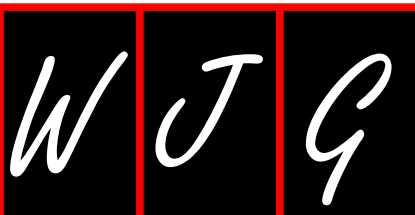


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EDITORIAL

- 5645 Direct-acting antiviral agents against hepatitis C virus and lipid metabolism

Kanda T, Moriyama M

REVIEW

- 5650 Liquid biopsy in patients with hepatocellular carcinoma: Circulating tumor cells and cell-free nucleic acids

Okajima W, Komatsu S, Ichikawa D, Miyamae M, Ohashi T, Imamura T, Kiuchi J, Nishibeppu K, Arita T, Konishi H, Shiozaki A, Moriumura R, Ikoma H, Okamoto K, Otsuji E

ORIGINAL ARTICLE

Basic Study

- 5669 Fluctuation of zonulin levels in blood vs stability of antibodies

Vojdani A, Vojdani E, Kharrazian D

- 5680 Effects of albumin/glutaraldehyde glue on healing of colonic anastomosis in rats

Despoudi K, Mantzoros I, Ioannidis O, Cheva A, Antoniou N, Konstantaras D, Symeonidis S, Pramateftakis MG, Kotidis E, Angelopoulos S, Tsalis K

- 5692 Cytoplasmic domain of tissue factor promotes liver fibrosis in mice

Knight V, Lourensz D, Tchongue J, Correia J, Tipping P, Sievert W

- 5700 *Schistosoma japonicum* attenuates dextran sodium sulfate-induced colitis in mice *via* reduction of endoplasmic reticulum stress

Liu Y, Ye Q, Liu YL, Kang J, Chen Y, Dong WG

- 5713 Metabolomic profiling for identification of metabolites and relevant pathways for taurine in hepatic stellate cells

Deng X, Liang XQ, Lu FG, Zhao XF, Fu L, Liang J

- 5722 Protective effects of *Foeniculum vulgare* root bark extract against carbon tetrachloride-induced hepatic fibrosis in mice

Zhang C, Tian X, Zhang K, Li GY, Wang HY, Wang JH

Retrospective Cohort Study

- 5732 Hypothesized summative anal physiology score correlates but poorly predicts incontinence severity

Young CJ, Zahid A, Koh CE, Young JM

- 5739 Minor endoscopic sphincterotomy followed by large balloon dilation for large choledocholith treatment
Xu XD, Chen B, Dai JJ, Qian JQ, Xu CF
- 5746 Diagnostic value of FIB-4, aspartate aminotransferase-to-platelet ratio index and liver stiffness measurement in hepatitis B virus-infected patients with persistently normal alanine aminotransferase
Tan YW, Zhou XB, Ye Y, He C, Ge GH
- Retrospective Study**
- 5755 Accuracy of endoscopic ultrasound-guided tissue acquisition in the evaluation of lymph node enlargement in the absence of an on-site pathologist
Chin YK, Iglesias-Garcia J, de la Iglesia D, Lariño-Noia J, Abdulkader-Nallib I, Lázare H, Rebolledo Olmedo S, Dominguez-Muñoz JE
- 5764 Doublecortin and CaM kinase-like-1 as an independent poor prognostic factor for resected pancreatic carcinoma
Nishio K, Kimura K, Amano R, Nakata B, Yamazoe S, Ohira G, Miura K, Kametani N, Tanaka H, Muguruma K, Hirakawa K, Ohira M
- 5773 Study to determine guidelines for pediatric colonoscopy
Yoshioka S, Takedatsu H, Fukunaga S, Kuwaki K, Yamasaki H, Yamauchi R, Mori A, Kawano H, Yanagi T, Mizuochi T, Ushijima K, Mitsuyama K, Tsuruta O, Torimura T
- 5780 Postoperative changes of manometry after restorative proctocolectomy in Korean ulcerative colitis patients
Oh SH, Yoon YS, Lee JL, Kim CW, Park IJ, Lim SB, Yu CS, Kim JC
- 5787 Threonine and tyrosine kinase may serve as a prognostic biomarker for gallbladder cancer
Xie Y, Lin JZ, Wang AQ, Xu WY, Long JY, Luo YF, Shi J, Liang ZY, Sang XT, Zhao HT
- 5798 Simple instruments facilitating achievement of transanal total mesorectal excision in male patients
Xu C, Song HY, Han SL, Ni SC, Zhang HX, Xing CG
- 5809 Donor-derived infections among Chinese donation after cardiac death liver recipients
Ye QF, Zhou W, Wan QQ

CASE REPORT

- 5817 Rarity among benign gastric tumors: Plexiform fibromyxoma - Report of two cases
Szurian K, Till H, Amerstorfer E, Hinteregger N, Mischinger HJ, Liegl-Atzwanger B, Brcic I
- 5823 Tegafur-uracil-induced rapid development of advanced hepatic fibrosis
Honda S, Sawada K, Hasebe T, Nakajima S, Fujiya M, Okumura T

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Retrospective Study

Donor-derived infections among Chinese donation after cardiac death liver recipients

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Abstract

AIM

To investigate blood cultures of deceased donors and report the confirmed transmission of bacterial infection from donors to liver recipients.

METHODS

We retrospectively studied the results of blood cultures among our donation after cardiac death (DCD) donors and calculated the donor-derived bacterial infection rates among liver recipients. Study participants underwent liver transplantation between January 1, 2010 and February 1, 2017. The study involved a total of 67 recipients of liver grafts from 67 DCD donors. We extracted the data of donors' and patients' characteristics, culture results and clinical outcomes, especially the post-transplant complications in liver recipients, from electronic medical records. We analyzed the characteristics of the donors and the corresponding liver recipients with emphasis put on donor-derived infections.

RESULTS

Head trauma was the most common origin of death among our 67 DCD donors (46.3%). Blood taken prior to the procurement operation was cultured for 53 of the donors, with 17 episodes of bloodstream infections developing from 13 donors. The predominant organism isolated from the blood of donors was Gram-positive bacteria (70.6%). Only three (4.5%) of 67 liver recipients developed confirmed donor-derived bacterial infections,

with two isolates of multidrug-resistant *Klebsiella pneumoniae* and one isolate of multidrug-resistant *Enterobacter aerogenes*. The liver recipients with donor-derived infections showed relation to higher crude mortality and graft loss rates (33.3% each) within 3 mo post transplantation, as compared to those without donor-derived infections (9.4% and 4.7%, respectively). All three liver recipients received appropriate antimicrobial therapy.

CONCLUSION

Liver recipients have high occurrence of donor-derived infections. The liver recipients with donor-derived multidrug-resistant *Enterobacteriaceae* infections can have good outcome if appropriate antimicrobial therapy is given.

Key words: Liver transplant; Donation after cardiac death donor; Infection; Multidrug resistant; Bacteria; Transmission

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Core tip: This study aimed to investigate blood cultures of donation after cardiac death (DCD) liver donors and report the confirmed transmission of bacterial infection from donors to liver recipients. The predominant organism isolated from the blood of donors was Gram-positive bacteria (70.6%). Only three (4.5%) of 67 liver recipients developed confirmed donor-derived bacterial infections, with two isolates of multidrug-resistant *Klebsiella pneumoniae* and one isolate of multidrug-resistant *Enterobacter aerogenes*. Our findings support that liver grafts from DCD donors with bloodstream infections owing to multidrug-resistant *Enterobacteriaceae* can be used if the donors and recipients receive appropriate antimicrobial therapy.

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INTRODUCTION

Liver transplantation is currently considered the therapy of choice for patients with end-stage liver disease. Organs from infected donors after cardiac death (DCD), such as those with bacteremia, are now utilized in response to the disparity between the available graft pool and the organ need for liver transplantation, which carries risk of transmission of infectious diseases and death^[1-5]. The risk of unanticipated disease transmission to liver recipients via donor grafts has been gaining research attention. Donor-derived transmission of infections remains a rare complication of liver transplantation and the studies have supported its overall safety and favorable outcomes^[6-13]; however, the outcome of this type of infection itself

among liver recipients is controversial and some authors suggest that it is associated with significant mortality^[14,15].

As the volume of liver recipients increases, the number of infections transmitted through DCD donors can also be expected to rise. Unfortunately, the data of DCD donor-derived infections following liver transplantation are currently lacking in China. We, therefore, aimed to investigate the blood cultures of DCD donors and report the cases of confirmed (proven/probable) transmission of bacterial and fungal infections from donors to liver recipients. The current study provided, to our best knowledge, the first finding of liver recipients experiencing confirmed donor-derived bacterial infections in China and this report represents the largest series of liver recipients with donor-derived infections due to multidrug-resistant (MDR) *Enterobacteriaceae* in the world thus far.

MATERIALS AND METHODS

Study population

This retrospective analysis of a single-center population was conducted with the purpose of recording all liver recipients with donor-derived bacterial infections. All involved human participants had been initially recruited to the study between January 1, 2010 and February 1, 2017. We then searched the medical record systems of the Third Xiangya Hospital (Changsha, China) to identify all DCD donors and liver recipients who received grafts from DCD donors. The recorded information allowed for identification of individual participants during or after data collection.

The final study population consisted of 67 liver recipients of grafts from 67 DCD donors who had been admitted to the intensive care unit (ICU) of the Department of Transplant Surgery, the Third Xiangya Hospital of Central South University before organ procurement and transplantation. Multi-organ transplant recipients were excluded from the study. Data recorded included donor age, sex, category, length of ICU stay, number of donors with/without available results of blood cultures, bacteria and fungi isolated from donors, antibiotic administration, and cause of death. The procedures used for donor screening, donor treatment for bacterial and fungal infections, and obtainment of the liver graft were also recorded. Liver graft recipient data representing variables associated with donor-derived infections were collected from the medical records as well, and included age, sex, underlying liver diseases, site of infection, time of infection onset, organisms, antimicrobial use, immunosuppressive therapy, and crude mortality/graft loss. The data of post-liver transplant complications were collected for all liver recipients. For all liver graft recipients, the maintenance immunosuppression was tacrolimus/cyclosporin complemented with prednisone tapered to 5-10 mg/d. All liver graft recipients were followed for at least 3 mo post transplantation or until death.

Donor screening and treatment for bacterial and fungal infections

In our hospital, any DCD donor with a history or suspicion of prior bloodstream infection from whom a liver graft will be harvested is subject to a detailed and appropriate investigation to ensure that infection is not present in the liver. To rule out the presence of active infection, our hospital also takes a complete history from the donor's family and performs a thorough review of the medical records, including vital signs and findings of physical, radiographic and any available microbiologic tests. Most of the donors in this study also underwent routine culturing of blood, urine and sputum. Blood cultures were obtained to rule out occult donor infection, especially among donors at "increased" risk for bacteremia or fungemia^[16]. Targeted antibiotics were administered to the infected donor for at least 24 h, with some degree of clinical response (improved white blood cell count and hemodynamics, and defervescence) and, if possible, the infected donor's treatment included documentation of the infection resolution prior to donation.

Obtaining liver grafts

All cases of organ donation were performed according to the protocols for China categories I, II and III donors^[17]. After informed consent was obtained from the donor's family, life supports were removed. After the legal 5-min standoff time, the donor immediately underwent a "super-rapid" procurement technique in the operating room. In brief, a rapid abdominal incision was made, followed by rapid cannulation of the abdominal aorta and superior mesenteric or portal vein. The liver was then perfused with University of Wisconsin solution and prompt hepatectomy was performed. The intra-abdominal organs were removed *en bloc*, submerged in University of Wisconsin solution at 4 °C, and placed in cold storage. The bile duct was flushed with physiological saline solution *in situ* and preserved *ex situ* with University of Wisconsin solution.

Recipient prophylactic strategies and treatments for bacterial and fungal infections

Second- or third-generation cephalosporins, semisynthetic penicillins/beta-lactamase inhibitors, or carbapenems, were prescribed according to the pre-transplant results of cultures and administered 1 h before the liver transplantation, with an additional dose given at 72 h post transplantation to the liver recipients without donor-derived infections. Recipients of liver graft from a bacteremic donor were treated with a 7-d to 14-d course of targeted antibiotics. Antifungal therapy was administered within 2 wk to a recipient of liver graft from a donor with fungemia if the liver recipient had no evidence of infection. Cases of established fungal infection were administered a 4-wk to 6-wk course, with at least 6 wk of treatment, when vascular involvement was present.

Definitions

The deceased-organ donations were classified as follows: China category I (C-I), organ donation after brain death; China category II (C-II), organ donation after circulatory death; and China category III (C-III), organ donation after brain death followed by circulatory death^[17].

Transmission of organisms was considered proven by clear evidence of the same infection in the donor and at least one of the recipients. Transmission of the organisms was considered probable by strong evidence suggesting but not proving infectious transmission, such as the infection being documented in more than one recipient but not diagnosed in the donor^[18]. Both proven and probable transmissions were considered as confirmed transmission of infections^[18]. Appropriate antimicrobial use in donors was considered when the infected donor had received targeted antimicrobial treatment for at least 24-48 h, optimally with some degree of clinical response^[19]. Appropriate antimicrobial use in recipients was considered if the isolated organisms showed *in vitro* susceptibility to empirical antibiotics, which were administered within 48 h of sampling for culture^[20].

We utilized the standardized definition of MDR *Enterobacteriaceae*, as previously defined by international consensus in 2012; specifically, MDR was considered with evidence of non-susceptibility to at least one agent in three or more appointed antimicrobial categories^[21].

RESULTS

DCD donor characteristics

There were 67 liver recipients of grafts from 67 DCD donors during the study period. The characteristics of the donors are shown in Table 1. The DCD donors showed a male-dominated sex ratio (nearly 1:4) and were largely represented by young adults. The pre-retrieval ICU length of stay ranged from 1 d up to 41 d. Head trauma was the most common cause of death, followed by benign central nervous system tumor. The majority of donors were classified as China category III, followed by China category II.

Cases of infectious transmission from DCD donors to liver graft recipients

For 53 of the donors (79.1%), the blood samples taken prior to the procurement operation were cultured and produced evidence of 17 bloodstream infections from 13 of the donors. Appropriate antimicrobial use, according to the positive blood culture results, was administered in 10 of those 13 donors. The results of blood cultures from the donors are shown in Table 2. The majority of pathogens isolated from the donor's blood were coagulase-negative *Staphylococci*. Among the three donors who elicited infectious transmission to three liver recipients, one donor did not have an available result of blood culture and the other two donors had negative

Table 1 Characteristics of the 67 donation after cardiac death donors *n* (%)

Characteristic	Value
Age in years, median (IQR)	29.0 (19.0-44.0)
Sex	
Male	55 (82.1)
Female	12 (17.9)
Origin of death	
HT	31 (46.3)
Benign CNS tumor	18 (26.9)
CVA	15 (22.4)
Anoxia	2 (3.0)
Meningitis	1 (1.5)
China classification of donation	
I	5 (7.5)
II	8 (11.9)
III	54 (80.6)
ICU stay in days, median (IQR)	5 (3.0-10.0)
Donors with positive culture	13
Blood culture, <i>n/n</i>	
Donors with/without available results	53/14
Donors with appropriate antimicrobial use/all donors with positive blood culture results	10/13

CNS: Central nervous system; CVA: Cerebrovascular accident; DCD: Donation after cardiac death; HT: Head trauma; ICU: Intensive care unit; IQR, Interquartile range.

Table 2 Classification and percentage of organisms isolated from donors' bloodstream, *n* = 17

Organism	<i>n</i> (%)
Gram-positive bacteria	12 (70.6)
<i>Staphylococcus aureus</i>	3 (17.6)
Coagulase-negative staphylococci	9 (52.9)
<i>S. epidermidis</i>	4 (23.5)
<i>S. hemolyticus</i>	1 (5.9)
<i>S. capitis</i>	1 (5.9)
<i>S. hominis</i>	2 (11.8)
<i>S. simulans</i>	1 (5.9)
Gram-negative bacteria	3 (17.6)
<i>Klebsiella pneumoniae</i>	2 (11.8)
<i>Acinetobacter baumannii</i>	1 (5.9)
Fungi	2 (11.8)
<i>Candida albicans</i>	1 (5.9)
<i>Candida parapsilosis</i>	1 (5.9)

results of blood culture after being admitted to the ICU; none of these three donors underwent blood culture within 10 d prior to organ procurement.

Infectious agents transmitted from DCD donors to liver graft recipients

Table 3 shows the characteristics of these three donors (D1-D3) and their corresponding liver recipients (R1-R3, representing 4.5% of the total recipient population), highlighting the relationship between donors and recipients with infection transmission. Several cultures (blood, urine, and abdominal drainage fluid) were routinely taken from the recipients following the liver transplantation. The confirmed donor-derived MDR bacterial infections included two isolates of *Klebsiella pneumoniae* and one isolate of *Enterobacter aerogenes*.

Both of the *Klebsiella pneumoniae* isolates were extended-spectrum beta lactamase-producing rods. All three of the isolates (all being *Enterobacteriaceae* family members) were carbapene-susceptible.

Recipient characteristics and outcomes of infectious transmissions from DCD donors to liver graft recipients

Additional isolates from four recipients of kidney grafts from these three donors (D1-D3) provided strong evidence of transmission of infectious bacteria through their similar resistance profiles. Thus, no recipient case of infection transmission could be classified as a proven donor-derived infection, and all three cases (R1-R3) were classified as probable donor-derived infections. No liver recipients developed donor-derived fungal infections. No recipients had a presumed or confirmed invasive bacterial or fungal infection before transplantation. The underlying liver diseases of these three recipients were polycystic liver disease, hepatocellular carcinoma and cirrhosis due to hepatitis B virus infection, and hereditary familial amyloidosis. All three donor-derived infections occurred within 3 d post transplantation, and were administered appropriate anti-microbial therapy prior to or immediately following diagnosis of the infection. All three recipients recovered from the donor-derived bacterial infections, but one died of septic shock with graft loss owing to other organisms. Liver recipients without donor-derived infections had lower rates of crude mortality and graft loss [6/64 (9.4%) and 3/64 (4.7%), respectively] within 3 mo post transplantation, as compared with those with donor-derived infections (33.3% each).

Post-liver transplant complications in liver graft recipients with and without DCD-derived infections

All complications experienced by the full liver recipient population (*n* = 67) are presented in Table 4. The most common complication was post-transplant infection; the 20 total infections occurred in the three liver recipients with donor-derived infections (4 infection episodes) and the 64 liver recipients without donor-derived infections (16 infection episodes). The next most common complication was vascular (9 vascular episodes), all cases of which occurred in the liver recipients without donor-derived infections. Tumor recurrence developed in six of the liver recipients without donor-derived infections and none of the recipients with donor-derived infections.

Survival of liver graft recipients with and without DCD-derived infections

Figure 1 shows the Kaplan-Meier curves for 3-mo survival after liver transplantation. There was no difference in survival between the liver recipients with and without donor-derived infection (log-rank test, *P* = 0.165).

DISCUSSION

Although there are numerous reports of fatal donor-

Table 3 Characteristics of donors and their corresponding liver recipients with donor-derived infections

Donor	Diagnosis	Blood culture result	Recipient (sex/age)	Underlying liver disease(s)	Culture result (specimen)/time to infection onset	Inappropriate antimicrobial/immunosuppressive therapy	Outcome
D1	Head trauma	Negative ¹	R1 ² (Female/48 yr)	Polycystic liver disease	<i>K. pneumoniae</i> (Blood and abdominal drainage fluid)/1 d	No/Pred	Patient death and graft loss
D2	Head trauma	Negative ¹	R2 ³ (Male/38 yr)	Hepatocellular carcinoma and cirrhosis due to hepatitis B virus infection	<i>K. pneumoniae</i> (Blood and abdominal drainage fluid)/1 d	No/FK506 + Pred	Patient and graft survival
D3	Head trauma	Not available	R3 ³ (Male/69 yr)	Hereditary familial amyloidosis	<i>E. aerogenes</i> (Blood)/3 d	No/FK506 + Pred	Patient and graft survival

¹Donors had a negative result of blood culture after being admitted to the intensive care unit, whereas they did not undergo blood culture within 10 d prior to organ procurement; ²Two kidney recipients of graft from the common donor, with this liver recipient having developed organ-space surgical site infection owing to *Klebsiella pneumoniae* within 20 d following the transplantation; ³One kidney recipient of graft from the common donor, with this liver recipient having also developed bloodstream infection owing to the same bacterium immediately after the transplantation.

Table 4 Comparison of post-liver-transplant complications in liver recipients with and without donor-derived infections

Complication	Episodes of complications in three liver recipients with donor-derived infections	Episodes of complications in 64 liver recipients without donor-derived infections
Infection	4	16
Pneumonia	1	7
Peritonitis	0	3
Bloodstream infection	3	5
Surgical site infection	0	1
Vascular complications	0	9
Portal vein thrombosis	0	1
Cerebral embolism	0	1
Hepatic artery thrombosis	0	1
Abdominal bleeding	0	5
Gastrointestinal bleeding	0	1
Biliary complications	3	2
Bile leakage	0	0
Biliary strictures	1	2
Stone formation	1	0
Bilomas	1	0
Recurrent tumor	0	6
Acute rejection	0	4
Graft-versus-host disease	0	2
Graft dysfunction	0	3
Adhesive ileus	0	1

derived infections affecting around 3% of solid organ transplants, in the current era of organ shortage marginal organ donors are increasingly utilized^[22,23]. More recent data demonstrate that most bacterial isolates appear to be irrelevant to subsequent recipient outcome and that the grafts from bacteremic donors may be safely used if bacteremia in the donor has been ideally treated and antibiotic therapy is continued in the organ recipient^[2,6,7,24,25].

Our present study found 19.4% (13/67) of donors having available results of blood cultures developed bloodstream infections, which is in line with literature reports suggesting that about 5%-11.3% of all deceased donors have unrecognized bacteremia at the time of donation^[2,6,8,25]. We also found that three (4.5%) of 67 donors transmitted bacterial infections to three liver

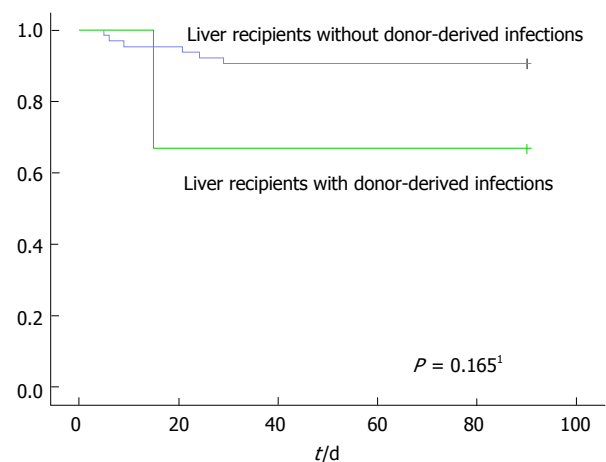


Figure 1 Kaplan-Meier curves for 3-mo survival after liver transplantation. ¹Log-rank test indicated no significant difference in survival between the two groups.

recipients, which agrees with the 2013 report^[26] from the Organ Procurement and Transplantation Network Ad Hoc Disease Transmission Advisory Committee that reported 15 (12.8%) out of 117 donors with infections developed proven/probable transmission of bacterial (except for tuberculosis) and fungal infections.

Doucette *et al.*^[3] proposed that the observed higher risk of transmission in liver recipients, as compared to other solid organ recipients, may be mainly attributed to bacterial retention in and poor antibiotic penetration of the liver graft. Some recipient-related factors were also proposed, such as a high Model for End-Stage Liver Disease (commonly known as MELD) score, leukopenia, and immunosuppression.

Coagulase-negative *Staphylococci* (such as *Staphylococcus epidermidis*) and *Staphylococcus aureus* represent the more commonly isolated microorganisms from donor blood cultures^[7,8,25]. In our donor blood cultures, the majority of isolates were coagulase-negative *Staphylococci* and *S. aureus* (together 70.6%; 12 of 17 pathogens). Coagulase-negative *Staphylococci* also represent the most common microorganisms isolated from preservation fluid^[2,15,27]. None of the cases

of donor-derived infections in liver recipients of our study were due to Gram-positive bacteria, agreeing with previous studies that have suggested lower risk of transmission of Gram-positive bacteria (vs Gram-negative bacteria) from a donor to a recipient^[6,28-30]. This could be due to several reasons, such as low pathogenicity of coagulase-negative *Staphylococci*, potential contamination in donor culture (*i.e.*, not a true pathogen), or catheter line-associated infection in donor (*i.e.*, non-systemic infections).

All three donor-derived infections in our current study were caused by MDR Gram-negative bacteria, agreeing with a previous report suggesting that Gram-negative bacteria account for about 80% of transmissions to recipients^[9]. Although rare, donor-derived infections caused by bacteria, in particular MDR bacteria, can have devastating consequences for organ transplant recipients^[9-11,29,31]. The data reported to the United States' Organ Procurement and Transplantation Network from 2005 to 2011 showed the donor-derived infection-attributable recipient mortality rate to be 29.2% (19/65)^[6]. These previous studies are consistent with our present study, wherein one (33.3%) of three liver recipients with MDR *Klebsiella pneumoniae* infection died from subsequent septic shock due to other organisms and the rate of graft loss was 33.3%. In contrast with our finding, however, others have reported a favorable outcome among liver recipients with donor-derived infections due to MDR Gram-negative bacteria or methicillin-resistant *S. aureus* (commonly known as MR SA)^[3,5,9-11,23,32-34]. Further data are needed to assess the effects of donor-derived bacterial or fungal infections and appropriate antimicrobial use on allograft function and recipient survival over a long-term follow-up period.

The current study has provided, to the best of our knowledge, the first data of liver recipients with confirmed donor-derived bacterial infections treated in a single transplant center in China; in addition, the report represents the largest of liver recipients with donor-derived infections due to MDR *Enterobacteriaceae* in the world thus far. Since both the morbidity and mortality rates of donor-derived infections are high in China, the findings from the current study support future efforts towards a better understanding of potential risks for disease transmission and highlight the necessity for a standardized critical incident reporting system in the Chinese transplant system to improve short- and long-term allograft and recipient survival.

The principal limitation of our study was the single-center, retrospective study design, which did not allow for the investigation of donor-derived MDR bacterial infections by genetic or molecular analysis. Improvements in new screening technologies, such as the use of whole genome sequencing, have recently proven a powerful advance in the investigation of donor-derived MDR bacterial infections^[35]. Since we used drug-sensitive test screening for donor-derived infections rather than a gene-level technique, it is possible that our testing algorithm over-estimated the transmission events.

Nonetheless, our findings underscore the importance of blood culture being performed as close to the donation time as possible and the importance of testing preservation fluid culture; since the reported contamination rates of the latter range widely (from 9.5% to 98.4%)^[2,15,27], this sample was not routinely obtained at our institution. Our findings also indicate that donors with infections should receive antibiotics directed at the identified bacteria or fungi 24-48 h prior to procurement, optimally yielding evidence of clinical improvement.

In conclusion, DCD donors in our institute had a high rate of bacterial infection, with Gram-positive bacteria being the predominant isolate, whereas the donor-derived infections developed by liver recipients were Gram-negative predominant. Our findings strongly support organ donation as the common source of bacterial infection in the liver recipients. Although the number of these cases in our study was too small to draw conclusions, we support the use of liver grafts from the DCD donor pool, including those with infections owing to MDR *Enterobacteriaceae* if the donors and recipients receive appropriate antimicrobial therapy.

COMMENTS

Background

Nowadays, the use of bacteremic donors to fulfill the disparity between the limited donor pool and the increasing need for organs is an expanding practice, which may result in an increased risk of transmission of infectious diseases and death. However, the data of donation after cardiac death (DCD) donor-derived infections following liver transplantation are currently lacking in China. As limited data are available in Chinese liver recipients of grafts from DCD donors, this study aimed to investigate the blood cultures of DCD donors and report the cases of confirmed (proven/probable) transmission of bacterial and fungal infections from donors to liver recipients.

Research frontiers

The use of infectious donors to fulfill the disparity between the limited donor pool and the increasing need for organs has become an important issue in the field of transplantation. Furthermore, the use of donors with infections caused by multidrug-resistant (MDR) bacteria is controversial and the recipients with MDR infections have a high mortality. This study shows excellent outcome for liver recipients with donor-derived MDR infections.

Innovations and breakthroughs

This is the first study to analyze liver recipients experiencing confirmed donor-derived bacterial infections in China and the largest report of liver recipients with donor-derived infections due to MDR *Enterobacteriaceae* in the world thus far.

Applications

Liver grafts from the pool of DCD donors with bloodstream infections owing to MDR *Enterobacteriaceae* can be used if the donors have been treated and have documentation of resolution of infection prior to donation, and if the corresponding liver recipients are treated with a 7- to 14-d course of antibiotics targeted to the organism isolated from a bacteremic donor.

Terminology

Confirmed transmission includes a proven or probable transmission. A proven transmission was indicated by clear evidence of the same infectious disease in the donor and at least one of the recipients. A probable transmission was indicated by strong evidence suggesting, but not proving, a disease transmission, such as the disease being documented in more than one recipient but not being diagnosed in the donor. MDR bacteria were defined as those non-susceptible to at least one agent in three or more appointed antimicrobial categories.

Peer-review

Although sample size was small, this paper provides important information. This report shows excellent outcomes for recipients with donor-derived infections.

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