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Original Article

Donor-derived carbapenem-resistant gram-negative bacterial infections in solid organ transplant recipients: Active surveillance enhances recipient safety

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ABSTRACT

Donor-derived infections (DDIs) caused by carbapenem-resistant gram-negative bacteria (CR-GNB) in solid organ transplant recipients are potentially life-threatening. In this prospective study, we evaluated the incidence, factors associated with transmission, and the outcome of recipients with unexpected CR-GNB DDIs after the implementation of our local active surveillance system (LASS). LASS provides for early detection of unexpected donor

Abbreviations: CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant *Enterobacterales*; CR-GNB, carbapenem-resistant gram-negative bacteria; DDI, donor-derived infection; HR, high risk; ID, infectious disease; IQR, interquartile range; ISMETT, Mediterranean Institute for Transplantation and Advanced Specialized Therapy; LASS, local active surveillance system; MDRO, multidrug-resistant organism; PF, preservation fluid; SOT, solid organ transplant; WGS, whole genome sequencing.

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active surveillance system
risk mitigation strategy
multidrug-resistant organism

CR-GNB infections, prophylaxis of recipients at high risk, and early diagnosis and treatment of DDIs. Whole genome sequencing confirmed DDI. Among 791 recipients, 38 (4.8%) were at high risk of unexpected CR-GNB DDI: 25 for carbapenem-resistant *Enterobacterales* (CRE) and 13 for carbapenem-resistant *Acinetobacter baumannii* (CRAB). Transmission did not occur in 27 (71%) cases, whereas DDIs occurred in 9 of 25 of CRE and 2 of 13 of CRAB cases. Incidence of CR-GNB DDI was 1.4%. Recipients of organs with CR-GNB–positive preservation fluid and liver recipients from a donor with CRE infection were at the highest risk of DDI. There was no difference in length of hospital stay or survival in patients with and without CR-GNB DDI. Our LASS contains transmission and mitigates the negative impacts of CR-GNB DDI. Under well-defined conditions, organs from donors with CR-GNB may be considered after a thorough evaluation of the risk/benefit profile.

1. Introduction

Donor-derived infections (DDIs) in solid organ transplant (SOT) recipients are potentially life-threatening and still represent one of the major challenges in the management of this population.[1,2]

In the last decade, infection with carbapenem-resistant gram-negative bacteria (CR-GNB), such as CR-Acinetobacter baumannii (CRAB) and CR-*Enterobacterales* (CRE), reached alarming incidence rates in Europe, especially in southern countries.[3-6] Potential donors are at risk of colonization or infection with CR-GNB due to hospitalization in intensive care units, the presence of invasive devices, and previous antimicrobial therapies.[7] Routine prophylaxis might fail to prevent infections due to the transmission of unrecognized CR-GNB from the donor at the time of organ procurement.[8-10] The precise incidence of CR-GNB DDIs is unknown due to challenges to recognize CR-GNB infections in recipients as transmitted from the donor because CR-GNBs are common causes of early posttransplant infections.[11] Prior reports of DDIs caused by these microorganisms have been associated with poor outcomes, including recurrent posttransplant infections, vascular complications, graft loss, and death.[12-14] Thus, CR-GNB infection in a potential donor is usually a contraindication for transplant[15,16]; however, cultures normally take a few days to become positive, and the donor infection might be diagnosed only after transplantation, leading to an unexpected DDI. The risk of posttransplant infection may increase when donor culture results are unknown at the time of transplant. In a previous retrospective study that included patients who underwent SOT from January 2012 to December 2013, our group assessed the outcomes of 30 transplant recipients from donors that were either colonized or infected with CR-GNB; 14 recipients were at high risk (HR) of DDI. In 6 HR cases, CR-GNB donor infection was miscommunicated or underestimated, leading to inappropriate, delayed, or insufficient pre-emptive therapy. DDI was diagnosed in 4 of the 6 patients, whereas no transmission occurred in the remaining 8 patients, who were properly managed[13].

As highlighted by the aforementioned study, early identification of donor CR-GNB and effective communication may be crucial in mitigating the risk of posttransplant infection and DDIs through earlier intervention in the recipient.[2,9,13,17-22]

Moreover, the clinical significance of a preservation fluid (PF) positive culture for CR-GNB is not well studied, but recent reports show that it may have adverse consequences for the recipient.[23-26]

In December 2015 at our institution, the Mediterranean Institute for Transplantation and Advanced Specialized Therapy (ISMETT) in Palermo (Italy), we implemented a local active surveillance system (LASS) to optimize our approach to donor testing, data sharing, and recipient management to mitigate the risk of unexpected CR-GNB DDI in SOT recipients.

The main aims of this study were as follows: (1) to describe the real incidence of CR-GNB DDI and the true risk of infection transmission using organs from donors who are infected with CR-GNB; (2) to evaluate factors associated with transmission and, in particular, the clinical significance of a positive PF culture; and (3) to evaluate the outcome of recipients with unexpected CR-GNB DDI after the implementation of our LASS.

2. Materials and methods

We conducted a prospective cohort study. All consecutive patients who underwent SOT from December 2015 to July 2021 were included in the study. The study was approved by our Institutional Research Review Board (ISMETT ethics committee; IRRB/06/18; protocol code 001-17612) and was conducted according to the guidelines of the Declaration of Helsinki. All patients gave written informed consent for the use of their anonymized data for research purposes.

2.1. Description of the active surveillance system

In Italy, as outlined by the National Transplant Centre guidelines, donor cultures are performed at the time of transplant evaluation and are processed at the donor hospital. When identification and antibiotic susceptibility tests are finalized, results are transmitted to the regional coordinating center, which transmits the information to the transplant coordinator of the recipient hospital and, lastly, to the receiving physician. The entire process can take up to 10 to 15 days (Fig. 1A).

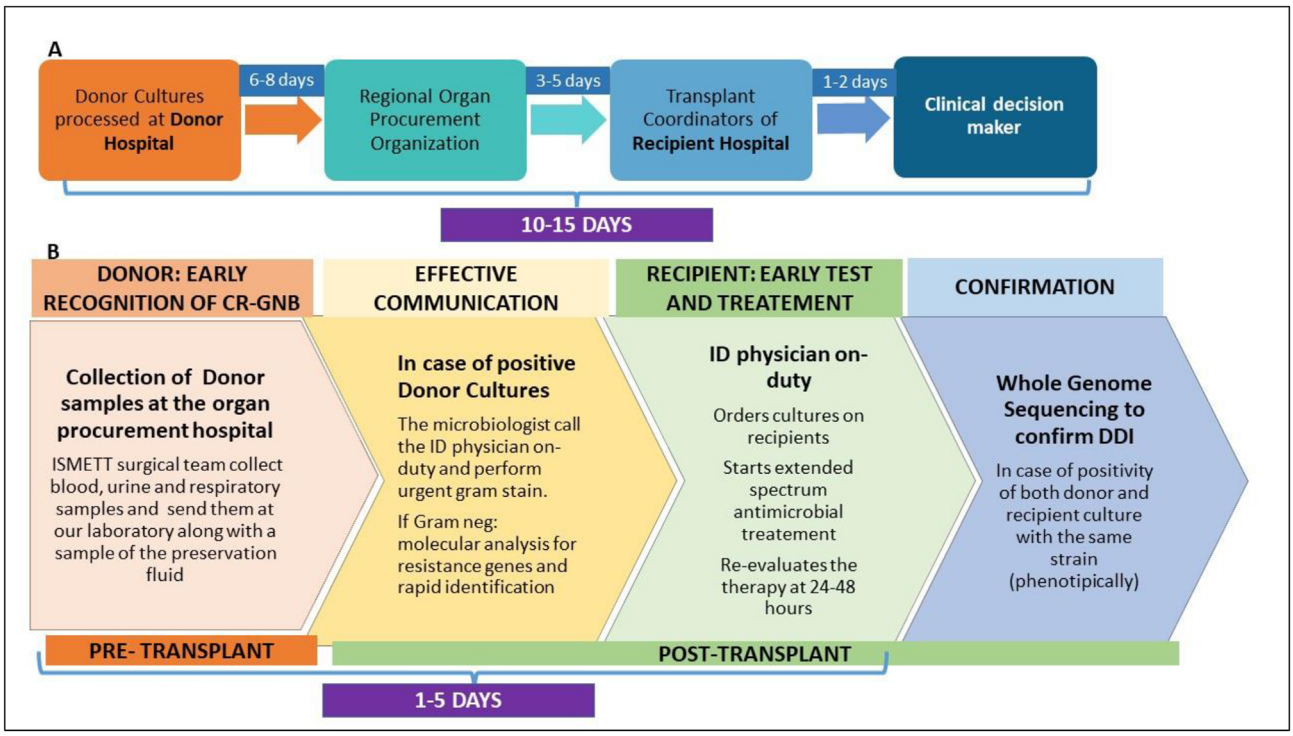

Figure 1. Description of (A) passive standard donor culture result reporting system in comparison to (B) local active surveillance system implemented at ISMETT. CR-GNB, carbapenem-resistant gram-negative bacteria; DDI, donor-derived infection; ID, infectious disease; ISMETT, Mediterranean Institute for Transplantation and Advanced Specialized Therapy.

A. In order to accelerate the process, we implemented a LASS described in Figure 1B characterized by the collection of blood samples and PF samples from all donors, urine samples from kidney donors, and respiratory samples from lung donors by the ISMETT surgical team at the time of organ procurement; microbiological analyses are performed at the ISMETT laboratory.
B. If donor cultures are positive, the biologist on duty communicates the results to the infectious disease (ID) physician on duty.
C. The ID physician, in the case of the following: (1) positive donor blood or PF culture, (2) positive urine culture from kidney donors, or (3) positive respiratory specimen culture from lung donors:
   - immediately orders blood samples and other appropriate surveillance cultures (urine, respiratory sample, or culture of perigraft drainage) from the recipient;
   - prescribes targeted antibiotic prophylaxis chosen on the basis of the preliminary culture results (Gram stain), rapid identification by matrix-assisted laser desorption/ionization - time of flight (MALDI-TOF), and detection of resistance genes by molecular analysis;
   - re-evaluates the regimen at 24 to 48 hours according to definitive microbiological results. In the case of isolation of CR-GNB from the donor sample, targeted prophylaxis is continued for at least 7 days. If DDI is confirmed, therapy is continued according to the type and severity of infection.
D. The ID nurse checks the donor culture results daily and communicates them to the attending physician and the regional coordinator of the transplant center so that they can inform other centers in case other organs have been recovered from the same donor;
E. In the case of isolation of the same microorganism in donor and recipient cultures, whole genome sequencing (WGS) of donor and recipient strains is performed.

Standard pretransplant antimicrobial prophylaxis protocol used at ISMETT and microbiological and WGS methods are described in the Supplementary Materials (Supplementary Table 1).

2.2. Definitions

2.2.1. Recipients at HR of donor-derived infection

Recipients were defined as at HR of CR-GNB DDI if they received the following: (1) an organ from a donor with positive blood cultures, (2) a kidney from a donor with a positive urine culture, (3) a lung from a donor with a positive respiratory specimen, or (4) an organ from a donor with positive PF (Table 1).

For this study, we decided to adopt the standpoint of the recipient's risk and not that of the donor for 2 main reasons. First, the combination of the site of infection and donated organ differs: a donor with a positive urine culture for multidrug-resistant bacteria is an HR donor for kidney recipients but not for the liver, lung, or heart recipients (Table 1). Second, we evaluated the appropriateness of treatment and clinical outcome, including rate of transmission and patient and graft survival, for each recipient at HR for DDI and not for the donor.

2.2.2. Donor-derived infection

We considered "proven DDI"[1] in the case of the following: (1) absence of pretransplant infection in the recipient, (2) evidence of the same microorganism in donor and recipient cultures, and (3) confirmed identity of donor and recipient strains by WGS.

Appropriate antibiotic-targeted prophylaxis was defined as the use of at least one active molecule in vitro (or the best available therapy), started within 72 hours after transplantation.

Table 1
Risk stratification according to the organ transplanted and the positive donor sample.

Positive donor sample / Organ transplanted	Blood	Urine	Respiratory specimen	Preservation fluid
Liver	High Risk	Low Risk	Low Risk	High Risk
Kidney	High Risk	High Risk	Low Risk	High Risk
Heart	High Risk	Low Risk	Low Risk	High Risk
Lung	High Risk	Low Risk	High Risk	High Risk
Pancreas	High Risk	Low Risk	Low Risk	High Risk

2.3. Statistical analysis

Continuous and categorical variables were expressed as median with interquartile range (IQR) and frequency with percentage, respectively. Wilcoxon tests were used to compare continuous variables, and Fisher exact tests were used to compare categorical variables among groups. The Kaplan–Meier survival method with log rank test was used to compare survival rates between CR-GNB HR recipients with or without DDI. We evaluated the possibility of using a Landmark analysis in order to avoid time-dependent bias.[27] However, results obtained with the 2 analyses, Landmark and Kaplan–Meier, were comparable. This is probably due to the short time interval between baseline dates and events. Therefore, the estimates will not be subject to time-dependent bias. The level of significance was set at P value of $<.05$. Statistical analyses were performed using SAS software version 9.4.

3. Results

3.1. Study population

During the study period, 791 consecutive patients who underwent SOT from 600 deceased donors were included. Characteristics of the cohort are detailed in Supplementary Table 2.

Of 791 recipients, 38 (4.8%) were at HR of CR-GNB DDI. Among them, 24 were at HR of infection with CR-*Klebsiella pneumoniae* (KP) (23 carbapenemase-producing KP and 1 oxacillinase-48–producing KP), 13 with CRAB, and 1 patient with metallo-β-lactamase–producing *Klebsiella aerogenes* (Table 2). All patients received targeted prophylaxis as soon as the donor results were communicated, in most cases within 72 hours from transplant (Fig. 1B).

3.2. Incidence of DDIs

In 38 recipients at HR of transmission of CR-GNB, 27 (71%) of donor infections were not followed by transmission, whereas 11 CR-GNB DDIs were diagnosed and confirmed by WGS with a sequence similarity $>94\%$ (Fig. 2 and Table 2). The overall incidence of CR-GNB DDI was 1.4% in all SOT recipients (11 out of 791) and 29% in HR recipients (11 out of 38). Median time to transmission was 1.5 days (IQR, 1-15).

Three additional cases of suspected CR-GNB DDI were identified (recipient's infection during the first 30 days after transplant caused by the same CR-GNB isolated from the donor), but WGS did not confirm the donor as the origin of the strain (Table 2). In Figure 2, the results of WGS analyses are represented by a dendrogram and a heatmap.

3.3. Factors associated with CR-GNB DDI

The type of donor specimen was the only significant predictor of CR-GNB DDI (Table 3). Interestingly, growth of CR-GNB in PF led to DDI in 87% of cases, whereas in the case of donor blood positivity, the rate of DDI was only 18%. One of 2 kidney transplant recipients at HR received a kidney from a donor whose urine and PF were positive for CR-GNB, and this recipient developed DDI. In lung transplant recipients, 3 were at HR for CR-GNB, and 1 DDI was observed when CR-GNB was isolated from both PF and respiratory samples.

Liver transplant recipients had a higher, but not statistically significant, risk of developing CR-GNB DDI compared with other organ recipients (9/22 [40.9%] vs 2/16 [12.5%], $P = .08$). Moreover, the highest risk of transmission was observed in liver recipients from a donor with CRE isolated from blood or PF cultures since transmission occurred in 50% of these patients (8/16, $P = .028$).

Transmission rates for CRE and CRAB were 36% and 15%, respectively, $P = .27$ (Table 3). All the CRE DDIs were detected in the immediate early posttransplant period, within 4 days, with a median time of transmission of 24 hours. CRAB DDIs occurred slightly later at a median time of 5.5 days (132 hours) after transplantation (Table 2).

Timing of introduction of appropriate antibiotic therapy in the recipient was comparable in the 2 groups and did not affect the outcome with respect to transmission (median time of introduction of appropriate antibiotics: transmission = yes, 30 hours [IQR, 24-72]; transmission = no, 24 hours [IQR 0-48], $P = .38$). Considering the data on donors, all of these cases were unexpected. This means that the information on donor's CR-GNB infection was not known at the time of transplant, and donors had not received appropriate antibiotics prior to donation.

3.4. Clinical outcomes of recipients

In our 38 patients at HR of CR-GNB DDI who received targeted prophylaxis treatment, the 60-day overall mortality was 8% (3/38). Among patients with confirmed DDI, one liver recipient died due to multiple complications not directly related to infection.

Table 2
Characteristics of carbapenem-resistant gram-negative bacteria high-risk recipients with the correspondent donors and description of outcome.

Recipient			Donor				Transmission			Outcome	
Recipient number	Organ	Year of transplant	Donor number	Micro organism	Specimen	LOS in ICU (d)	Transmission	WGS% (ST)	Onset DDI from SOT (d)	Infection resolution (30 d)	60-d survival
1	Lung	2015	1	KPC	BAL	1	No				
2A	**A** Heart	2016	2	CRAB	Blood	15	No				
2B	**B** Liver						No				
3	Liver	2016	3	KPC	Blood	23	No				
4	Kidney	2016	4	CRAB	Blood	12	No				
5A	**A** Liver	2017	5	CRAB	Blood	19	No				
5B	**B** Kidney						No				
6A	**A** Kidney	2017	6	KPC	Blood	15	No[a]	23.5			
6B	**B** Liver						Yes	99.6 (ST307)	1	Yes	No
7	Liver	2017	7	CRAB	Blood	15	No				
8	Liver	2017	8	KPC	Blood	13	Yes	99.6 (ST512)	2	Yes	Yes
9	Lung	2017	9	CRAB	BAL	5	No				
10A	**A** Kidney	2018	10	KP OXA-48	Blood	10	No				
10B	**B** Liver						No				
11	Liver	2018	11	KPC	Blood	12	No[a]	61			
12A	**A** Liver	2018	12	KPC	Blood	8	No				
12B	**B** Kidney						No				
13	Liver	2018	13	CRAB	Blood	8	No				
14	Kidney	2018	14	CRAB	Blood	6	No				
15	Kidney	2018	15	KPC	Urine + PF	11	Yes	97.4 (ST512)	3	Yes	Yes
16A	**A** Kidney	2018	16	KPC	Blood	10	No				
16B	**B** Liver						No				
17[b]	Liver	2019	17	KPC	PF	10	Yes	99.8 (ST512)	1	Yes	Yes
				CRAB	Blood		No				
18	Liver	2019	18	KPC	Blood	15	No				
19A	**A** Liver	2020	19	KPC	Blood	3	Yes	99.4 (ST101)	1	Yes	Yes

(*continued on next page*)

Table 2 (*continued*)

Recipient			Donor				Transmission			Outcome	
Recipient number	Organ	Year of transplant	Donor number	Micro organism	Specimen	LOS in ICU (d)	Transmission	WGS% (ST)	Onset DDI from SOT (d)	Infection resolution (30 d)	60-d survival
19B	**B** Kidney						No				
20	Liver	2020	20	KPC	PF	3	No				
21A	**A** Kidney	2020	21	KPC	Blood	6	No[a]	90.2			
21B	**B** Liver						No				
21C	**C** Kidney						No				
22	Kidney	2020	22	CRAB	Urine	11	No				
23	Liver	2020	23	*K. aerogenes* MBL	Blood	15	Yes	99.4 (n.a.)	1	Yes	Yes
24A	**A** Lung	2020	24	CRAB	PF + BAS	5	Yes	99 (ST1806-ST208)	6	Yes	Yes
24B	**B** Liver				PF		Yes	99 (ST1806-ST208)	15	Yes	Yes
25	Liver	2020	25	KPC	PF	19	Yes	99.4 (ST307)	2	Yes	Yes
26	Liver	2021	26	KPC	PF	47	Yes	95 (ST258)	1	Yes	Yes
27	Liver	2021	27	KPC	Blood + PF	11	Yes	94.6 (ST307)	0.9	Yes	Yes

ABT, antibiotic therapy; BAL, bronchoalveolar lavage; BAS, bronchoaspirate; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant *Enterobacterales*; CR-GNB, carbapenem-resistant gram-negative DDI, donor-derived infection; ICU, intensive care unit; IQR, interquartile range; KP, *Klebsiella pneumoniae*; KPC, *Klebsiella pneumoniae* carbapenemase-producing; LOS, length of stay; MBL, metallo-β-lactamase; n.a., not available; OXA, oxacillinase; PF, preservation fluid; SOT, solid organ transplant; ST, sequence type; WGS, whole genome sequencing.

[a] In these cases DDI was suspected because recipients developed an infection caused by the same donor pathogen, but ST was different, and WGS showed low sequence similarity percentage.

[b] One liver recipient was at risk of 2 different CR-GNB pathogens: donor blood cultures were positive for CRAB, and liver PF was positive for CRE.

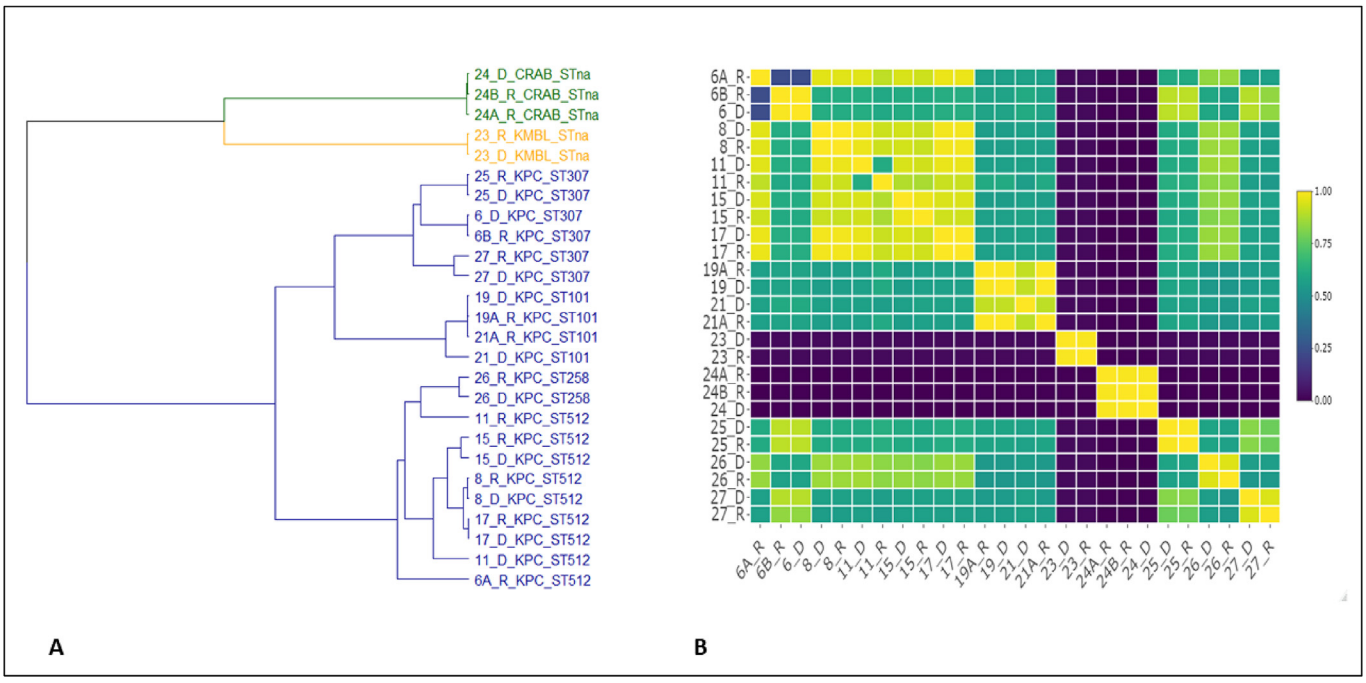

Figure 2. Results of whole genome sequencing analysis. Dendrogram (A): The closer the samples are on the y-axis, the more similar they are, whereas on the x-axis, the branches, like that of a tree, also indicate similarity; the longer the branch that joins 2 samples, the more dissimilar they are. Each group of similar samples has the same colored branches. Heatmap (B): Each identity relationship of 2 samples is graphically represented by a colored square, which has the reference samples as coordinates. The square changes color based on the percentage identity (0 = 0%, 1 = 100%), and the color changes from purple = 0 to yellow = 1. CRAB, carbapenem-resistant *Acinetobacter baumannii*; D, donor; KPC, *Klebsiella pneumoniae*-producing; KMBL, *Klebsiella pneumoniae* metallo-β-lactamase–producing; R, recipient; ST, sequence type; STna, ST not available.

Mortality, length of stay in the intensive care unit, and length of stay in the hospital did not differ between HR patients with (n = 11) and without (n = 27) CR-GNB DDI (Table 3).

Survival at 60 days after SOT was not different between the cohort of patients with DDI (n = 11) and the patients without DDI (n = 780) (log rank, $P = .68$) (Table 3 and Fig. 3).

4. Discussion

This study describes the results of our LASS implemented to mitigate the negative impacts of unexpected CR-GNB DDI, considering the high prevalence of multidrug-resistant organisms (MDROs) in our country[8] and our previous experience,[13] which highlighted that communication gaps were associated with infection transmission. With enhanced surveillance and communication and early targeted prophylaxis, DDI did not occur in 71% of HR recipients and, in the event of transmission, we were able to mitigate negative impact. In fact, in the remaining 29% of cases, transmission was detected very early in asymptomatic recipients through surveillance cultures, leading to prompt administration of appropriate therapy and probably improvements in recipient outcomes.

It is known from the available literature that DDIs complicate approximately 0.2% to 1.7% of deceased SOTs.[28-30] We found that 4.8% of recipients in our cohort were at HR of CR-GNB DDI, with an overall rate of CR-GNB DDIs of 1.4%. The high rate of CR-GNB DDI found in our study could be explained by the active surveillance system: most of the current surveillance systems that identify transmission events are passive, resulting in underrecognition and underreporting and making any attempt to mitigate the risk difficult. The real transmission rate of these pathogens and the impact on recipient outcome is still not known.

The high percentage of recipients at HR of CR-GNB DDI reflects the high prevalence of these bacteria in our geographic area.[5,6] A similar prevalence was described in the DRIn study, an Italian observational study conducted by Procaccio et al[14] in 2012 in 190 intensive care units in which CR-GNB was detected in 3.6% of all donors.

Several reports have illustrated the potentially catastrophic consequences of unrecognized transmission of CR-GNB from donor to recipient, typically due to inappropriate or delayed active antimicrobial therapy resulting from underestimation of the risk and miscommunication of donor microbiology results.[8,9,13,18,23,31,32] A review from 2016[12] of all published cases of multidrug-resistant GNB DDI described an attack rate of 52% (17 DDIs among 33 recipients at risk) and very poor outcomes; 59% of recipients died or lost the allograft. Most of these infections were unexpected and probably recognized and treated with substantial delay. Our intervention directed at early identification of donor CR-GNB and early appropriate treatment of the recipient led to much lower rates of transmission. Even when transmission occurred, early and appropriate treatment of the recipients resulted in no significant increase in the length of stay or mortality in patients with CR-GNB DDIs. Our results are comparable with a recent study by Anesi et al,[33] which evaluated the impact of donor multidrug-resistant bacteria on SOT recipient outcomes. They observed an increased risk of infection when the donor had an MDRO, especially when results were not known at the time of transplant, but the positivity of donor

Table 3
Predictors of donor-derived infection and outcome in recipients at high risk of carbapenem-resistant gram-negative bacteria donor-derived infection.

			Recipients HR CR-GNB DDI (n = 38)	DDI (n = 11)	No DDI (n = 27)	*P* value
Pathogen						.2679
	Specimen	Organ				
CRE, n (%)			**25**	9 (36%)	16 (64%)	
	Blood	Liver	11	4	7	-
		Kidney	7	0	7	-
	Urine + PF	Kidney	1	1	0	-
	PF	Liver	5	4	1	-
	Respiratory samples	Lung	1	0	1	-
CRAB, n (%)			13	2 (15%)	11 (85%)	
	Blood	Liver	5	0	5	-
		Kidney	3	0	3	-
		Heart	1	0	1	-
	Urine	Kidney	1	0	1	-
	PF	Liver	1	1	0	-
						-
		Lung	1	1	0	
	Respiratory samples	Lung	1	0	1	-
Organ, n	Liver[a]		22	9 (41%)	13 (59%)	.0776
	Kidney		12	1 (8%)	11 (92%)	.1209
	Lung		3	1 (33%)	2 (67%)	1.000
	Heart		1	0 (0%)	1 (100%)	1.000
Specimen, n	Blood		28	5 (18%)	23 (82%)	.0193
	Urine		2	1 (50%)	1 (50%)	1.000
	Respiratory specimen		2	0 (0%)	2 (100%)	1.000
	PF[b]		8	7 (87%)	1 (13%)	.0002
Liver & CRE[c], n (%)			16 (42%)	8 (50%)	8 (50%)	.0280
Timing of start of appropriate antibiotics in hours, median (IQR)			24 (9-48)	30 (24-72)	24 (0-48)	.3789
Outcome						
Total LOS (median, IQR)			29 (14-48)	35 (24-57)	26 (12-46)	.2063
LOS in ICU (median, IQR)			6 (2-10)	6 (5-26)	3 (1-9)	.1016
60-d mortality, n (%)			3 (8)	1 (9%)	2 (7.4%)	1.000
60-d survival probability			0.9499	0.9091	0.9504	.6819

Comparisons between categorical variables among groups were made using Fisher exact test. 60-d survival probability between CR-GNB HR recipients with or without DDI was evaluated using Kaplan–Meier with log rank test.
CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant *Enterobacterales*; CR-GNB, carbapenem-resistant gram-negative bacteria; DDI, donor-derived infection; HR, high risk; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; PF, preservation fluid.

[a] One liver recipient was at high risk of 2 different CR-GNB bacteria (case 17 in Table 2).

[b] CR-GNB positivity only for PF or PF plus other samples.

[c] Recipient of a liver whose PF was positive for CRE or whose donor had blood cultures positive for CRE.

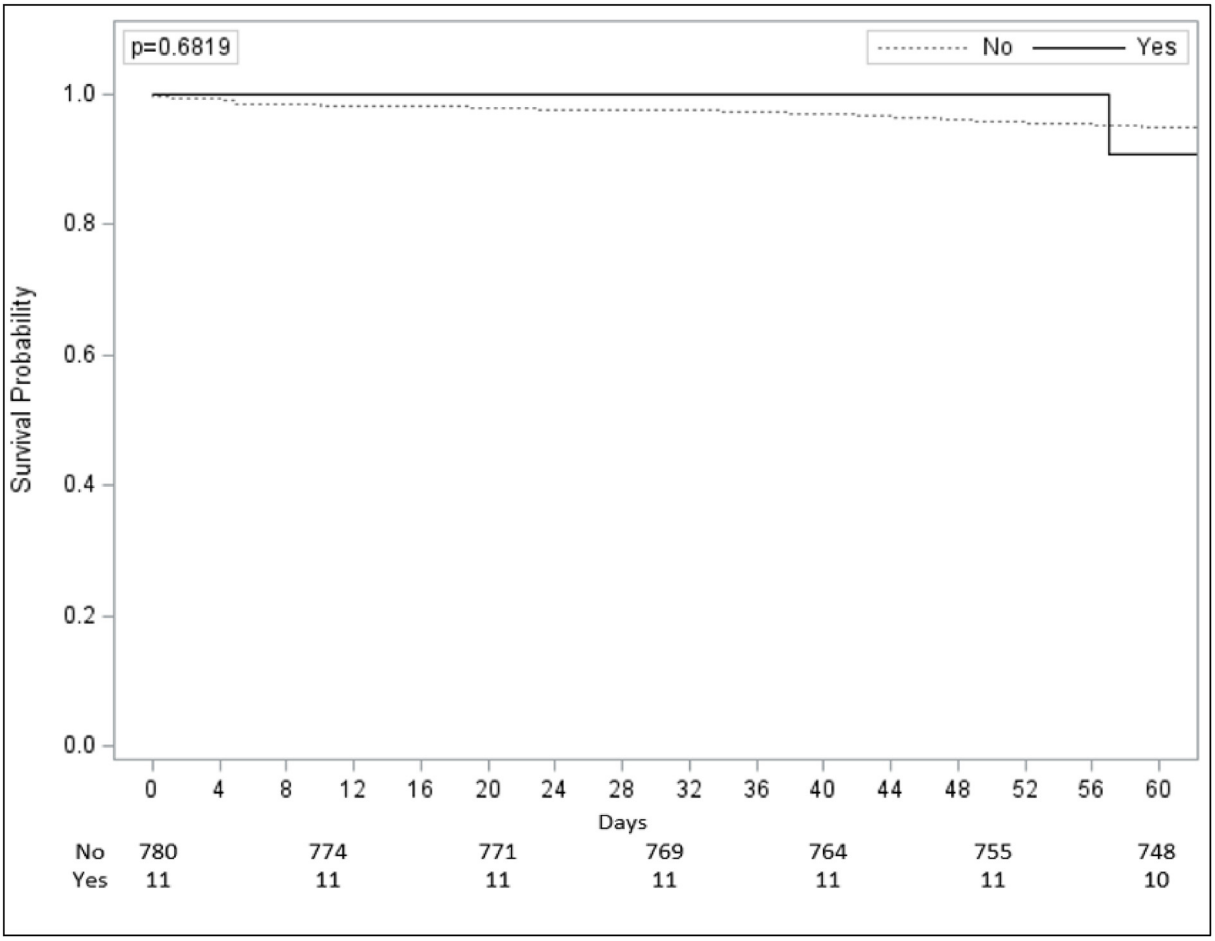

Figure 3. 60-day survival probability in recipients with (n = 11) and without (n = 780) carbapenem-resistant gram-negative bacteria donor-derived infection.

cultures for MDRO did not negatively affect recipient outcomes. Therefore, they suggested that organs from donors infected with MDROs may be used safely, and early identification of donor MDROs may potentially mitigate the risk of posttransplant infection.[33]

We analyzed which risk factors, such as type of pathogen, type of transplanted organ, and type of carbapenem-resistant specimens, were associated with an increased risk of CR-GNB DDI. Our results highlight the clinical significance of CR-GNB–positive culture of PF, since transmission occurred in 87% of recipients whose PF culture was positive. Collection of PF for culture is not standardized, and its role remains controversial, with positive results usually considered contamination.[34,35] However, in a recent multicenter prospective study, Oriol et al[36] showed that in SOT recipients whose PF tested positive for a high-risk microorganism, targeted prophylaxis was a protective factor for infection in the recipient. Moreover, in the case of PF positive for CR-GNB, devastating consequences of DDI have been reported.[23,24] In a recent systematic review and meta-analysis by Rinaldi et al,[26] a significantly higher risk of graft arteritis was observed when PF was positive for a "high-risk" pathogen, especially in liver and kidney transplant recipients. Based on the results of their review, the authors concluded that they support the clinical relevance of PF culture results together with appropriate management of recipients.[26] Considering that PF culture is easy to perform at the transplantation hospital, and its positivity for CR-GNB is associated with a high rate of DDIs, the growth of a CR-GNB in PF should trigger surveillance cultures, drainage of eventual perigraft collection for microbiological examination and source control, and targeted prophylaxis in the recipient.

In our cohort, the highest risk of transmission was recorded in liver recipients whose donor had positive CRE culture from PF (4/5) or blood (4/11). A possible explanation could be the high-bacterial burden of *Enterobacterales* in the liver acting as a "filter." On the contrary, overall lower rates of transmission in cases of isolated positive blood cultures of any organ donor (18%) could be due to the effectiveness of the systemic targeted prophylaxis in a setting with a lower bacterial burden compared with PF culture positivity.

The strengths of our study include prospectively collected data on the exact rate of CR-GNB transmission from donor to recipient confirmed with WGS. Moreover, our active surveillance system represents a significant innovation over the current practice as we implemented a holistic (donor testing, data sharing, recipient management, and WGS confirmation[11,37]), innovative intervention plan that was able to mitigate the risk of unexpected CR-GNB DDI. Furthermore, we provided information on factors associated with increased risk of donor-derived transmission of CR-GNB and

novel data on the clinical significance of PF culture positive for CR-GNB. This approach, together with the availability of new drugs effective against CR-GNB, may help mitigate the consequences related to transplanting organs from donors unexpectedly infected or colonized with CR-GNB.

Among the limitations of our study is its monocentric nature, which means our results are not necessarily generalizable to all SOT settings. In fact, being implemented in an endemic area for CR-GNB, our system of rapid detection of CR-GNB may not be suitable or cost-effective for centers located in countries with a low burden of MDROs. On the other hand, rapid recognition of HR recipients for any DDI, regardless of antibiotic susceptibility of the bacteria, is crucial for the management of transplanted patients to ensure optimal clinical outcomes. Additionally, antibiotic treatment was not standardized for all patients. In fact, new drugs active against CR-GNB became commercially available only in 2018, and patients received different regimes during the study period.[38-41] Finally, in the absence of a control arm without intervention, we were unable to assess, in a controlled manner, the impact of LASS in preventing DDI and improving clinical outcomes. Multicentric studies in CR-GNB endemic areas and standardized treatment could help define the efficacy of LASS. Further studies should also focus on other issues that might have a role in transmission from donor to recipient, such as inoculum of the pathogen, the comorbidities of both donor and recipient, and type of immunosuppression used. Nevertheless, being at risk of CR-GNB DDI should be better investigated as a risk factor, among other variables, in prediction models to stratify the risk of posttransplant CR-GNB infections.[42]

In conclusion, unexpected CR-GNB donor infections represent an emergent challenging problem for SOT recipients in endemic settings. Currently, there are more individuals who could benefit from organ transplantation than available organs. As such, discarding organs from donors with risk factors needs to be minimized. Although it is impossible to eliminate the risk of infection transmission, risk mitigation strategies, such as our active surveillance system, could be implemented, contributing to improving recipient outcomes and, in the future, could allow the policies on the use of organs from CR-GNB–positive donors to be reconsidered. However, further studies are needed to verify the safety of the use of organs from donors with ongoing CR-GNB infections.

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Data availability

The data presented in this study will be available from the corresponding author on reasonable request.

Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2024.02.005.

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