR bacterial infections is increasingly globally [22, 23], and thus we are likely to see a greater number of DDIs caused by MDR bacteria as well. In this review of all published cases of MDR bacterial DDIs, we found an overall 56 % attack rate, which is higher than what has previously been published. In the Spanish experience [27], 18 liver donors and 11 heart donors were found to be bacteremic at the time of organ procurement, and transmission of the same bacteria was not seen in any recipients, even in six patients in whom perioperative antimicrobial prophylaxis was not appropriate for treating the donor isolates. Also in our review, the mortality rate of all patients at risk for acquisition of an MDR bacterial DDI was 19 % and the mortality rate for those who did develop a MDR bacterial DDI was 33 %.

The high attack rate and high mortality associated with MDR bacterial DDIs raises the question of whether the risk of accepting an organ from donors infected with MDR bacteria is "excessive." In the majority of cases in this review, the MDR bacterial infection in the donor was unrecognized at the time of organ procurement. Strategies to risk-stratify potential donors, as is done with other high-risk pathogens including HBV, HCV, and HIV, should be developed to better inform those institutions potentially accepting organs from donors who are at increased risk of harboring MDR bacterial infections. For example, surgical procedures the donor undergoes (particularly if left with an "open abdomen" [9]), duration of mechanical ventilation, duration of intensive care unit stay, and exposure to broad-spectrum antibiotics are all possible factors that may increase the risk of colonization or infection with MDR pathogens and subsequently the risk of DDI; however, these factors are likely to be present in the majority of donors and may not distinguish "increased risk" from typical donors. Further study is needed to better define donor factors that are associated with a higher risk of transmission of MDR bacteria to recipients.

Another approach to minimize the risk of transmission of MDR bacteria from a donor is to have advanced knowledge of the organisms with which the donor is infected or colonized. Standard microbiology laboratory techniques require time for incubation and growth of the organism prior to identification and determination of antibiotic susceptibility, and time is of

the essence when decisions must be made about the suitability of donor organs and appropriate targeted antibiotic treatment for the recipient. This may be where rapid diagnostics would be of great utility. Advanced technologies such as matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS), multiplex polymerase chain reaction (PCR), and whole genome sequencing [28] could be used to rapidly identify the pathogens colonizing or infecting the donor. Transplant clinicians caring for potential recipients would thus be armed with the necessary information to accept or reject the organ offer and to formulate a preemptive antibiotic management plan if the organs are accepted.

It is worth emphasizing that the risk of MDR bacterial DDI may be mitigated with accurate recognition of infection in donors, and effective communication of donor culture results to the receiving institutions. This review suggests that prompt administration of targeted preemptive antibiotic therapy to the recipients of organs from donors infected with MDR bacteria appears to substantially reduce the risk of transmission, although this risk is not entirely eliminated. It is also important to note that negative surveillance blood cultures after initiation of therapy in an infected donor do not rule out transient bacteremia or contamination of perfusate. Recipients of organs from these donors are still at risk for acquisition of MDR bacterial DDI, as was seen in the two discussed cases of MRSA DDI [18•, 19•].

Conclusion

It is important for transplant clinicians to appreciate the lessons that can be learned from these cases of MDR bacterial DDIs; however this review also raises many unanswered questions. Further study is needed to identify donor factors that are associated with transmission of MDR bacteria to recipients so that transplant clinicians can risk-stratify donors with regard to their likelihood of transmitting MDR bacterial infection and develop a more informed management plan. To our knowledge, there are no published reports of how well antibiotics used in preemptive treatment of MDR bacteria in recipients are tolerated, so one area for additional exploration includes determining what factors make a recipient better able to tolerate a potential MDR bacterial DDI and its treatment. The optimal duration of antibiotic courses for potential and confirmed MDR bacterial DDI is not well-defined and is guided by expert opinion, but should be studied systematically. In addition, the role of rapid advanced diagnostics, such as MALDI-TOF MS and multiplex PCR, has yet to be explored in the management of DDIs. Finally, new molecular technologies like whole genome sequencing, whose use in this arena has thus far been limited to investigation of Gram-positive DDIs [18•, 19•], could be a powerful tool to define transmission of both MDR bacteria and resistance genes from donors to recipients. Ongoing systematic review of MDR bacterial DDIs and carefully designed prospective studies are needed to inform these areas of uncertainty.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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