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Organ donor screening for carbapenem-resistant gram-negative bacteria in Italian intensive care units: the DRIn study

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The 759 cases of brain death declaration (BDD [Italian law, 6 hours of observation time]) that occurred in 190 Italian intensive care units (ICUs) between May and September 2012 were studied to quantify carbapenem-resistant gram-negative bacteria (CR-GN) isolated in organ donors, to evaluate adherence to national screening guidelines, and to identify risk factors for CR-GN isolation. Mandatory blood, bronchoalveolar lavage, and urine cultures were performed on the BDD day in 99% of used donors. Because results were rarely made available before transplant, >20% of transplants were performed before obtaining any microbiological information, and organs from 15 of 22 CR-GN cases were used. Two (lung–liver) of the 37 recipients died, likely because of donor-derived early CR-GN sepsis. ICU stay >3 days (odds ratio [OR] = 7.49, P = .004), fever (OR = 3.11, P = .04), age <60 years (OR = 2.80, P = .06), and positive ICU epidemiology (OR = 8.77, P = .07) were associated with CR-GN isolation. An association between single ICU and risk of CR-GN was observed, as a result of differences across ICUs (ICC = 29%; 95% confidence interval [CI] 6.5%-72%) probably related to inadequate practices of infection control. Continuous education aimed at implementing priority actions, including stewardship programs for a rational use of antimicrobials, is a priority in healthcare systems and transplant networks. Improved awareness among ICU personnel regarding the importance of early CR-GN detection and timely alert systems might facilitate decisions regarding organ suitability and eventually save recipient lives.

KEYWORDS
clinical research/practice, donors and donation: donation after brain death (DBD), donors and donation: donor evaluation, infection and infectious agents - bacterial, organ procurement and allocation, risk assessment/risk stratification

Abbreviations: actual donor, donor with at least 1 organ recovered; BAL, bronchoalveolar lavage; BDD, brain death declaration; BSI, bloodstream infection; CI, confidence interval; CPE, carbapenemase-producing Enterobacteriaceae; CR, carbapenem resistant; DRIn, Donor and Recipient Infection study; GN, gram-negative; ICC, intraclass correlation coefficient; ICU, intensive care unit; LRT, likelihood ratio test; OR, odds ratio; PMP, per 1 million population; SOT, solid organ transplant; used donor, donor with at least 1 organ transplanted.

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1 | INTRODUCTION

Optimization of the number of organ donors is one of the most important targets for national health systems in all countries where patients with severe organ dysfunction suffer and die waiting for a transplant.[1] Deceased organ donation, which is still mainly based on brain-dead subjects with acute devastating cerebral lesions in intensive care units (ICUs), is the most relevant source of usable organs. Accordingly, proper medical screening to minimize the risk of donor–recipient transmission of infectious agents has become a key factor to ensure safety for recipients without inappropriate organ discards.[2-4]

In recent years, the strong concern regarding the safety of deceased organ transplant reflects the clusters of infections and severe complications associated with the donor–recipient transmission of carbapenem-resistant gram-negative (CR-GN) microorganisms[5-10] within the context of the rapid and uncontrolled diffusion of CR-GN microorganisms in hospitals[11,12] and ICUs[13-15] in various countries, including Italy.[16-19] In Italian hospitals, the prevalence of CR-GN is significantly higher than the European average, as shown by data from the European Antibiotic-Resistance Surveillance Network.[20]

In 2012, the National Transplant Center implemented a web-based national surveillance program, the Donor and Recipient Infection study (DRIn), for collecting data on all potential organ donors and related recipients in all Italian ICUs and transplant centers. Clinical safety guidelines include clinical history and mandatory cultures (blood, urine, respiratory secretions) on the day of brain death declaration (BDD [Italian law, 6 hours of observation time], or BDD day. At the time of the DRIn study, the isolation of CR-GN bacteria from any site except for rectal swab was considered, as a precaution, a risk factor for organ discard.

Although the quality and safety of transplants were found to be maintained in the nationwide scenario, significant mortality due to CR-GN infections in organ recipients has been documented.[21] These results led to the design of a prospective national study based on bacterial observational cultures from organ recovery to 30 days after transplant.[22]

In the present study, DRIn data regarding all subjects for which death had been declared by neurological criteria in the ICU (BDD) were analyzed. The objectives are as follows:

1. To describe the occurrence of CR-GN bacterial isolation in brain-dead patients and BDD organ donors in Italian ICUs
2. To evaluate adherence to national screening guidelines aimed at preventing donor–recipient transmission of bacterial infection
3. To identify factors related to the risk of CR-GN bacterial isolation and potential transmission

2 | PATIENTS AND METHODS

2.1 | Study design

The DRIn study was designed as a cohort study based on data from the national surveillance program established to assess the burden of gram-negative bacteria in potential organ donors and related organ recipients. The National Transplant Center coordinates all activities regarding organ donation through the regional transplant centers in all Italian ICUs (~350) in 21 regions.[23]

2.2 | Study population and methods

In the study cohort, eligible subjects were BDD patients treated in Italian ICUs during the study period (May 15-September 30, 2012).

A web function (client-server-system-Database, MySql-v5.1.73) was developed to collect ICU data, including bacterial isolations, from admission to BDD and subsequent organ recovery. The same function was used to collect data on related transplants. The results of antibiotic susceptibility tests were noted taking into consideration the timing of availability: before BDD and organ recovery and before and after organ transplant.

The epidemiology of the ICU, defined as 1 or more cases of CR-GN isolation from any patient in the previous 15 days, was recorded for each BDD.

CR-GN isolation, occurrence of sepsis, and patient outcomes were monitored for 3 months in the recipients of organs recovered from all used donors. These data have been previously analyzed and published.[21]

2.3 | Microbiological data source

In addition to the data from mandatory cultures on BDD days, microbiological results were collected from admission to death in the ICU and in recipients after transplant according to clinical judgment and center-based procedures. Cultures and antibiotic susceptibility tests were performed in local laboratories according to national standards and interpreted following the European Committee on Antimicrobial Susceptibility Testing criteria.[24]

2.4 | Outcome and exposure to risk factors

The risk of CR-GN isolation in potential donors and the possible transmission of CR-GN bacteria to the recipient were analyzed for 2 groups of factors:

1. Potential donor factors: age, sex, etiology of brain death, ICU length of stay, fever and clinical signs of infection, GN isolation during ICU management, and CR-GN epidemiology in a single ICU
2. Management factors: adherence to BDD day cultures, cultures in the ICU and timing of information regarding BDD day culture results

2.5 | Statistical analysis

For descriptive analysis, the results are illustrated as the median with ranges and interquartile intervals (25th, 75th percentiles) or numbers (percent). When appropriate, the χ^2 test or Fisher exact test was used to calculate the significance level of the association

between CR-GN positivity and covariates and factors. The rate per 1 million population (PMP) is shown for the population data.

A univariate mixed-effects logistic model with clustering by ICU (random intercepts) was used to evaluate associations between risk factors and the risk of CR-GN isolation, in line with the hierarchical data structure.[25] Fixed-effect variables in the model were potential donor factors, including donor age (<60 years; ≥60 years), ICU length of stay (≤3 days; >3 days), and region (grouped into 3 macrogeographical areas).

Clinical relevance, in combination with the results of univariate analyses, was used to select variables for the multivariable mixed-effects logistic model. The latent intraclass correlation coefficient (ICC), likelihood ratio test (LRT), and median OR (as a measure for quantification of the cluster-level effect)[26] were used to choose the final multivariable model.

Secondary multivariable analyses were conducted on the subgroup of BDD patients stratified by length of stay in the ICU (>3 days) according to the results of the DRIn study on transplant recipients.[21]

Statistical significance was assessed at the $P = .05$ level; $P > .19$ is not specified, and "n.s." is indicated. STATA Software, Release 13 (StataCorp LP, College Station, TX) was used,[27] and the results are reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology[28] statement.

2.6 | Ethics

Information at enrollment was obtained through the mandatory national database (established by law 91/1999), which collects donor and recipient data. Personal data were anonymized and deidentified before analysis. No intervention was planned for the purpose of this study, and potential donors and recipients underwent medical intervention (including diagnostics) according to clinical guidelines and Italian regulations for safety and quality in solid-organ transplant (SOT). According to these factors, no specific consent from transplant recipients was needed.

3 | RESULTS

3.1 | Potential, actual, and used donors

A total of 759 patients in whom death was declared based on neurological criteria (BDD) in 190 Italian ICUs were enrolled in the DRIn study (Table 1). The cohort covers >91% of all potential donors in the period of 138 days in 2012. All Italian regions were included in the study. Remarkable differences were found in the number of BDDs per population, which is a proxy of potential donation after brain death organ donors, as well as in the ICU disclosure of epidemiological risk of CR-GN transmission (Table S1).

The median age of the BDD patients was 62 (minimum-maximum: 1-92), and stroke was the most frequent cause of brain death (58.9%). The ICU stay before death was <6 days in approximately 80% of cases. Fever was present in 12.0% of cases, and infection was suspected in 74.7% of febrile cases.

In 143 cases (18.8%), donor and/or organ unsuitability for transplant was defined before or after organ recovery by mandatory screening examinations (ie, national safety recommendations) and, in some cases, autopsy. In this group, potentially transmittable disease prevented organ recovery in 75 cases (9.9%), including 2 untreated fulminant meningitis and 7 documented CR-GN isolations. Finally, because the rate of family refusal was 27.8%, 405 donors and 1071 organs were used for 987 transplants.

3.2 | Adherence to guidelines and efficiency of filtering

At least a set of cultures was performed for 619 (81.6%) BDD patients and 401 (99.0%) used donors. Blood, bronchoalveolar lavage (BAL), and urine cultures were performed on BDD day, as requested by the national safety recommendations, but for 26.9% of used donors, no culture had been obtained during the ICU stay before BDD day (Table 2).

Results of the BDD day cultures were made available and communicated to the centers before transplant in only 14.7% of cases. Consequently, considering the unavailable results of cultures carried out on BDD day, 21.9% of transplants were performed before obtaining any microbiology results.

Bacterial isolates were detected in 51.7% (Table 2) of all tested BDD patients, with at least 1 GN isolation in 36.4% of used donors (Table 3).

Finally, CR-GNs were isolated in 22 cases, but only 7 potential donors, with culture results available before transplant, were excluded and not used. In 1 case, in which CR-GN bacteria had been isolated from rectal swab and superficial sites, the organs were used following expert second opinion consultation. In the remaining 14 cases, the donors were not excluded because the culture results were obtained only after organ recovery and transplant (Table 3).

3.3 | GN and CR-GN isolates

A total of 240 GN isolates were obtained for 189 (30.5%) BDD patients with microbiological tests. GN isolation was more frequent (65.4%) when using BAL but <10% for blood cultures. *Klebsiella pneumoniae* represented 28.3% of all GNs isolated.

Fifteen percent of the GNs were resistant to carbapenems; in particular, 26.4% of the *K. pneumoniae* isolates were CR. No CR-GN was identified when the ICU length of stay was <3 days (Table 4).

When a CR-GN isolate was detected in the ICU in the 15 days before the BDD day, the potential donor had a higher frequency of having a CR-GN isolation than did the potential donor staying in an ICU with negative epidemiology (7.3% vs 2.7%; OR = 2.89, $P = .01$).

3.4 | Risk analysis

A considerable association between single ICU and risk of CR-GN isolation was observed in the bivariate as well as in the multivariable mixed-effects logistic model with clustering by ICUs: the

TABLE 1 Brain death declarations, actual donors, and utilized donors

	BDDs		Actual organ donors		Utilized organ donors	
	N	%	N	%	N	%
	759	**100**	**423**	**55.7**	**405**	**53.4**
Age (y)						
Median (Q1-Q3)	62 (47-74)		60 (47-72)	—	60 (47-72)	—
Min-Max	1-92		1-88		1-88	
Sex						
M/F	420/339	55.3/44.7	235/188	55.6/44.4	222/183	54.8/45.2
Etiology						
Stroke	447	58.9	249	58.9	240	59.3
Brain injury	231	30.4	142	33.5	134	33.1
Anoxia	49	6.5	27	6.4	27	6.7
Infection	14	1.8	2	0.5	2	0.5
Cerebral tumor	12	1.6	1	0.2	1	0.2
Other	6	0.8	2	0.5	1	0.2
ICU length of stay (days)						
≤1	259	34.1	149	35.2	141	34.8
2	143	18.9	78	18.4	75	18.5
3-5	196	25.8	109	25.8	106	26.2
>5	161	21.2	87	20.6	83	20.5
Clinical data						
Fever[a]	91	12.0	59	13.9	57	14.1
Infection[b]	68	9.0	41	9.7	38	9.4
Opposition to organ donation	211	27.8	—		—	
Donor medical contraindications	75	9.9	2	0.5	—	
HIV	2					
CR-GN	7				(15)[c]	(3.7%)[c]
Meningitis	2					
Malignancy	39		2			
Other	25					
Organ unsuitability	50	6.6	16	3.8	—	

Abbreviations: BBD, brain death declaration; ICU, intensive care unit.
[a]Temperature ≥38.4°C.
[b]Clinical diagnosis.
[c]From 14 of 15 culture results obtained after organ transplant; 1 was used after an expert second opinion was obtained.

relevance of the ICUs accounts to a median OR = 4.9 in the bivariate approach and, in the final multivariable model, one-third of the variability in the outcome is the result of the differences across ICUs (ICC = 29% with 95% CI 6.5%-72%) (Table 5). In the ICU-adjusted analysis, ICU length of stay >3 days before BDD (OR = 12.49, $P < .001$), presence of fever (OR = 6.48, $P < .002$), clinical suspicion of infection (OR = 4.59, $P < .001$), and age <60 years (OR = 3.01, $P = .04$) were associated with CR-GN isolation among BDD cases. The relevance of these factors was confirmed in the multivariable model (Table 5, last columns): ICU length of stay (OR = 7.49, $P = .004$) and fever (OR = 3.11, $P = .04$) showed a statistically significant association. Nevertheless, a high OR was obtained for a younger age and positive epidemiology (2.80 and 7.49, respectively), which approached statistical significance.

Considering the subgroup of BDD cases with ICU stays >3 days, the presence of CR-GN bacteria was associated with fever (OR = 3.62, $P = .012$), ICU epidemiology positive for CR-GN (OR = 3.01, $P = .029$), and southern regions in Italy (OR = 3.36, $P = .017$) (Table S2).

In the cases of BDD with cultures both before and on BDD day, GN isolation (excluding CR-GN) before BDD day was associated with

TABLE 2 Microbiological tests in brain death declarations, actual donors, and utilized donors

	BDDs (n = 759)		Actual organ donors (n = 423)		Utilized organ donors (n = 405)	
	No.	%	No.	%	No.	%
BDDs with microbiological tests in ICU	619/759	81.6	416/423	98.3	401/405	99.0
Both before and on BDD day	347	56.0	290	69.7	285	71.1
Only before BDD day	123	19.9	12	2.9	8	2.0
Only on BDD day	149	24.1	114	27.4	108	26.9
BDDs with bacterial isolation	320/619	51.7	259/416	62.3	251/401	62.6
Both before BDD day and BDD day	76	23.7	61	23.6	60	23.9
Only before BDD day	55	17.2	34	13.1	31	12.4
Only on BDD day	189	59.1	164	63.3	160	63.7

BBD, brain death declaration; ICU, intensive care unit. BDD day: the day of BDD (in Italy, a 6-hour period of observation is mandatory).

TABLE 3 Intensive care unit length of stay (timing of brain death declaration), gram-negative carbapenem-resistant isolates, and timing of gram-negative carbapenem-resistant isolate results[a]

	BDD					Utilized donors					
ICU length of stay (days)	With microbial culture[c]	GN isolation cases		CR-GN isolation case[b]		With microbial culture[c]	GN isolation cases		CR-GN isolation cases[b]		Information available after transplant
	N	N	%	N	%	N	N	%	N	%	N
≤2	322	71	22.0	0	—	213	58	27.2	0	0	—
3-5	164	55	33.5	5	3.0	105	44	41.9	4	3.8	4
6-14	116	49	42.2	11	9.5	75	37	49.3	8	10.7	7
15+	17	14	82.4	6	35.3	8	7	87.5	3	37.5	3
Total	619	189	30.5	22	3.6	401	146	36.4	15	3.7	14

BDD, brain death declaration; ICU, intensive care unit; GN, gram negative; CR, carbapenem resistant.
[a]BDDs or donors are considered only once, even if they have more isolates.
[b]The percentages were calculated based on the number of cases with microbial culture in BDD and utilized donors.
[c]At least a set of blood, bronchoalveolar lavage, and urine cultures.

TABLE 4 Gram-negative isolates in 189[a] of 619 brain death declarations with microbiology cultures: site, species, and percentage of carbapenem resistance

	Blood		BAL		Urine		Other sites[b]		Total	
GN isolate	n	% CR	n	% CR	n	% CR	n	% CR	n	% CR
Klebsiella pneumoniae	9	44.0	40	17.5	9	22.0	10	50.0	68	26.4
Pseudomonas aeruginosa	4	0.0	27	7.4	3	0.0	2	0.0	36	5.5
Escherichia coli	2	50.0	9	0.0	10	0.0	3	0.0	24	4.2
Acinetobacter baumannii	2	100	10	60.0	3	75.0	3	75.0	18	66.7
Other GN	4	0.0	71	4.2	16	0.0	3	0.0	94	3.2
Total	21	33.3	157	11.5	41	9.7	21	33.3	240	15.0

BDD, brain death declaration; BAL, bronchoalveolar lavage; GN, gram negative; CR, carbapenem resistant.
[a]189 BDDs presented at least one isolate for a total of 240 isolates.
[b]In some cases, rectal swab or other sites cultures (surgical site, drain, skin) were performed according to clinical judgment or surveillance purpose.

TABLE 5 Analysis of factors associated with gram-negative carbapenem-resistant isolation in brain death declaration cases (22 cases of 619 cases with microbial culture)

	CR-GN			Bivariate analysis[a]		Multivariable analysis[a] (final model)	
	No	Yes	Total				
	597	22	619	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Fixed effects							
Sex							
Male	327	12	339	Ref.			
Female	270	10	280	1.02 (0.39-2.63)	n.s.		
Age (years)							
≥60	331	7	338	Ref.			
<60	266	15	281	3.01 (1.08-8.44)	.04	2.80 (0.95-8.24)	.06
Cause of death							
Injury	183	5	188	Ref.			
Stroke	353	15	368	1.8 (0.54-5.99)	n.s.		
Infection	12	1	13	6.83 (0.41-112.78)	n.s.		
Others	49	1	50	0.78 (0.07-9.19)	n.s.		
ICU length of stay (days)							
≤3	391	3	394	Ref.			
≥4	206	19	225	12.49 (3.22-48.5)	<.001	7.49 (1.93-29.07)	.004
Fever in ICU (>38.4°C)							
No	517	13	530	Ref.			
Yes	80	9	89	6.48 (2.11-19.94)	<.002	3.11 (1.03-9.39)	.04
Clinical suspicion of infection (either in ICU or at BDD day)							
No	499	12	511	Ref.	-		
Yes	98	10	108	4.59 (1.64-12.81)	<.001		
Negative ICU epidemiology[b]							
No	232	12	244	Ref.			
Yes	365	10	375	0.35 (0.12-0.99)	.049	0.44 (0.15-1.30)	.1
Positive ICU epidemiology[b]							
No	458	11	469	Ref.			
Yes	139	11	150	10.1 (0.9-112.9)	.06	8.77 (0.84-91.04)	.07
Macro geographical area							
North	298	4	305	Ref.			
Center	186	7	190	0.86 (0.18-4.04)	n.s.		
South and islands	113	11	124	3.71 (0.97-14.17)	.06	2.76 (0.80-9.53)	.1
Random effect: ICUs	Empty model[c]			Final model			
Latent ICC	46% (95% CI 21%-73%);		*P* (LRT χ^2)[d]: .0001	29% (95% CI 6.5%-72%); *P*-(LRT χ^2)[d]: .04			
Median OR	4.9						

BDD, brain death declaration; GN, gram negative; CR, carbapenem resistant; OR, odds ratio; CI, confidence interval; ICC, intraclass correlation coefficient; LRT, likelihood ratio test.

[a]OR ICU-adjusted of the mixed-effects logistic analysis.

[b]Missing disclosure in 94 cases, included in the nonnegative epidemiology and in the nonpositive epidemiology, respectively.

[c]Model with only ICU (random) effect included.

[d]LRT: test to evaluate the goodness-of-fit of the model.

the subsequent isolation of CR-GN on BDD day (OR = 3.08, *P* = .09) (Table S3).

3.5 | Used CR-GN donors and transplant outcomes

Thirty-seven patients received an organ from 15 donors with a CR-GN–positive culture—when the transplant was not related to the site of CR-GN isolation, total mortality at 90 days was 2/24 (8.3%), without any association with sepsis or CR-GN infection. When transplants were performed in the presence of CR-GN in the same site and/or in blood (9 kidney, 4 liver, 3 lung, 1 heart, 1 liver–kidney), mortality was 3/13 (23.1%). In 2 cases (1 lung, 1 liver) death was associated with early post-SOT CR-GN sepsis because of same donor CR-GN species (*K. pneumoniae* in BAL, *Acinetobacter B*. in blood, respectively). Genome typing was not performed (Table 6).

4 | DISCUSSION

In this national observational study, all patients with BDD in Italian ICUs were reviewed to quantify multidrug-resistant gram-negative bacteria in potential and utilized organ donors. To our knowledge, the DRIn study is the largest nationwide study focused on bacterial isolation in brain-dead subjects in a country where reporting of death declaration based on neurological criteria is mandatory by law, independent of the clinical possibility of organ donation and family consent.

4.1 | Adherence to safety recommendations

This study shows that 99% of used donors have been correctly screened for any bacteria isolated in blood, BAL, urine, and local infection sites before organ recovery. Nevertheless, ~20% of all BDDs were never tested by bacterial culture, regardless of the length of ICU stay, with concurrence of early family opposition to organ donation and improper attitude with regard to neglecting surveillance of dying patients. Finally, around one-fourth of donors had cultures only on the BDD day. These data are a warning sign concerning policies aimed at controlling spread of multidrug-resistant bacteria in several ICUs around the country.[29] Consequently, even safety standards regarding infections in organ donors and recipients may be weakened.

Unfortunately, Italy is among the countries with the highest prevalence of carbapenem-resistant Enterobacteriaceae. The rate of carbapenem resistance of *K. pneumoniae* has remained stable during the past few years (from 29.1% in 2012 to 29.7% in 2017). Thus, strategies aimed to prevent nosocomial transmission, particularly in the ICU setting, are strongly required. Screening of patients with rectal swab on admission has become a widely diffuse practice in many ICUs in Italy. However, patients with devastating brain injuries are often not adequately followed compared with patients with a potential to recover, and the concept that organ donation must be

TABLE 6 Transplants from 15 donors with carpapenem-resistant gram-negative bacteria: 3-month mortality due to sepsis probably related to donor-derived carbapenem-resistant gram-negative bacteria

	Organ transplanted and cause of death in recipients																	
	Heart			Lung			Liver			Kidney			Total transplants					
		Cause of death			Cause of death			Cause of death			Cause of death			Cause of death			Cause of death	
Site of isolation in donors CR-GN[a]	n	CR-GN sepsis	Other cause	n	CR-GN sepsis[b]	Other cause	n	CR-GN sepsis[b]	Other cause	n	CR-GN sepsis	Other cause	n	CR-GN sepsis[b]	Other cause[c]
Blood	1	—	—	—	—	—	1	1 (a)		6	—	—	8	1 (a)	0
Organ related	—	—	—	3	1 (b)	1	—	—	—	2	—	—	5	1 (b)	1
Organ unrelated	2	—	1	—	—	—	9	—	1	13	—	—	24	0	2
Total	3	0	1	3	1	1	10	1	1	21	0	0	37	2	3

GN, gram negative; CR, carbapenem resistant; BAL, bronchoalveolar lavage.

[a]CR-GN species and site of 24 isolations in 15 used donors: blood: 2 *Acinetobacter baumannii*, 1 *Klebsiella pneumoniae*; organ related: BAL 1 *Klebsiella pneumoniae*, 1 *Acinetobacter baumannii*, 1 *Pseudomonas aeruginosa*; urine: 1 *Acinetobacter baumannii*, 1 *Klebsiella pneumoniae*. Organ unrelated: BAL 5 *Klebsiella pneumoniae*, 3 *Acinetobacter baumannii*, 1 *Pseudomonas aeruginosa*; urine 2 *Acinetobacter baumannii*; rectal swab 3 *Klebsiella pneumoniae*, 2 *Acinetobacter baumannii*.

[b]CR-GN isolation in donors and sepsis in recipients: (a) liver transplant *Acinetobacter baumannii*; (b) lung transplant *Klebsiella pneumoniae*.

[c]Deaths unrelated to infection.

part of end-of-life treatment has not become a standard of care yet. Cultures are not performed for many brain-dead donors, despite the fact that the clinical grounds would require them. In addition, performing surveillance cultures, particularly of respiratory secretions, could allow an early detection of the colonization status. Although surveillance cultures could potentially lead to antibiotic overprescribing, consequently increasing the risk of antimicrobial resistance, the availability of microbiological information in the selected group of brain-dead potential organ donors might increase the safety of organ transplant.

4.2 | Bacterial detection

Bacterial detection was achieved in 51.7% of all tested BDDs and 62.6% of used donors, although only 9% and 9.4% of infections were clinically suspected in BDDs and used donors, respectively. Bacteremia was present in 10.2% of BDDs and 11.1% of used donors, confirming published rates in organ donors ranging from 14%[30] to 21%.[31] Possible negative effects of bacteremia on transplant outcome have been suggested in a large retrospective study in which information about the specific organisms isolated was not available.[32] Regardless, caution in interpreting these results is recommended to avoid wasting good organs for life-saving procedures.[33]

The present study focused principally on GN bacteria isolations and GN resistance to carbapenem, as indicated by antibiotic susceptibility in routine laboratory tests in each donor hospital based on European Committee on Antimicrobial Susceptibility Testing criteria.[24] No identification based on specific advanced and centralized analysis was addressed.

GN bacteria were isolated in 30.5% of all tested BDD subjects and were much more frequent in BAL than in samples from other sites. In particular, bloodstream GN isolates were not frequent, comprising only 10% of the total, but CR was found in one-third of the isolated GN bacteria. *K. pneumonia* was the most frequent GN, with a high rate of CR.

4.3 | CR-GN bacteria detection

CR-GN bacteria were detected in only 3.6% of all BDDs with at least a microbiological test performed in the ICU. Globally, DRIn data showed a rare occurrence of donors at risk for CR-GN transmission to recipients, despite the high diffusion of carbapenem resistance in Italian ICUs,[13] as confirmed by centers disclosing the proven or possible concomitant presence in the ICU of bacterial resistance in ~50% of enrolled BDD cases. The occurrence of CR-GN colonization/infection in the DRIn used donors is far lower than the percentage of CR-GN isolates (10.5%) not recognized before transplant among 170 donation after brain death donors retrospectively studied in 10 hospitals across southern Italy during the same year.[10]

Interpretation of this global incidence should be prudent considering that the highest rate of CR-GN isolations among BDDs (14%) belongs to the region with the lowest PMP rate of BDDs and a high number of missing disclosures regarding CR-GN isolations in ICU, possibly because of the heterogeneity of diffusion of carbapenem resistance among ICUs and suboptimal adherence to surveillance policies.[10,13,29] The large number of missing epidemiological disclosures may indicate a possible underestimation or overestimation of CR-GN presence in several ICUs.

4.4 | Risk factors for CR-GN bacteria isolation

Brain death occurred and was declared within 1 week of ICU stay, with possibly fewer risk factors for multidrug resistance than in the general ICU population, which experiences longer ICU stays, frequent comorbidities, previous hospital admissions, and repeated antibiotic treatments.[13]

Of 22 total cases with CR-GN isolation, none occurred when death was declared within 48 hours of ICU stay (51% of total BDDs). The association of CR-GN isolation in organ donors with prolonged ICU stay has been previously described.[31,34] DRIn data analysis by multivariable models suggested that the risk of CR-GN isolation was independently higher with ICU stays >3 days, fever, or clinical suspicion of infection during ICU management and in younger patients.

Considering the DRIn cases with at least a microbial test before the BDD day, previous isolation of non–CR-GN organisms during management in the ICU was associated with CR-GN isolation on the BDD day. In published cases with rectal swabs positive for CR *K. pneumoniae*, previous bloodstream infections (BSIs) caused by other pathogens (particularly *Enterococcus* spp. and Enterobacteriaceae) were associated with an increased risk of CR *K. pneumoniae* BSIs.[35] In a large meta-analysis, 16 risk factors, including longer ICU stay, previous antibiotic treatment, and carbapenem exposure, were associated with the development of CR *K. pneumoniae* infection.[34]

Finally, a considerable association was found between individual ICUs and CR-GN isolation, without a specific confinement in specific regions, even if the centers located in the southern part of the country, where preventive measures may be more tenuous, appear to have an increased risk (OR = 2.43) of CR-GN presence in brain-dead ICU patients. Because ICU characteristics were not included in the study design and no information was collected regarding antibiotic policies and infection preventive measures, the reasons for this variability cannot be further investigated. Nevertheless, ICU unfavorable epidemiology, antibiotic overprescribing, and inadequate infection control (ie, lack of antimicrobial stewardship programs) may be the most important avoidable risk factors for the diffusion of CR organisms among brain-dead potential organ donors.

National guidelines for the prevention and control of multiresistant microorganisms and for screening policies at hospital admission are limited to the recommendations for carbapenemase-producing Enterobacteriaceae (CPE) issued in 2013 by the Ministry of Health.[36] However, improvement actions have been implemented in few regions, including screening recommendations for the identification of asymptomatic carriers.[37]

Because efficacy of recommendations for the prevention of donor and recipient infections depends on concrete adherence to general preventive measures in ICU, including appropriate antimicrobial use, different results among regions and ICUs included in the DRIn study may be consequently explained. Recently, a national plan to combat antimicrobial resistance has been launched, one of its objectives being the production of national guidelines to prevent the spread of multidrug-resistant bacteria in hospitals and in ICUs.[38]

4.5 | CR-GN donor-derived transmission: miscommunication and site of isolation

Unexpected donor-derived infections causing severe complications in SOT patients occur in <1% of grafts.[4] Most adverse events related to donor-recipient transmission are the result of miscommunication [5,39] and delayed sharing of data among laboratories, coordinators, and transplant centers. In the present study, poor outcomes in transplant recipients may have been caused by a preventable delay in information or miscommunication of the results of cultures performed on the BDD day, in the absence of any previous data during the ICU stay. Thus, a lack of cultures for dying patients during ICU management before the day of death declaration may be an unacceptable and avoidable risk factor. Because no CR-GN isolation occurred within the early 48 hours in ICU and 80% of brain deaths were declared within 5 days, at least 1 set of cultures might be advisable on days 3 to 4 in addition to rectal swab on admission, particularly in ICUs at higher epidemiological risk.

The timing of proper information at the transplant center about CR-GN isolation in the donor may be a critical factor. Indeed, the results regarding BDD day cultures were not available in a timely manner for 14 of 15 used donors with CR-GN isolations, and 2 deaths related to CR-GN infection occurred among the recipients of organs recovered from these donors. In both recipients, transplanted organs were related to the site of CR-GN isolation (lung) or CR-GN BSI (liver). Thus, the site of CR-GN isolation in the donor appears to be critical for specific organ suitability and risk minimization: the use of organs from donors with CR-GN may be safe and appropriate if BSI is excluded and the site of isolation is carefully considered.[10,40]

The prospective nationwide surveillance study (Infection Surveillance in Transplantation)[41] that shortly followed the DRIn data collection and included lung and liver transplants during a 1-year period suggested a low risk of donor–recipient transmission of CPE: only 3 events of transmission were confirmed, involving *K. pneumonia* (in two cases) and Verona Integron-Mediated Metallo-beta-lactamase-producing *Enterobacter aerogenes*.[42] Notably, transmission occurred from 3 of 4 lung donors positive for CPE.

4.6 | Study limitations

This study reflects the specific and severe epidemiological situation of an endemic spread of carbapenem-resistant organisms in Italy. Nevertheless, the general principles and considerations could be relevant particularly to other developed countries.

The results should be interpreted considering the limitations of the study design. Local management policies and treatment have not been modified by the study, and data on antibiotic treatment and local practices of infection surveillance have not been collected. Moreover, the clinical trigger and the number and methodology of cultures might have introduced bias leading to the underrecognition of both gram-negative bacterial colonization and infection; results on agent isolation and carbapenem resistance might be affected by hospital laboratory standards and methods in ~200 different centers. Finally, no other clinical data for fever and clinical suspicion were requested to differentiate colonization from infection.

Because data were collected in 2012, important differences may currently exist in CR-GN prevalence and preventive policies; nevertheless, more recent prospective studies in transplant[41,42] and surveillance reports[20] suggest that the problem has been only partially controlled and that communication improvements and adequate awareness among ICU personnel and donor-transplant network are still pending.

A possible bias may arise from the marked differences among Italian regions in the number of BDDs per million population (from 20 to 72 PMP). In fact, multiple clinical, cultural, and organizational factors, including donor suitability pre-selection, may lead to a number of "silent" missing brain deaths, estimated as 10%-25% in the entire country,[43] eventually affecting the enrolled BDD subjects in the DRIn study.

Despite these limitations, the data represent the reality of the national clinical scenario and the information considered for decisions on donor suitability and organ utilization.

5 | CONCLUSIONS

Absolute prevention of donor–recipient transmission of bacterial infections is not possible, but strict adherence to clinical guidelines and optimal compliance with multimodal infection control and cost-effective surveillance programs[41] can minimize the risk of infection caused by multidrug-resistant agents in organ donors and transplanted patients.

A structured antimicrobial stewardship program should be implemented throughout the country as recommended, for example, by the Italian National Plan to Combat Antimicrobial Resistance issued in 2017.[38]

The possibility of consulting, through the national transplant network for 24 hours a day, a second expert opinion (expert in infectious disease and transplant medicine)[2,44] may increase the number of used donors, promoting both recipient safety and ICU environmental control.

The results of the DRIn study suggest that a prolonged ICU stay, fever, and clinical suspicion of an ongoing infection are associated with the isolation of carbapenem-resistant gram-negative bacteria in utilized organ donors.

Cases of probable donor–recipient transmission of carbapenem-resistant gram-negative bacteria were few, but clinical consequences

included sepsis and death when CR-GN was isolated from the blood or transplanted organ. The Italian recommendations for organ suitability have been consequently updated.[45]

All network actors should have culture results such as antibiotic susceptibility before deciding about organ use. Overall, the results of this study suggest that organ transplant outcomes can be further improved by implementing better practices in the ICU and enhancing targeted information management in a more integrated transplant network.[46]

Consequently, a major aim is to increase awareness among ICU personnel and donor-transplant networks regarding the prevention and early detection of CR-GN infection/colonization in all the possible donors. Simple improvements in ICU-laboratory procedures for timely communication would facilitate decisions regarding organ suitability and eventually save the lives of recipients.

Specific safety procedures may be adopted, as follows: a laboratory trigger system for early CR-GN alert and expert second opinion consultation in cases of preliminary CR-GN positivity; serial timely cultures (ie, ≥2 or more serial cultures), including rectal swab and surveillance cultures of respiratory secretions to allow an early detection of the colonization status, in addition to the mandatory BDD day cultures; use of advanced test methodology for multidrug resistance identification ensuring rapid and reliable results in selected cases[6,47-49]; postponed organ utilization with ex situ perfusion; and, in the next future, ex situ organ antibiotic treatment.[50,51]

Continuous education of intensive care, laboratory, and coordination office and transplant center personnel aimed at implementing incisive priority actions,[52] including stewardship programs for a rational use of antimicrobials and effective prevention of infections among hospitalized patients, represents a top priority in health systems and transplant networks.

DISCLOSURE

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX

Donor-Recipient Infection (DRIn) Collaborative Study Group

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