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Case Report

Donor-Derived Bacteremia in Liver Transplant Recipients Despite Antibiotic Prophylaxis

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As the disparity between the number of candidates listed for transplant and the number of donors continues to grow, marginal organ donors are increasingly utilized. This includes bacteremic donors which may carry an increased risk of transmission of infection. It is recommended that recipients of organs from bacteremic donors receive antibiotic prophylaxis based on the susceptibilities of the donor isolate to prevent transmission. Here, we present four cases of donor-derived bacteremia, despite appropriate antimicrobial prophylaxis, in four liver transplant recipients. Transmitted pathogens included *Staphylococcus aureus* in two cases, and Escherichia coli and Group B Streptococcus each in one case. Interestingly, none of the nonhepatic organs (n = 10) utilized from these bacteremic donors resulted in transmissions. These cases highlight the fact that risk of transmission from bacteremic donors is not eliminated with antimicrobial therapy in the donor and recipient. As no transmissions occurred in recipients of nonhepatic organs from these donors, these cases also suggest that liver recipients may be at higher risk of donor transmitted bacteremia.

Key words: Bacterial infection, donor-to-host-transmission, infectious complications, liver transplantation

Abbreviations: LT, liver transplantation; MELD, model for end-stage liver disease; MSSA, methicillin-susceptible *S. aureus*; PELD, pediatric end-stage liver disease.

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Background

The number of patients awaiting organ transplantation is continuously rising and deaths on the transplant wait list are increasing (1). Accepting "marginal" donors, including those with increased risk to transmit diseases to their recipients, can expand the donor pool. Although bacteremia in the organ donor can result in early posttransplant sepsis or mycotic aneurysm formation at the site of the vascular anastomosis (2), studies have shown no evidence of transmission when directed antimicrobial prophylaxis is given to the recipient posttransplant (3,4).

Between March 2009 and April 2012, we detected four cases of transmission of donor-derived bacteremia to liver transplant (LT) recipients at our center, despite appropriate antibiotic prophylaxis. Here we describe the cases and outcomes and discuss the potential implications of our observations and areas for future research.

Case 1

A 25-year-old woman with a model for end-stage liver disease (MELD) score of 28 underwent LT for autoimmune cirrhosis. The donor was a 67-year-old woman with bacterial meningitis on empiric therapy with vancomycin, ampicillin and ceftriaxone. Blood and cerebrospinal fluid (CSF) cultures were positive for *Staphylococcus aureus.* Eleven hours after admission she was declared brain dead. The liver, lungs and kidneys were accepted for transplant. The donor had been on 24 hours of antimicrobial therapy with negative repeat blood cultures at organ procurement.

With susceptibilities pending, the liver recipient received 1 g of intravenous vancomycin on call to the operating room. Surveillance blood cultures drawn 50 min after the end of the case became positive for *S. aureus* at 21.5 h of incubation. The recipient was afebrile with no clinical evidence of infection. The donor and recipient isolates were confirmed to be methicillin-susceptible *S. aureus* (MSSA) with an indistinguishable fingerprinting pattern by pulsed field gel electrophoresis (PFGE; Ref. 5); Figure 1). A Doppler ultrasound of the transplanted liver revealed normal flow in the hepatic artery and no evidence of abscess. Repeat blood cultures were negative. The recipient remained clinically stable and completed 4 weeks of cefazolin. At 3 years posttransplant, there have been no sequelae attributable to her donor transmitted infection.

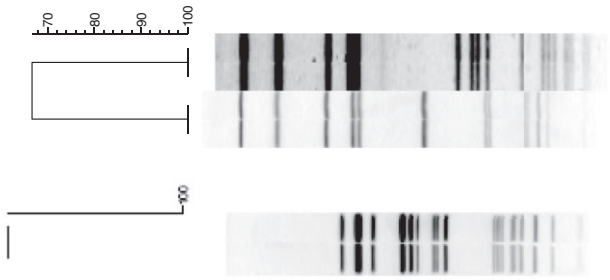

Figure 1: A (Case1) and B (Case2) Pulsed field gel electrophoresis demonstrating indistinguishable donor and recipient strains of *S. aureus*. Fingerprints were generated by PFGE analysis with the protocol as described by Mulvey et al. (5). 1C (Case 3): Pulsed field gel electrophoresis demonstrating indistinguishable donor and recipient strains of *E. coli*.

The double-lung and two kidney recipients had negative postoperative surveillance blood cultures. They each received 2 weeks of antimicrobial therapy active against the donor isolate with no evidence of donor-derived infection on long-term follow-up.

Case 2

A 60-year-old man with end-stage liver disease secondary to alcohol and hepatitis C had a MELD of 42 and received a LT from a 57-year-old donor. The donor had MSSA bacteremia, wound infection, septic pulmonary emboli and meningitis 2 weeks following lumbar spine laminectomy. After 36 hours of empiric therapy with vancomycin, clindamycin and ceftriaxone, he was declared brain dead and organs offered. Repeat blood cultures were negative at the time of the offer of organs; however, these were reported as positive during procurement, at 18 h of incubation.

The liver and kidneys were accepted. All recipients were started on cloxacillin 2 g intravenously every 4 h preoperatively. Surveillance blood cultures from the liver recipient 90 min postoperatively, were positive for MSSA after 20 h of incubation. The isolate from the recipient was confirmed to be indistinguishable from the donor isolate by PFGE (Figure 1). A Doppler ultrasound of the transplanted liver revealed normal flow in the hepatic artery and no evidence of abscess. The recipient remained clinically stable throughout with no signs of infection. Repeat blood cultures were negative. Intravenous cloxacillin was continued for 4 weeks. At 2 years post-LT, there is no evidence of sequelae from his infection, however, he does have recurrent hepatitis C with moderate fibrosis.

Both kidney recipients had negative postoperative blood cultures and completed 2 weeks of intravenous cloxacillin.

Case 3

An 11-month-old girl with pediatric end-stage liver disease (PELD) score 28 underwent LT for biliary atresia. The donor was an 11-month-old with cardiac arrest and anoxic brain injury 5 days following complex congenital heart disease surgery. The donor was resuscitated and placed on extracorporeal membrane oxygen support. There was no clinical evidence of infection; however, there was an open sternotomy and empiric antimicrobial therapy with vancomycin and piperacillin-tazobactam was initiated. Forty-eight hours later, brain death criteria were met. Donor blood cultures were negative at the time of organ procurement.

Antimicrobial prophylaxis for the recipient was cefotaxime on call to the operating room and continued 48 h postoperatively. The donor hepatic artery was small and was reconstructed with a splenic artery patch. Good flow in both the portal vein and hepatic artery was confirmed by Doppler at the end of the LT. Blood cultures drawn 10 h posttransplant were negative.

Day 2 posttransplant, the recipient became febrile and multiple blood cultures were positive for *Escherichia coli*. There was also rise in aspartate aminotransferase to 2000 U/L and poor flow in the portal vein noted on Doppler ultrasound. On the same day, blood cultures from the donor were reported to be positive for *E. coli* at 2 days incubation. The recipient was taken back to the operating room for portal venous thrombectomy, anticoagulated, and antibiotic therapy was changed to piperacillin-tazobactam. Blood cultures remained positive for 24 h, and then cleared.

The donor and recipient *E. coli* isolates had the same antibiogram pattern; susceptible to cefotaxime/ceftriaxone, piperacillin-tazobactam and carbepenems as well as amikacin, cefazolin and ciprofloxacin. PFGE confirmed the donor and recipient strains were indistinguishable (Figure 1).

The recipient remained hemodynamically unstable, and developed hepatic artery thrombosis with progressive liver failure on day 6 postttransplant. On day 9, she was retransplanted urgently with an ABO-incompatible liver. The postoperative course following the second transplant was complicated by a biliary leak requiring surgical repair. Normal flow in the hepatic artery and portal vein were documented with no evidence of hepatic or intraabdominal abscess. Two weeks of therapy with cefazolin for the *E. coli* bacteremia was completed. At 2 months posttransplant, a diagnosis of posttransplant lymphoproliferative disorder (PTLD) was made. This was treated with immunosuppression reduction and four doses of rituximab. Almost 2 years posttransplant, she is doing well with no evidence of recurrent PTLD or other consequences of her infection.

One kidney was also transplanted from this donor under routine peri-operative prophylaxis with cefazolin. The transplant was uncomplicated with no evidence of postoperative infection.

Case 4

A 50-year-old man with a natural MELD of 7 underwent LT for epitheliod hemangioendothelioma. The donor was a 32-year-old female declared brain dead after a cocaine overdose and cardiac arrest. Serology and nucleic acid testing were negative for HIV and hepatitis C. Donor blood cultures were reported positive for gram positive cocci in chains and one gram of cefotaxime was given just before organ procurement. The recipient received 1 g of ceftriaxone 40 min before the start of the transplant procedure. Surveillance blood cultures drawn 1 h following the end of the case were positive for gram positive cocci in chains. Ultimately, both the donor and recipient isolates were confirmed to be Group B *Streptoccocus*, serotype VI. Although PFGE analysis was not performed, a review of our provincial database over the preceding 5 years (July 2007 to July 2012) revealed a total of 815 invasive Group B Streptococcal isolates, of which only 16 (2%) were serotype VI. Based on published criteria, this meets the definition of proven donor-derived infection (6).

The posttransplant course of was complicated by severe reperfusion coagulopathy and primary graft nonfunction that required urgent re-transplantation 2 days later. Following the re-transplant he had a slow, but complete recovery. He received 4 weeks of antimicrobial therapy (ceftriaxone then piperacillin-tazobactam due to concomitant pneumonia) for the Group B *Streptoccocus bacteremia*. At 3 months posttransplant, he has normal hepatic function and ultrasound shows a possible hepatic artery stenosis, but no other abnormality.

The remainder of the recipients from this donor (double lung, heart, 1 kidney and islets) had negative postoperative surveillance blood cultures and all received 2 weeks of antimicrobial therapy directed at the Group B *Streptoccocus*.

Discussion

We describe four cases of donor-derived bacteremia in LT recipients, in the face of appropriate antimicrobial prophylaxis. All of the recipients ultimately had good outcomes, but in case 3, donor derived *E. coli* bacteremia and sepsis, may have contributed to the hepatic artery thrombosis and need for urgent early re-transplant. The explanted failed LT pathology showed bland thrombus without mycotic aneurysm. Pathology of the explanted failed LT in case 4 also demonstrated massive hepatic necrosis with no evidence of thrombus.

An estimated 5% of organ donors are bacteremic at the time of procurement (3,4). We were not able to determine the frequency of bacteremia in our donor pool as this has not been prospectively tracked. In the 3-year-period these cases occurred however, there were 29 pediatric and 144 adult deceased donor LT's at our center, giving a rate of documented donor transmitted bacteremia despite appropriate prophylaxis of 2.3% in our LT population. As we believe, based on clinical observation, that these cases represent a minority of the bacteremic donors, the estimated rate of 5% for donor bacteremia may be an underestimate in the current era.

A study of 95 donors with bacteremia documented no transmissions with directed antimicrobial therapy given to the recipients for a median of 3.8 days (3). These data, combined with the increasing gap between organ supply and demand, has led to increased utilization of these organs. It has been recommended that organ donors with bacteremia should be treated, and ideally cured, before organ procurement (7). In clinical practice, however, documentation of clearance of donor bacteremia is often not feasible before transplantation due to the limited time window for procurement and incubation period required for cultures. When organs are utilized from donors bacteremic with virulent organisms, such as *S. aureus* and *Pseudomonas aeruginosa* in particular, recipients should receive a longer (2–4 week) antibiotic course (8) as we did in our cases. Two of the donors in our series also had complicated bacteremia with meningitis and seeding of other organs which likely increased risk of transmission.

Donor bacteremia due to gram negative bacilli has been shown to pose a higher risk of transmission and be associated with poorer outcomes in the recipient than that due to gram positive bacteria (9). However, *S. aureus* is a potentially more virulent gram positive organism and transmission may result in serious sequelae. Doig et al. described a case of probable donor transmitted *S. aureus* in which both kidney recipients from one donor developed infection and mycotic aneurysm with devastating consequences (10). In our cases, where prophylaxis was initiated before transplant, *S. aureus* bacteremia was detected on surveillance cultures early posttransplant, was associated with no clinical symptoms, cleared with continued antimicrobial therapy and had no long-term consequences. On the other hand, the *E. coli* transmission presented later, at 2 days posttransplant, with sepsis, despite appropriate antimicrobial prophylaxis. Although the donor bacteremia only became known around the time of the clinical presentation in the recipient, routine peri-operative antimicrobial prophylaxis (cefotaxime) administered to the recipient offered appropriate antimicrobial coverage.

The four cases presented here highlight the need for follow up of recipients of organs from bacteremic donors, as appropriate prophylaxis does not eliminate the risk of transmission. Although surveillance blood cultures in

recipients of organs from bacteremic donors are not routine in all centers, it has been our practice. As such, we believe it is unlikely, though possible, that we missed episodes of donor transmitted bacteremia.

Interestingly, in the four cases we present, there was transmission to each of the liver recipients, but not recipients of the other organs (n = 10) from these donors. In a recent review of 610 LT's performed in Italy, 69 donors had pathogens isolated from blood cultures prior to procurement and in 4 (5.8%), there was transmission to the recipient despite directed antimicrobial prophylaxis (11). This combined with our observations, suggests LT recipients from bacteremic donors may be at higher risk of transmission despite prophylaxis. Although speculative, possible explanations for this include: (1) the relatively large tissue and vascular volume of the liver compared particularly to kidney or heart; (2) phagocytosis of the microorganisms by Kupffer cells in the donor liver (12) with poor killing in the setting of brain death and organ procurement; (3) leukopenia, which is more common in LT than other organ transplant groups, on the basis of hypersplenism; (4) the severity of recipient illness at the time of transplant as evidenced by the high MELD/PELD scores in 3 of our 4 cases; (5) the unknown pharmacokinetics of antibiotics in the setting of brain death. In critically ill patients with sepsis, altered pharmacokinetics and pharmacodynamics may lead to decreased efficacy of antibiotics (13) and the circulatory, hormonal and metabolic changes that occur in brain death may as well and (6) variable penetration of antibiotics, particularly cephalosporins, into bile as opposed to the high concentrations achieved in urine (14).

These cases illustrate that donor-derived transmission may occur from bacteremic donors despite appropriate antimicrobial prophylaxis. When it occurs, donor transmitted bacteremia carries a high-attributable mortality (10,15). In three of our cases, bacteremia was detected on surveillance cultures in the absence of clinical signs of infection. It is likely therefore that donor-derived transmission of bacterial infection may be under-recognized. Close follow up of recipients of organs from bacteremic donors should be maintained as transmission, although uncommon, may have serious consequences. Further research is needed to confirm an increased risk of transmission in LT, the reasons for this, and to re-evaluate the frequency of donor bacteremia in the current era.

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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