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Review

Is it Possible that Cadaver with Proven or Suspected Bacterial Infection be a Kidney Donor?

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Abstract

Kidney transplantation constitutes the primary treatment option in end-stage renal failure by offering advantages in terms of quality of life and survival. Considering that the prevalence of end-stage renal disease is rapidly increasing worldwide, the number of patients in need of kidney transplantation is also increasing. Additionally, organ transplantation comes to the fore with increasing frequency in potential donors to be patients in intensive care units who died due to different reasons. In such cases, the development of donor-derived infection in the recipient is the most important issue to consider. Donor-derived infection development puts the life of the recipient at significant risk. Also, there is no clear consensus on possible bacterial infections. In order to help prevent the development of donor-derived infection, the main theme of this article is the identification of which issues should be considered when accepting the deceased donor in terms of infectious conditions threatening the recipient and kidney.

Keywords: cadaver, kidney donor, infection

Introduction

Kidney transplantation is the primary treatment option in patients with end-stage renal failure. Successful kidney transplantation both increases the quality of life of patients and reduces the risk of mortality compared to other renal replacement therapies [1]. The available organ pool is declining, but the demand for kidney transplantation is not. To address this gap, an expanded donor concept has become popular in recent years, and marginal donors are being accepted. Individuals with risk factors for transmitting a range of infectious diseases are among these donors. Particularly, donors with multidrug-resistant (MDR) bacterial infections are encountered more frequently.

Although transplantation is a well-intentioned initiative, donor-derived infections can be associated with serious complications in kidney transplant recipients [2-4]. It is especially important to recognize potential disease transmission to recipients in terms of donor-derived infections during the deceased donor organ transplantation period, where decision-making processes are shortened. Depending on the organ transplanted, the incidence of bacteremia varies between 8.6-26%, and it is considered to be the most important cause of morbidity and mortality. A major threat to this improvement has emerged from the progressive increase in the incidence of post-transplant infectious complications due to MDR microorganisms. These are known as the "ESKAPE pathogens," which are Vancomycin-resistant Enterococcus faecium, methicillin-resistant Staphylococcus aureus, extended-spectrum beta-lactamase-producing Klebsiella pneumoniae, carbapenem-resistant Acinetobacter baumannii, carbapenem- and quinolone-resistant Pseudomonas aeruginosa, and derepressed chromosomal beta-lactam and extended-spectrum beta-lactamase-producing Enterobacter species With the rise of MDR bacteria in hospital environments, an increasing number of potential donors are exposed to these kinds of bacteria in intensive care units. This exposure poses a significant risk for the development of donor-derived infections.

There is no clear consensus on possible bacterial infections. Two points are important in this regard: donors diagnosed and actively treated for bacterial infections and the presence of undiagnosed infections before organ procurement. In general, organs from individuals with diagnosed infection can be used with a low risk of disease transmission, since treatment is given beforehand. However, the main risk for recipients is donors with undiagnosed infection. If this situation is overlooked at first, complications may occur that are late for intervention and may cause high mortality of the recipient.

In this review, we aim to present what should be considered when accepting the deceased donor in terms of infectious conditions threatening the recipient and kidney due to immunosuppressive therapy after transplantation.

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We further seek to note the presence of undiagnosed latent infections in the donor by examining the international guidelines and case series through a literature search and provide suggestions that can be made in this regard.

Epidemiology and definitions

The term donor-derived infection is mostly used for deceased donors because if any infectious process is encountered in living donors, organ transplantation is mostly delayed, and the ideal time is expected. Donor-derived infections are defined as any infection present in the donor that is transmitted to one or more recipients [5]. Frequency of donor-derived infection is shown between 0.2% and 8% in all deceased donor organ transplantation [3,6-7]. Because of the lack of standardized reporting, the true incidence is not known.

Donor-derived infections are classified into two groups: expected and unexpected infections. Expected transmissions occur when the donor is known to have an infection, as demonstrated by positive serology or positive cultures in the donor at the time of donation. Unexpected transmissions occur when a donor is not known to be infected prior to donation [8]. In a systematic review, Rashmi *et al*. analyzed unexpected donor-derived infectious transmissions by kidney transplantation from 139 donors. Twenty bacterial (14.4%), 21 fungal (15.1%), and 18 (12.9%) parasitic transmitted infections were reported. The most frequent bacterial infections were caused by *Mycobacterium tuberculosis* (10, 4.8%) and *Pseudomonas aeruginosa* (9, 4.3%). *Candida* species were the most frequent causes of fungal donor-derived infections (8, 3.9%) [9,10].

Helpful risk-mitigation tips

Risk assessment begins with the careful evaluation of the social and medical history of the deceased donor. Behavioral risk factors (IV drug abuse, high-risk sexual contacts) of the donor should be investigated. Terminal hospitalization period and cause of death may give an idea in terms of the presence of MDR bacterial infection. Culture and other serological tests sent during hospitalization should be reviewed in detail. Physical examination of the donor and explanted organ is also an important part of risk assessment. Additionally, the surgical team should evaluate abscesses, genital ulcers, lymphadenopathies, bowel perforation and intestinal contents in the peritoneal cavity, and the presence of granuloma in the explanted organ. Echocardiography and CT examinations may be required for any metastatic, granulomatous, or ongoing infection. Deceased donor characteristics and risk factors for donor-derived infections are summarized in Table 1.

Table 1. Deceased donor characteristics and risk factors for donor-derived infections

❖ High-risk sexual contacts
❖ Intravenous drug abuse
❖ Homelessness, incarcerated, prison more than 72 consecutive hours in preceding 12 months
❖ Travel to tropical/subtropical countries where sanitation conditions are substandard
❖ Extented length of stay in intensive care unit
❖ Follow up with open abdomen procedure
❖ Critical illness requiring vasopressor support and the need for cardiopulmonary resuscitation
❖ Unexplained eosinophilia
❖ Bowel perforation
❖ Contaminated preservation fluid
❖ Unexplained mental illnes or meningoencephalitis
❖ Unexplained fever, sweats, weight loss, pneumonia, non-calcified pulmonary nodules or lymphadenopathy
❖ Granulomas on explanted organ or unexplained organomegaly
❖ Genital ulcers

Bacteremic donors

Actively treated bacteremic donors with susceptible microorganisms may become eligible for donation. However, different data are available regarding unexpected donor infections. In a study by Freeman *et al*. from the USA in which bacteremic donors were evaluated between 1990-1996, bacteremic donor frequency was reported as 5%. *Staphylococcus*, *Streptococcus*, *Enterococcus*, gram-negative, and *Candida* species were found in the cultures of bacteremic donors. They further indicated that almost all recipients should receive a mean of 3.8±2.5 days' appropriate antibiotics postoperatively [11].

In another retrospective analysis, contaminated allografts were evaluated by Zibari *et al*. This study reviewed 599 organ transplants performed between 1993-1997 in a US state; positive blood culture was detected in 46 (7.5%), and positive urine culture was detected in 25 (4.5%) of the donors. A total of 179 recipients received organs from these contaminated donors. *Staphylococcus*, *treptococcus* and gram-negative microorganisms were found in the blood or urine cultures of donors. Both donors and recipients received prophylactic broad-spectrum antibiotics which were adjusted based on culture and sensitivity results. No disease transmission was observed in any of the 16 kidney recipients in their center [7].

Similar results have been reported in other case series. For example, successful liver and kidney transplantation (five kidney, two liver) from deceased donors with left-sided bacterial endocarditis (with *Staphylococcus epidermidis*, coagulase-negative *Staphylococcus, Staphylococcus hominis,* and *Streptococcus viridans*) from Spain, and five kidney, two liver, three lung, and two hearts transplantations from donors with *Acinetobacter baumanii* septic shock from Israel were performed, and donor-derived infections were not transmitted to any recipients [12,13].

Another report evaluated the effect of bacteremia that is not recognized before transplantation on the outcome of heart and liver recipients. Organisms such as *Staphylococcus aureus*, *Enterococcus faecalis, Acinetobacter baumannii, Streptococcus viridans, Streptococcus agalactiae*, coagulase-negative *Staphylococcus*, *Enterococcus faecium*, *Pseudomonas aeruginosa,* and *Serratia marcescens* were isolated from donors' blood cultures. Vancomycin and ceftazidime were administered to recipients as a surgical prophylaxis until the third day after transplantation. The study showed that unrecognized bacteremia in the donor does not have a negative clinical impact on the outcome of organ transplant recipients [14].

Essentially the question to be answered is, if the donor has a multidrug-resistant bacteremia (such as extended-spectrum β-lactamase or carbapenemase-producing *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* and multi-drug resistant *Pseudomonas aeruginosa* or *Acinetobacter baumanii*) that was not cleared by standard antibiotic prophylaxis, should organs be procured?

There is no unity in the guidelines for this type of bacteremia. Experiences in the literature consist of case series and expert opinions. However, it is worth noting that different results from different cases have been reported in the literature.

As an example from Goldberg *et al*., a 36-year-old man with no significant medical background was admitted to the hospital after near drowning. Both lungs, both kidneys and the liver were recovered and transplanted into five recipients. Two days after organ procurement, sputum and bronchoalveolar lavage cultures were reported as positive carbapenem-resistant Klebsiella pneumoniae (CRKP). Antibiotic sensitivity was limited to gentamicin, colistin, and tigecycline. Regarding the two kidney recipients, no transplant infectious complications were noted, and graft functions were normal for both recipients at sixth months. Both patients received preoperative cefazolin treatment through the local protocol. However, the lung transplant recipient died. These experiences suggest that some respiratory colonized CRKB positive donors may be considered as candidate donors for organs other than the lungs [15].

In an experience from Italy, both kidneys from a donor who was an asymptomatic CRKP carrier were transplanted to a single recipient. Two days after transplanttation, the same bacteria were isolated in donor urine cultures. The recipient applied to the hospital with a high-grade fever 15 days after transplantation due to CRKP. The patient was started on meropenem, colistin, and tigecycline treatment. Antibiotic treatment was revised to ertapenem, meropenem, and colistin since bacteremia continued despite antibiotic treatment. The recipient died two months after transplantation due to resistant infection [16].

In an example reported from Brazil, a lung transplant was made from a donor who had only been in the hospital two days. Fever, hypotension, and respiratory failure developed in the recipient two days after transplanttation. The same day, A. Baumanii was isolated in the donor's bronchoalveolar lavage fluid. The recipient died on the 65th day of the lung transplant due to pneumonia and recurrence of infection at the surgical wound even though immunosuppression was stopped [17].

In another case, kidneys procured from a 21-year-old patient who was evaluated as a donor due to a gunshot were transplanted into two recipients. In the urine and peritoneal cultures taken during the transplant, MDR P. aeruginosa growth occurred three days after the transplantation. One of the recipients died shortly after transplantation due to pseudomonas infection. The other recipient was treated with colistin and amikacin for six weeks, and one year later was alive with normal kidney functions [18].

In another case presented for another resistant bacterium, methicillin-resistant S. aureus (MRSA), an intravenous drug abuser applied to the emergency department with confusion and fever. Antibiotic treatment was started, considering meningitis. Intracranial hemorrhage was detected on brain CT imaging. MRSA was isolated in blood cultures which were taken at the time of admission to the emergency room. The donor had been treated with vancomycin and remained afebrile for 48 hours. Lung, kidney, pancreas, and liver transplants were performed 36 hours after brain death. The patients with kidney and pancreatic transplantation continued with vancomycin, and no signs of infection were observed. The liver and lung recipients were successfully treated despite various MRSA infections such as cellulitis and pneumonia [19].

The lesson to be learned from these examples is that transplantation of the organ with infected or colonized with MDR bacteria poses a significant problem for transmission of donor-derived infections.

Although there are encouraging examples, there is insufficient evidence to use donors with multiple drug-resistant bacteremia. Management of donor-derived infections caused by MDR microorganisms is very difficult because of drug resistance, drug toxicities, and drug interactions with transplant medicine [20]. The results of virulent bacteremia, such as post-transplant

sepsis, graft artery rupture, or mycotic aneurysm, can be disastrous [21-23].

European guidelines recommend that organs from donors returning positive cultures for MDR bacteria may be considered for transplantation in well-defined circumstances provided there is close recipient follow-up, unless the organ to be transplanted is itself colonized [24].

Urinary tract infections (UTIs) and pyelonephritis are common among potential donors due to bacteria ascending along the urethral catheter. Any suspected UTI in potential donors should be confirmed by urine culture, and potential kidney donors with UTI should be investigated to rule out upper urinary tract infection. In case of a UTI restricted to the lower urinary tract, kidneys may be used, as they are not infected. All other organs can be safely used for transplantation [25]. European guidelines state that uncomplicated UTI/bacteriuria is not a contraindication for the utilization of kidneys, provided that adequate antibiotic treatment is given to the donor and recipient [24].

Organs from donors with bacterial meningitidis due to *Neisseria meningitidis*, *Streptococcus pneumonia, Haemophilus influenza,* and *Escherichia coli* can be transplanted safely [26-29]. It is important to note that not all infections carry the same risk for disease transmission; donors with meningoencephalitis with unknown etiology, *Listeria monocytogenes* meningitis, Mycobacterial meningitis, or metastatic virulent bacteremia have an unpredictable risk for donor-derived infections and mortality. Listeria species may cause a disseminated infection that is difficult to treat in the immunosuppressed patients with high-risk of relapse [30]. Similarly, meningitis caused by disseminated *M. tuberculosis* infection may be transmitted to the recipient with fatal consequences and is a contraindication for transplantation [31]. Donors with these type of infections should be avoided [3,5,32]. Also, donors with active tuberculosis infections should not be utilized [33].

To summarize international guidelines and expert opinions, it is recommended that the infected donor with readily treatable microorganisms receive appropriate antibiotic therapy for at least 24-48 hours, optimally with some degree of clinical response or improved inflammatory markers. In some cases, delaying organ procurement until the donor has received targeted antibiotics for at least 48 hours may be reasonable. After that, bacteremic donors with susceptible microorganisms may become eligible for procurement. Also, it is recommended that the recipient is treated with one or more weeks' course of antibiotics targeting the organism isolated from the donor [34,35]. General recommendations for deceased donors diagnosed with actively treated bacterial infections are reviewed in Table 2.

Table 2. Recommendations for deceased donors diagnosed with actively treated bacterial infections

❖ Important to define the isolate's resistance profile.
❖ Donor colonization should not constitute a contraindication to transplantation, except active infected kidney.
❖ Donors with a positive rectal swab for any MDR GN microorganism: all organs could be accepted for transplantation.
❖ Donors with MDR GN microorganisms isolated from airway secretions: organs other than lungs are appropriate for transplantation.
❖ Donors with a positive urine culture for MDR GN microorganisms: all organs could be accepted, except fort the kidneys.
❖ Donor with bacteremia with susceptible microorganisms who has received appropriate antibacterial treatment for at least 48 hours can be safely used as long as the same effective antibiotic therapy is continued in the recipients.
❖ There should be some evidence of a clinical response to the effective antibiotic therapy such as normalization of markers of ongoing infection before procurement.
❖ Donor should be assessed for disseminated foci of infections, this mas represent a higher risk of transmission of infection.
❖ Any meningitis caused by an unknown pathogen is an absolute contraindication for organ donation.
❖ If the donor has a positive urine culture for CRKP or CRAB, transplantation of their kidneys should be avoided unless the infection is eradicated.
❖ The organs from donors with highly resistant bacteria (ESKAPE pathogens) have rarely been used safely.
❖ Decisions regarding the use of organs that might be infected with antimicrobial resistant pathogens must be made on an indivudual basis.
❖ MDR GN: multi-drug resistant gram negative. CRKP: carbapenem resistant *Klebsiella pneumoniae*. CRAB: carbapenem resistant *Acinetobacter baumannii*.
❖ ESKAPE pathogens: vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus*, extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*, carbapenem-resistant *Acinetobacter baumannii*, carbapenem- and quinolone-resistant *Pseudomonas aeruginosa*, and derepressed chromosomal beta-lactam and extended-spectrum beta-lactamase-producing *Enterobacter species.*

Fungal infections

Donor-derived fungal infections can be associated with serious complications, so a potential transmissible fungal infection in the donor is a contraindication for transplantation [36]. It is very important to recognize donors at risk of fungal infection. Blood and urine cultures should be taken in recipients with intestinal perforation in the donor or if *Candida* species are isolated from presservation fluids. Doppler ultrasound should be evaluated at intervals for a mycotic aneurysm that may develop in the vascular anastomosis line. Prophylactic antifungal therapy (fluconazole) should be initiated when yeast is visualized on stain or *Candida* species are isolated from preservation fluid or organs from donors with intestinal perforation [37].
C. neoformans should be considered in donors with unexplained mental illness or meningoencephalitis [38]. Also, cryptococcosis can be manifested as pulmonary nodules. Use of organs from untreated donors with cryptococcosis is not recommended. The standard regimen for the treatment of cryptococcosis is induction with lipid formulation of amphotericin B and flucytosine followed by consolidation and maintenance therapy with fluconazole. Antifungal treatment duration is 6-12 months [37].
Explanted organs that may have granuloma should undergo fungal culture and testing for antigen and antibodies to *Histoplasma capsulatum*, especially donors from the endemic regions for Histoplasma infections [37]. Positive antigen tests would be an indication for treatment for histoplasmosis, which is lipid formulation of amphotericin B for two weeks followed by itraconazole for at least one year [39].

Parasitic infections

Toxoplasmosis is caused by the intracellular protozoan parasite, *Toxoplasma gondii*. Toxoplasma seropositivity poses a great risk for the development of active toxoplasmosis in heart transplant recipients, but is rare in liver and kidney recipients [40,41]. Routine trimethoprim-sulfamethoxazole prophylaxis is effective in preventing toxoplasmosis transmission [42]. Screening for endemic infection, including *T. Cruzi* and *Strongyloides,* should be performed based on local epidemiologic guidelines [36].
As a future perspective, Yang and colleagues provide important clues to define donor-derived infections. They analyzed the non-human cell-free DNA to test for infections in the recipient's plasma. This method, which can be used to monitor broad-spectrum infections for recipients, provides comprehensive information for clinicians to optimize immunosuppression therapy [43]. Moreira *et al*. showed early increases of total cfDNA levels during acute rejection, systemic infection, and graft function after kidney transplantation [44]. Plasma dd-cfDNA levels have shown marked increases both during acute rejection and graft infection, pointing to the necessity of a combined pathogen monitoring strategy [45]. In this way, deaths due to donor-derived infections may decrease with the help of advanced laboratory techniques.

Conclusion

As a conclusion, transplantations with the expanded donors we have to consider due to the high requirements are very important for a successful transplant, while also not putting the patient at risk, especially for donor-induced infections. Therefore, all recipients of organs from suspicious donors should be informed of the risk of potential disease transmission. To minimize donor-derived infections, when obtaining deceased donor information, the entire history of the donor should be taken in great detail. Suspected or proven bacterial, viral and fungal infection status, culture results, infection sources, etc. should be thoroughly investigated. With this collected information, risk should be determined based on the severity of immunosuppressive treatment. In each transplant, the decision should be made individually according to the condition of the recipient and the donor. After the transplantation, the recipient should be followed up closely for infection; frequent monitorring of vital signs, and infection parameters such as WBC, CRP, procalcitonin and daily culture monitoring should be performed. Rapid inter-institutional communication and antibiotic prophylaxis based on in vitro susceptibility testing are crucial approaches.
The available organ pool is declining, but the demand for kidney transplantation is not. Of course, care must be taken to find the appropriate balance between minimizing the risk of disease transmission and organ wastage.
Respectfully submitted in memory of all the healthcare professionals who have died in the fight against Coronavirus all around the world.

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