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Donor infection with multi-drug resistant organisms:

Should we change our approach to peri-operative prophylaxis?

Transmission of disease from donor to recipient remains an inevitable consequence of solid organ transplantation. In fact, the intentional transmission of viruses such as cytomegalovirus is routine; management strategies reduce the negative consequences of these transmissions. Unexpected transmission of disease is much less common, complicating less than 1% of organ transplants. Nonetheless, consequences can be severe with significant recipient morbidity and mortality and the potential to reduce public trust in the safety of the organ procurement system.

Much of the regulatory attention regarding donor-derived disease has focused on blood borne viruses, particularly - in light of the opioid epidemic -hepatitis C virus (HCV). More sensitive testing methods combined with direct acting antivirals that cure post-transplant HCV have reduced the risk and consequence of donor transmission of HCV. What then should the transplant community prioritize in decreasing the impact of donor disease transmission? One emerging and poorly studied area is donor infection with multidrug-resistant organisms (MDRO). The World Health Organization cites antibiotic resistance as “one of the biggest

threats to global health, food, and security" and that "new resistance mechanisms are emerging and spreading globally, threatening our ability to treat common diseases" (1). According to the CDC, 2 million infections with MDROs resulting in 23,000 deaths occur yearly in the United States (2). In some circumstances, no reliably effective antibiotics are available to treat these organisms.

The published literature on the impact of donor-derived infection with MDROs is limited, but transmission of infection from donors infected at various sites (blood, sputum, preservative fluid, peritoneal fluid) with significant recipient morbidity has been described (3-5). In a large cases series from Italy, 30 recipients were exposed to donors infected with carbapenem resistant gram negative bacteria. In 14 of these 30 recipients, the donor had either bacteremia or infection of the transplanted organ. Four of six exposed recipients not promptly receiving active antimicrobial therapy developed clinical infection or colonization, and one died. Interestingly, the 8 recipients effectively treated for at least 7 days did not develop donor-derived infection (4).

Deceased donors have many of the traditional risk factors for infection with MDROs including prolonged hospitalization, receipt of antimicrobials, treatment in an intensive care unit, and mechanical ventilation. When culture and sensitivity information is available pre-procurement (e.g., isolation of multi-drug resistant *Acinetobacter* from a tracheal aspirate isolated a few days prior to lung procurement) tailored antibiotics can be administered to the recipient reducing the risk of infection. The more common scenario, however, is that hospital cultures (obtained as part of routine care) or those performed specifically as part of the donation evaluation process become available after transplantation. In this issue, Anesi and colleagues studied if specific donor characteristics predicted donor infection ("active" infection not distinguished from colonization) with MDROs (6). The investigators reviewed deceased donors who donated to one of 4 Philadelphia transplant centers and were evaluated by the local organ procurement organization (OPO). Time to donor isolation of an MDRO was the primary outcome, and donor characteristics including antibiotic treatment were used to identify risk factors for MDRO infection.

The most important finding was that MDRO infection rates increased with length of stay with 20% of donors infected by hospital day 10. Methicillin resistant *Staph aureus* (MRSA) was the most frequent pathogen, and most infections involved the respiratory tract with only 5 (1%) blood stream infections. Important risk factors for MDRO infection on multivariable analysis included HCV viremia (largely for MRSA), dialysis, receipt of narrow-spectrum gram negative antibiotics, and asphyxiation (for resistant *Enterobacteriaceae*). Interestingly the T4 protocol (which uses glucocorticoids and extensive central vascular access), was also associated with MRSA infection.

How can the above findings be used to reduce donor-derived infection? While the rates of MDRO donor colonization are alarming, most of the cultures are from respiratory samples which –while they might indicate colonization at other sites- have not been shown to require targeted interventions in non-lung recipients, and certainly universally broadening antimicrobial prophylaxis is likely to worsen the MDRO problem. Rather, these findings may represent an important early step toward a targeted approach where a combination of factors (*e.g*., prolonged duration of hospitalization, colonization with MDRO organisms at multiple sites, prolonged antimicrobial treatment) may identify donors at a high enough risk of MDRO infection to justify enhanced peri-operative prophylaxis. Such an approach would be complex, and would need to account for local differences in MDRO ecology, and distinguish between gram positive and gram negative MDROs since treatment would differ. Importantly, given the risk of creating further resistance, a better understanding of recipient outcomes associated with donor MDRO infection is required before enhanced prophylaxis can be recommended. While the Anesi study is an excellent beginning, in addition to assessing recipient outcomes, future studies should involve multiple OPOs as local differences in resistance patterns and MDROs of greatest concern would be expected. Hopefully, research in this area will help us make the most informed choice when faced with the decision to accept or decline an organ offer from a donor infected with an MDRO.

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