Transmission of Methicillin-Resistant *Staphylococcus aureus* Infection Through Solid Organ:

Transplantation: Confirmation Via Whole Genome Sequencing

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Abstract

We describe two cases of donor-derived methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia that developed after transplantation of organs from a common donor who died from acute MRSA endocarditis. Both recipients developed recurrent MRSA infection despite appropriate antibiotic therapy, and required prolonged hospitalization and hospital readmission. Comparison of *S. aureus* whole genome sequence of DNA extracted from fixed donor tissue and recipients' isolates confirmed donor-derived transmission. Current guidelines emphasize the risk posed by donors with bacteremia from multidrug-resistant organisms. This investigation suggests that, particularly in the setting of donor endocarditis, even a standard course of prophylactic antibiotics may not be sufficient to prevent donor-derived infection.

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Introduction

Unexpected donor-derived infection transmission is confirmed in less than 1% of solid organ transplants and may lead to allograft failure or recipient death (1). When organ donors are deemed to be at high risk for infection with viral blood-borne pathogens, specific recipient informed consent regarding the risk of viral infection transmission is advised (2). However, available guidelines do not describe risk-stratification related to transmission of bacterial infections from donors with endocarditis. Although successful use of organs from donors with subacute bacterial endocarditis without evidence of distant septic emboli has been reported (3,4), recent reports have described increased recipient morbidity and mortality associated with transmission of multidrug-resistant organisms (MDROs) (5–7). Potential donor-derived disease transmission events are reported to the Organ Procurement and Transplantation Network (OPTN) per policy and reviewed by the ad hoc OPTN Disease Transmission Advisory Committee (DTAC) which categorizes each as to the likelihood of disease transmission. Through representation on DTAC, Centers for Disease Control and Prevention (CDC) leads investigations of select cases of public health importance. We investigated two cases of posttransplant methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in solid organ recipients whose common donor died of MRSA-related endocarditis complications. These cases highlight the need for careful monitoring and follow-up among recipients of organs from donors with acute MDRO endocarditis for increased risk for donor-derived infections.

Case Reports

Epidemiologic review

Medical records of the donor and all organ recipients were reviewed to characterize clinical courses, diagnostic evaluations, and laboratory and radiographic data. Organ donor autopsy records were reviewed. The organ donor and both symptomatic recipients were hospitalized at different facilities.

Organ donor

In December 2012, a male with history of nonmedical injection drug use (IDU) was evaluated at an Emergency Department (ED) for 2 days of progressive confusion and somnolence. He was minimally responsive and febrile (105.9°F). Broad-spectrum antimicrobial therapy was initiated for presumed bacterial meningitis. Computed tomography (CT) of the head revealed a large right parietal intracranial hemorrhage. Peripheral blood cultures collected during the ED evaluation revealed the presence of MRSA. The antimicrobial susceptibility test results are shown in Table 1. His neurologic condition worsened and he was declared brain dead within 24 h.

Donor eligibility screening included review of premortem laboratory and radiographic data. A standardized medical and social history questionnaire was administered to next-of-kin. Given the history of active IDU, the donor was deemed to be at increased risk for window period viral blood-borne pathogen infection; serology and nucleic acid testing for HIV, hepatitis B virus and hepatitis C virus were nonreactive. Broad-spectrum antibiotics, including vancomycin, were continued and no bacterial growth was noted on subsequent

donor blood cultures. The last donor blood cultures were collected 3 days prior to organ recovery. Pretransplant chest CT scan was remarkable for left upper lobe lung infiltrate and transthoracic echocardiogram revealed a 1-cm mobile mitral valve vegetation.

The lungs, kidneys, pancreas and liver were recovered approximately 36 h after brain death and transplanted into four recipients. By the time of organ recovery, the donor had received antimicrobial therapy against MRSA infection, consisting of 2 g of vancomycin in the ED and 1 g after transfer to the tertiary referral center, and had remained afebrile for >48 h. Independent of organ donation, an autopsy was performed and cause of death was attributed to cerebral hemorrhage resulting from septic emboli.

Standard informed consent along with informed consent for increased risk donors due to IDU was obtained from recipients but did not specify donor MRSA endocarditis.

Lung recipient

The bilateral lung recipient had no previous history of MRSA infection or colonization, including a negative screening nasal swab collected 7 days before transplantation for hypersensitivity pneumonitis and interstitial lung disease related to common variable immunodeficiency. A routine intraoperative lung biopsy culture was positive for MRSA. Vancomycin therapy was initiated at the time of transplantation given donor MRSA bacteremia. However, surveillance blood cultures collected 6 days after transplantation revealed MRSA growth. Despite targeted antibiotic therapy continued at therapeutic doses, MRSA growth was observed on four surveillance bronchoalveolar lavage (BAL) cultures collected during the subsequent 6 weeks (Table 1). The patient did not develop signs or symptoms consistent with MRSA infection during this time. After completion of 9 weeks of antibiotic therapy, a negative BAL culture result was obtained 99 days after transplantation.

Nearly 6 months posttransplantation, the patient was readmitted with complaints of increasing dyspnea on exertion. Admission vital signs were within normal limits. Chest radiography revealed large right-sided pleural effusion and chest CT suggested extensive right-sided multifocal consolidation. Diagnostic bronchoscopy was performed and BAL culture revealed MRSA. Following 4 weeks of vancomycin therapy, symptoms resolved. Throughout the clinical course, vancomycin dosing was appropriate (trough levels maintained between 15 and 20μg/mL) and mean inhibitory concentration was 1μg/mL on all isolates.

The blood isolate from day 6 and the BAL isolate from day 159 posttransplant were submitted to CDC for characterization by *spa*-typing, pulsed-field gel electrophoresis (PFGE) and whole-genome sequence analysis.

Liver recipient

The liver recipient had a history of ulcerative colitis and primary sclerosing cholangitis, and was receiving empiric daptomycin at 4 mg/kg for lower extremity cellulitis at the time of transplantation. The intraoperative liver biopsy culture was negative, but when MRSA growth was observed on blood cultures collected from the recipient 3 h after transplantation, daptomycin therapy was continued at 6 mg/kg dose for 14 days. Subsequent blood cultures

were negative. The patient was discharged to a long-term care rehabilitation facility but was re-admitted 58 days later with fever and chills. Blood cultures were positive for MRSA and this isolate was submitted to CDC for characterization. No evidence of hepatic abscess was observed on CT scan. The patient was unable to tolerate trans-esophageal echocardiogram, but trans-thoracic echocardiogram did not identify valvular vegetation. A 6-week course of vancomycin therapy was initiated with resolution of symptoms and subsequent negative blood cultures.

Neither of the symptomatic recipients had chronic indwelling devices, both received tacrolimus, mycophenolate mofetil, and prednisone for immunosuppression, and both remained asymptomatic at 1 year follow-up.

Kidneys and pancreas recipients

Screening peripheral blood cultures collected from the left kidney and pancreas recipient and the right kidney recipient revealed no growth. These recipients received transplants for complications related to type 1 and type 2 diabetes mellitus, respectively. Both patients received five doses of vancomycin prophylaxis following transplantation and had no signs or symptoms consistent with MRSA infection.

Laboratory Methods

Histopathological analysis

Archived formalin-fixed paraffin-embedded (FFPE) autopsy tissue specimens of the mitral valve and central nervous system tissue of the donor were evaluated using hematoxylin and eosin and Lillie-Twort Gram stain. Tissue sections were also evaluated using an immunohistochemical assay to detect specifically *S. aureus* with a hyperimmune mouse anti-*S. aureus* ascitic fluid diluted at 1:100 (8).

Characterization of *S. aureus*

DNA was extracted and amplified from single 16-μmsections of FFPE mitral valve tissue as previously described (9), from the lung recipient's blood and BAL isolates, and from the liver recipient's blood isolate (10,11). Real-time polymerase chain reaction (PCR) was performed to detect the *nuc* gene, an *S. aureus*-specific marker; *mec*A, which confers methicillin resistance; and *luk*S-PV (Panton-Valentine) leukocidin (PVL) (10,12,13). Assignment of SCC*mec* type and PFGE were performed as previously described (11).

The polymorphic X region of *spa* was amplified and sequenced as described (14). The *spa* typing plug-in tool of BioNumerics v5.1 (Applied Maths, Austin, TX) synchronized with the SeqNet/Ridom *spa* server (15) was used to assign *spa* types. A pulsed-field type of USA300 was inferred for *S. aureus* whose *spa* types correlated with multilocus sequence clonal complex 8 and were PCR-positive for PVL and SCCmec IVa subtype.

Broth microdilution antimicrobial susceptibility was performed on all isolates submitted to CDC (16).

Whole genomic sequencing (WGS) was performed using DNA extracted from each transplant-associated isolate and FFPE mitral valve tissue of the donor on the Illumina MiSeq Benchtop sequencer, as similarly described (9,17). Reads were aligned against the reference USA300-0114 genome, FPR3757, using Novoalign (http://www.novocraft.com), and single nucleotide polymorphisms (SNPs) were determined using GATK (http://www.broadinstitute.org/gatk/). Reads containing insertions or deletions, and those mapping to multiple locations in the reference were removed from the final alignments. SNPs were excluded if they did not meet a minimum coverage of 10× and if the variant was present in less than 90% of the base calls for that position. Finally, loci that were not present in all strains were removed and a matrix containing the remaining orthologous SNPs was generated. Phylogenetic trees of recipient and background isolate genomes were constructed using maximum parsimony analysis in MEGA5 (http://www.megasoftware.net). Background genomes included 10 previously-sequenced epidemiologically unrelated isolates recovered between years 2004 and 2012 from eight states with indistinguishable PFGE patterns (Figure 1).

Laboratory Results

Histopathological analysis

Histological examination of the mitral valve of the donor revealed a large fibrinous vegetation containing abundant colonies of Gram-positive and coccoid bacteria. Small clusters of Gram-positive cocci were also identified with numerous septic emboli in the central nervous system of the donor. An immunohistochemical assay specific for *S. aureus* demonstrated intense staining specific in these same tissues (Figure 2).

Strain characterization

MRSA isolates from the lung and liver recipients were indistinguishable by PFGE and were designated USA300-0114 (not shown), the dominant community-associated MRSA strain in the United States (11). Like these isolates, *S. aureus* DNA extracted from the donor's mitral valve demonstrated *spa* type t008, *mec* type IVa, and was PVL-positive. All isolates had identical antibiotic susceptibility test results (Table 1). Phylogenetic analysis using WGS showed the donor and recipient isolates were more closely related to each other than the 10 background isolates. Only one SNP was identified among the recipient isolate genomes; 508 SNPs were identified among the recipient and background *S. aureus* genomes analyzed here. These data support previous conclusions that the USA300-0114 strain type is highly clonal (11), and provide empirical evidence that the recipients' isolates originated from the same source.

Discussion

This report describes MRSA transmission through solid organ transplantation from a deceased donor with acute MRSA endocarditis and embolic stroke. These findings underscore the challenges of transplant-transmitted MRSA infection management among immunosuppressed solid organ recipients. Furthermore, they emphasize the need to balance the risks of using organs from donors with acute MDRO endocarditis with the potential life-

saving benefits of organ transplantation. Organs from donors with acute MDRO endocarditis should be accepted only after a careful risk-benefit analysis of potential recipient adverse outcomes, and clinicians should carefully monitor solid organ recipients for delayed development of refractory, or recurrent donor-derived infections. This report further highlights the importance of linking novel laboratory methods with epidemiologic investigation when investigating donor-derived bacterial infections.

The risk of fatal neurologic complications from MRSA endocarditis among injection drugs users has been described (18). U.S. Public Health Service guidelines define medical and behavioral characteristics among organ donors associated with increased risk of blood-borne viral infections (2), but currently there are no guidelines for infection risks associated with using organs from donors with acute MDRO bacterial endocarditis. While organ transplantation may be the optimal treatment for many patients with end-stage organ disease, MDRO infection in the transplant setting is associated with increased mortality risk for the recipient due to immunosuppression and limited therapeutic options (7). An increasing number of potential organ donors are admitted to intensive care units where they are exposed to MDROs, and organ recovery and transplantation may occur prior to knowledge of final MDRO culture results (19). Given the growing number of patients awaiting transplantation, shortage of available organs, and increasing numbers of donors with potential multidrug-resistant infections, donor-derived transmission of MDRO bacterial infections may increase in the future (20,21). Expansion of guidelines to include potential risks of adverse recipient outcomes associated with using organs from donors with acute MDRO endocarditis should be considered.

In this investigation, two organ recipients developed recurrent or persistent MRSA infection following transplant. Occult septic embolization, particularly from mitral valve vegetation, in the setting of MRSA bacteremia and endocarditis has been described (22,23). The median time to clearance of MRSA bacteremia is typically between 7 and 9 days (24). In the liver recipient, the MRSA-positive blood cultures collected 3 h after transplantation may reflect persistence of the donor MRSA bloodstream infection, despite antibiotic therapy, at the time of liver procurement. The recurrence of bacteremia in the liver recipient after 2 weeks of vancomycin therapy may reflect incomplete treatment. High-grade donor bacteremia likely resulted in extensive infection in transplanted organs. While clinical guidelines for MRSA bacteremia recommend 2 weeks of antimicrobial therapy for uncomplicated infections, extending therapy to 4 weeks may provide further benefit in resolving infection in immunosuppressed solid organ recipients (24,25). While radiographic evidence did not suggest abscesses in either recipient, it is also possible that the persistence of MRSA in the lung recipient's BAL cultures and recurrence of MRSA bacteremia in both the liver and lung recipients may have resulted from occult, undetected micro-abscesses which did not resolve despite prolonged antibiotic therapy.

This report also highlights the importance of linking novel laboratory methods with epidemiologic investigation when investigating donor-derived bacterial infections. Donor cultures are frequently performed at reference laboratories distant to the donor organ procurement organization and communication of findings is often slower than for hospital-based laboratories, particularly when highly resistant organisms are cultured. While donor

sera must be archived for 10 years following organ procurement, there are no public health recommendations or policy standards for archiving donor bacterial culture isolates. As a result, these specimens may not be available for laboratory testing when donor-derived transmission events are suspected.

In the present investigation, the novel application of molecular characterization of DNA extracted from FFPE tissue, combined with characterization of isolates, permitted comparison of MRSA from donor and recipient sources, all of which were characterized as USA300, the most common cause of community-acquired MRSA infection in the United States (11). The predominance of this clone among community-acquired MRSA infections left open the possibility that the organ recipients had acquired this strain as a cause of remote infection from a community source rather than an indolent transplant-associated infection.WGS analysis was employed to investigate relatedness of strains infecting the donor and recipient, and strongly supported organ donation as the common source of infection in the lung and liver recipients by clearly showing that the donor and recipient isolates were more closely related to each other than they were to the background isolates. Furthermore, only one SNP among the transplant group indicates that these strains are from a common source. Estimates of the mutation rate for *S. aureus* have been calculated repeatedly at one SNP every 6–7 weeks (26). In instances where FFPE tissues are available, novel laboratory tools can be used to confirm transplant transmission when suspected in association with donors at increased risk.

The increased risk of morbidity and mortality associated with virulent MDROs underscores the importance of recipient informed consent and vigilant posttransplant clinical surveillance for timely and pathogen-appropriate treatment in the event of donor-derived infection. Solid organ donors with acute MDRO endocarditis with risks of septic embolization may pose an additional morbidity and mortality risk for organ recipients, and solid organ transplantation should proceed only after an extensive risk-benefit evaluation. Recognition and reporting of donor-derived bacterial transmissions events is crucial to improving recipient outcome and tracking the magnitude of the public health burden. Communication is crucial concerning donor infection such as antimicrobial susceptibility, virulence of the pathogen, and location in sites refractory to treatment in gauging the risk of transmitted disease in the recipient.

Abbreviations

BAL	bronchoalveolar lavage
CDC	Centers for Disease Control and Prevention
CT	computed tomography
DTAC	Disease Transmission Advisory Committee
ED	Emergency Department
FFPE	formalin-fixed paraffin-embedded
HBV	hepatitis B virus
HCV	hepatitis C virus

IDU	nonmedical injection drug use
MDRO	multidrug-resistant organism
MRSA	methicillin-resistant *Staphylococcus aureus*
OPTN	Organ Procurement and Transplantation Network
PCR	polymerase chain reaction
PFGE	pulsed-field gel electrophoresis
PHS	U.S. Public Health Service
PVL	Panton-Valentine leukocidin
SNP	single nucleotide polymorphism
WGS	whole genomic sequencing

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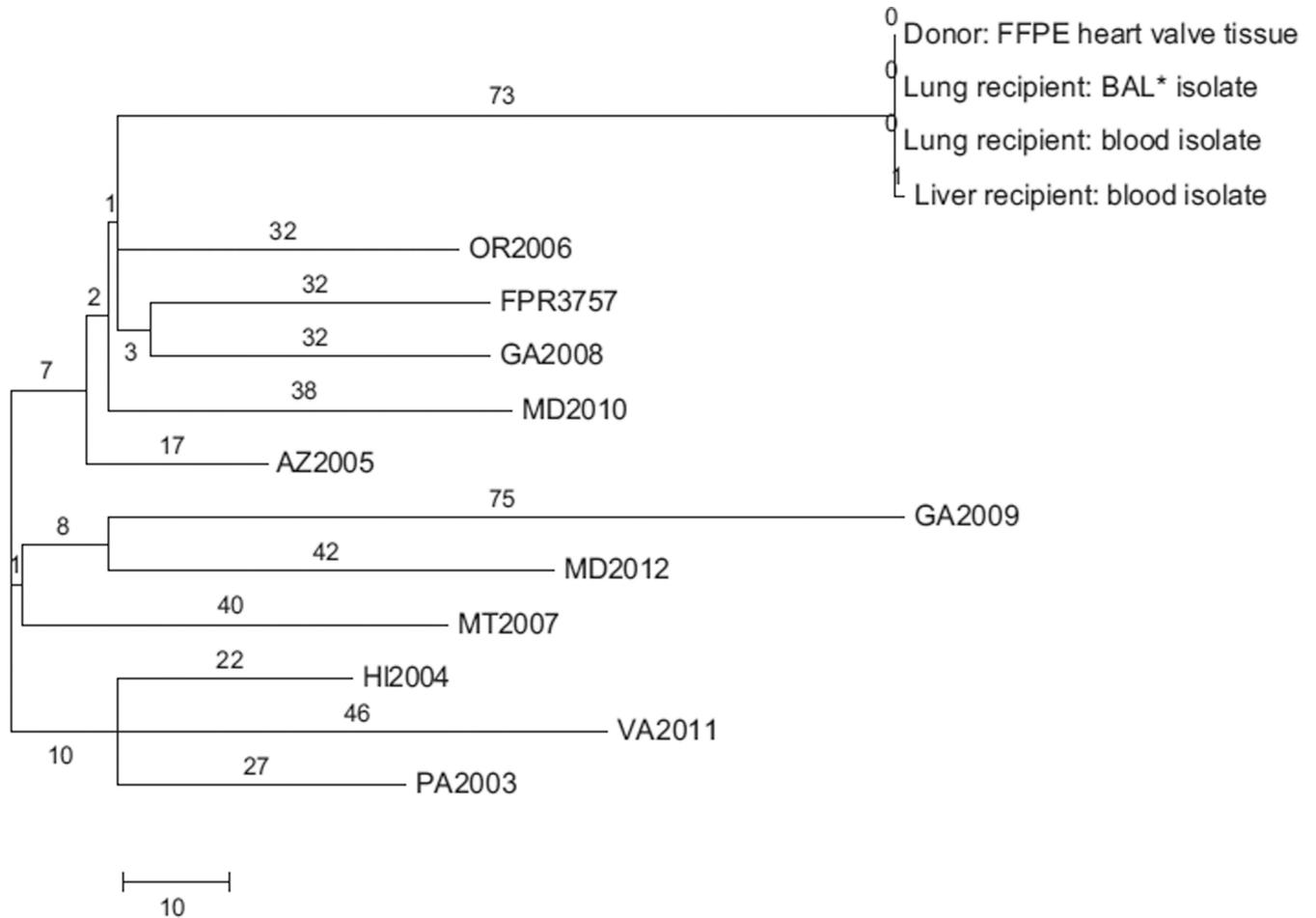
Figure 1. A single maximum parsimony tree was reconstructed using 508 SNPs from 15 whole genome USA300-0114 sequences of 3 MRSA recipient isolates, 1 donor isolate, 1 reference (FPR3757) and 10 background USA300-0114 isolates

Background genomes are labeled with the state and year collected. Donor and recipient isolates are labeled as such with the clinical source indicated. Branch lengths represent the genetic distance with the numbers on each branch indicating the number of SNPs between genomes. The bar represents 10 SNPs. Tree constructed using MEGA5. *BAL, bronchoalveolar lavage. MRSA, methicillin-resistant *Staphylococcus aureus*; SNPs, single nucleotide polymorphisms.
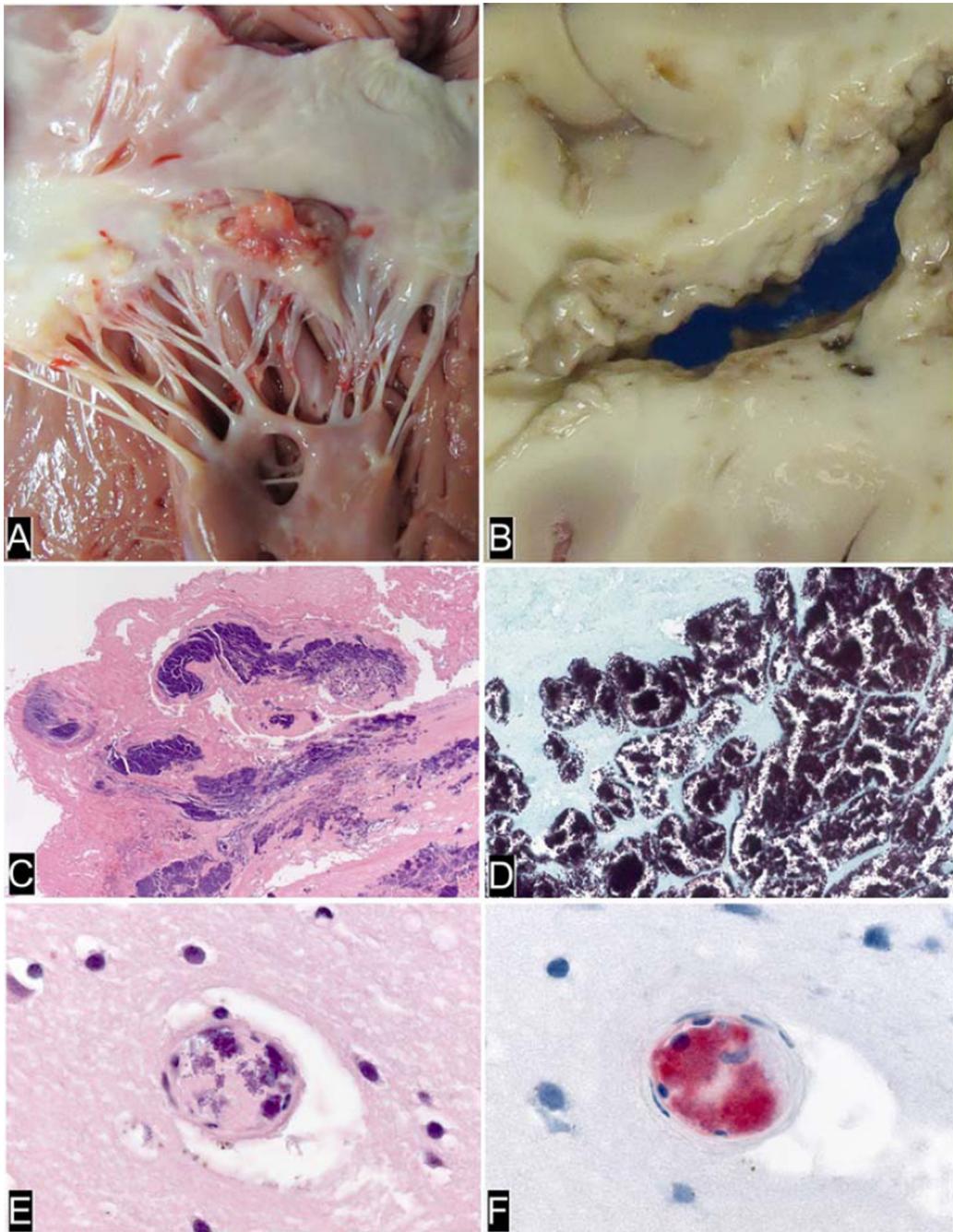
Figure 2.
(A) Gross appearance of a perforating bacterial vegetation on the posterior leaflet of the mitral valve in the heart of the donor. (B) Gross appearance of a cystic lesion in the white matter of the right cerebral hemisphere of the donor formed by a large intracerebral hematoma. (C) Histological appearance of the mitral valve vegetation showing fibrin (pink) admixed with innumerable clumps of bacteria (blue). Hematoxylin and eosin stain, original magnification × 12.5. (D) Tissue Gram stain of mitral valve lesion showing coalescing colonies of Gram-positive, coccoid bacteria. Lillie-Twort stain, original magnification ×

100. (E) Occlusive septic embolus in a small vessel in the cerebral cortex, revealing numerous coccoid bacteria enmeshed in fibrin. Hematoxylin and eosin stain, original magnification × 158. (F) Same vessel as image (E), demonstrating immunohistochemical evidence of infection with *Staphylococcus aureus* (red). Immunoalkaline phosphatase technique with naphthol-fast red and hematoxylin counterstain, original magnification × 158.

Table 1

Staphylococcus aureus antimicrobial susceptibility testing results with minimum inhibitory concentration (MIC) and susceptible/intermediate/resistant (SIR) determination for cultures collected from a common organ donor and lung and liver recipients

	Organ donor		Lung recipient													Liver recipient			
	Blood		Lung biopsy		Blood[1]		BAL		BAL		BAL		BAL[1]		Blood		Blood[1]	
Specimen type	Day −3		Day 0		Day 6		Day 15		Day 20		Day 43		Day 159		Day 0		Day 72	
Antibiotic	MIC	SIR	MIC	SIR	MIC	SIR	MIC	SIR	MIC	SIR	MIC	SIR	MIC	SIR	MIC	SIR	MIC	SIR
Clindamycin	0.5	S	0.25	S	0.25	S	0.25	S	0.25	S	0.25	S	0.25	S	0.25	S	0.25	S
Daptomycin	0.5	S	0.5	S	0.5	S									0.5	S	0.5	S
Gentamicin	0.5	S	0.5	S	2	S	0.5	S	0.5	S	0.5	S			0.5	S	2	S
Levofloxacin	>4	R	>4	R	8	R	8	R	8	R	8	R			8	R	8	R
Linezolid	2	S	2	S	2	S	2	S	2	S	2	S	2	S	2	S	2	S
Oxacillin	>2	R	>2	R	>16	R	4	R	4	R	4	R			4	R	>16	R
TMP/SMX	2/38	S	10	S	0.5/9.5	S	10	S	10	S	10	S	10	S	10	S	0.5/9.5	S
Vancomycin	2	S	2	S	0.5	S	1	S	1	S	1	S	1	S	1.5	S	2	S

BAL, bronchoalveolar lavage; Day 0, day of transplant; TMP/SMX, trimethoprim/sulfamethoxazole.

[1] Tested at the Centers for Disease Control and Prevention using broth microdilution.