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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

Should Antimicrobial Resistance Limit Access to an Organ Transplant?

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Abstract

Burkholderia cenocepacia (*B cenocepacia*) is a gram-negative bacteria associated with significant morbidity and mortality following lung transplantation. Most US transplant programs consider *B cenocepacia* colonization to be an absolute contraindication to transplantation. This article argues that, if clinicians have good clinical reasons to expect poor outcomes for patients with *B cenocepacia*, then offering transplantation anyway is an abrogation of clinicians' fiduciary duties. This article also discusses other fiduciary obligations transplant programs might have to patients with *B cenocepacia,* such as referring to another transplant center, considering novel treatment options, and investigating how the infection's virulence factors stratify that patient's risk for poor transplant outcomes.

Case

J is a 26-year-old person with advanced lung disease due to cystic fibrosis (CF) being evaluated for lung transplantation. Throughout their life, J has had recurrent exacerbations of respiratory symptoms that have been treated with a wide range of antibiotics. As part of the pretransplant evaluation, lung transplant and infectious diseases specialists review J's past respiratory cultures. A multidrug-resistant *Burkholderia cenocepacia* (*B cenocepacia*) is growing in multiple recent samples. The bacterium is resistant to most commonly used antibiotics. The few antibiotics to which it remains susceptible have a high rate of toxicities, including kidney injury or kidney failure. Some strains of *B cenocepacia* are also readily transmissible between patients with CF. It does not seem like *B cenocepacia* has ever made J sick, but it has clearly persisted in J's lungs over many months.

J is asked to isolate from other CF patients to avoid spreading *B cenocepacia* to others. This means J cannot easily participate in in-person educational and social events related to CF or lung transplantation. The lung transplant and infectious diseases specialists reviewing J's case are worried that the presence of *B cenocepacia* increases the risk that J will have serious complications after a lung transplant. Transplant recipients must take lifelong immunosuppression to prevent their bodies from rejecting the donor organs. In an immunosuppressed patient, bacteria like *B cenocepacia* could grow in the lungs or spread throughout the body, leading to serious infection. If there are few antibiotics available to safely treat the infection, it could be fatal. The transplant

program has many patients waiting for lung transplants, many of whom die each year before they are able to get a transplant. They meet to discuss whether J should be added to their waiting list or not.

Commentary

In 2021, the International Society for Heart and Lung Transplantation published consensus guidelines for lung transplant candidate selection.[1] Among the conditions labeled "factors with high or substantially increased risk" were infectious diseases—such as *Burkholderia gladioli* and *B cenocepacia* infections—that are extremely difficult to treat following immunosuppression or whose treatment carries significant toxicity. *B cenocepacia*, in particular, has a complex history with CF and lung transplantation.

B cenocepacia is a member of a group of environmentally widespread gram-negative bacteria. *B cenocepacia* is naturally resistant to several antibiotic classes and can undergo transcriptional reprogramming to adapt to host immune responses and antimicrobial therapy. Patients with CF and other forms of bronchiectasis are particularly susceptible to *B cenocepacia* infection.[2] While some patients with CF maintain stable lung function following *B cenocepacia* infection, others have a rapid pulmonary decline.[2] In severe cases, they can develop a clinical entity referred to as cepacia syndrome, which carries high mortality.[3] Unfortunately, lung transplantation does not guarantee *B cenocepacia* eradication because of sinus reservoirs, intraoperative spillage with infection of the chest cavity, or reinfection of the allograft from upper airway colonization.

B cenocepacia is associated with life-threatening posttransplant complications, including bronchial anastomotic dehiscence, empyema, sepsis, and persistent bacteremia.[4] Treatment includes antimicrobial regimens with significant renal, hepatic, and bone marrow toxicities. It also requires net reduction in immunosuppression, which can increase the likelihood of acute and chronic rejection. In 2 centers, the rate of 1-year survival for patients with *B cenocepacia* infection was 25% and 60%.[5,6] There are, however, case reports and case series of successful transplantation of patients with *B cenocepacia* infection or colonization.[7,8] These are generally from programs that employ highly protocolized care pathways, such as the University of Pittsburgh Medical Center.[5] Successful approaches include irrigation of the chest and bronchi with 0.5% povidone-iodine solution or taurolide, continuous antibiotic infusions, or uncommonly employed antibiotic combinations.[5,7] Most centers, however, are reluctant to offer transplantation for patients with *B cenocepacia* because of concern for poor posttransplant outcomes. Is this ethically justified?

Transplant Centers' Fiduciary Duties

Rather than applying the traditional organ allocation principles of utility, respect for persons, justice, and so on, I will approach the question of whether a transplant program should list a patient with *B cenocepacia* from the perspective of the fiduciary duties between transplant centers and their patients. While fiduciary duties have legal dimensions, my focus here will be on fiduciary duties as developed within normative ethics.[9]

Fiduciary duties derive from a relationship in which one party is entrusted with the welfare of another party who has a particular vulnerability. These relationships have 3 characteristics: (1) the beneficiary's vulnerability makes them dependent on the fiduciary; (2) the fiduciary has superior knowledge and skills related to the beneficiary's

vulnerability; and (3) the beneficiary trusts the fiduciary to use their knowledge and skills to promote the best interests of the beneficiary.[10] The patient-physician relationship is a paradigmatic fiduciary relationship. Transplant committees—which are composed of individual health care professionals who stand in a fiduciary relation to their patients—also have a fiduciary relationship with transplant candidates. Patients with advanced lung disease are dependent on the committee; the committee has superior knowledge and skills related to their advanced lung disease; and patients trust that the committee will use its experience and skills to act in their best interests.

Fiduciary duties—like all duties—create specific obligations, organized around the idea that the fiduciary must act to protect and promote the best interests of the beneficiary with respect to their vulnerability. In the transplant setting, these include a mix of positive and negative duties: to obtain informed consent for transplant evaluation and listing, to avoid conflicts of interest in the decision-making process, not to abandon a patient before or after transplant, and not to recommend or pursue treatments that will not benefit or are significantly more likely to harm than benefit the patient. This last obligation is central to the decision of whether to offer transplantation to *B cenocepacia* patients.

Decisions about transplant candidacy are often framed as being about patients' contraindication to transplantation instead of the centers' ability to offer them a high enough probability of the outcome they desire. The way that rejections are expressed—"you are not a candidate for lung transplantation"—might subtly shift responsibility or blame to the patient. There is a counterfactual implicit in this framing—namely, that if the patient had not acquired *B cenocepacia*, had worked harder to lose weight, or had not developed cardiac disease, and so on, they would otherwise have been an acceptable candidate. If we take the idea of fiduciary duties seriously, however, the limitation is not on the patient's side but on the program's. If the center has not had successful outcomes—or, in reviewing others' experiences, does not believe it would have successful outcomes—with patients with a certain condition, it is an abrogation of the center's fiduciary duties to offer transplantation anyway. Part of standing in a fiduciary relationship with a patient is not to offer treatments that are significantly more likely to cause harm than benefit.

But what if the alternative is death or what if the patient is willing to take the risk, no matter how unlikely a good outcome? The traditional response is to shift to the stewardship role of transplant committees and to point out that programs are responsible to donors, their families, and society not to "waste" organs. Taking fiduciary duties seriously, however, means that, even if the program has available organs, not everyone will be a candidate. This is true even if the alternative is death or patients are willing to take any risk. The fact that a patient's vulnerability increases their willingness to assume the risks is a sign that more—not fewer—protections are needed. Just as surgeons do not offer certain interventions—total bowel resection in a patient with widely metastatic cancer or extracorporeal membrane oxygenation in refractory septic shock—that are significantly more likely to cause harm, so transplant committees must acknowledge similar limitations. A clinician who performs an intervention that causes suffering and then death for a patient who was going to die regardless of the intervention abrogates their fiduciary duties to the patient.

Regulations and Fiduciary Duties

The current US regulatory environment adds an additional layer of complexity for a program assessing its fiduciary responsibilities to patients with *B cenocepacia*. Private insurance and government agencies, such as the Centers for Medicare and Medicaid Services, have thresholds for poor posttransplant outcomes, including survival, that trigger program flags.[11] In extreme cases, flagging can result in loss of insurance contracts, referral relationships, and regulatory authorization to continue to offer transplantation. While regulatory flags can have serious institutional financial implications, the reason to avoid regulatory flags is not because transplant committees have specific obligations in this regard to their hospitals. Rather, failure to meet regulatory standards has a direct impact on their patients, including those who are listed and those who are undergoing evaluation. For example, flagged programs display a set of compensatory behaviors, including decreasing transplant volume, increasing selectivity of donor offers, and declining to list perceived high-risk patients.[12] Perceived high-risk patients include currently listed candidates and patients known to the program who would have accepted before being flagged. When deciding to list a patient—or patients—with *B cenocepacia*, centers must consider not just their ability to provide an acceptable outcome. The impact of an unanticipated mortality on the program's ability to transplant other candidates also matters (including to other patients with *B cenocepacia*).

As an example of one approach to considering conflicting fiduciary duties, the program with which I am affiliated is willing to list patients with a history of *B cenocepacia* in a limited set of circumstances. First, they cannot have recent sputum cultures with *B cenocepacia* growth, even if it is felt to be colonization rather than active infection. Second, at the time of their transplant evaluation, repeat sputum, bronchioalveolar lavage (when safe), and endoscopic sinus cultures are collected to confirm the absence of *B cenocepacia*. If these are negative and the patient is otherwise an appropriate candidate, the committee will authorize listing. Surveillance sputum cultures are obtained while the patient is awaiting an organ offer. Short- and long-term outcomes utilizing the program's protocol have been favorable, allowing the committee to fulfill its fiduciary obligations to this group of patients.

Alternatives

A program's decision that it cannot offer transplantation does not exhaust its obligations to patients with *B cenocepacia*. First, it should provide referral to another program that has had better outcomes for *B cenocepacia*. If treatment at another facility would entail extensive travel or relocation, the original program should partner with the referral group to coordinate evaluation testing and pretransplant care. Following transplantation, the original program should offer to collaborate on or fully transition the patient's care after a defined period. Second, because the treatment of *B cenocepacia* patients has evolved significantly, transplant programs should stay abreast of advances in the management of *B cenocepacia* infections by learning from peer programs that offer *B cenocepacia* patients transplantation, evaluating virulence determinants for specific *B cenocepacia* strains, exploring novel therapeutics such as bacteriophage therapy, and understanding the role of new antimicrobial drugs with a lower toxicity profile in treating *B cenocepacia*.[13,14] Some of these avenues—such as bacteriophage treatment—are superogatory in the sense that they are morally praiseworthy rather than obligatory.

Does the etiology of the *B cenocepacia* infection have moral relevance for the committee decision? Molecular typing has made it possible to identify *B cenocepacia*

clusters, often within a CF program or clinic site.[15] However, the extent to which transmission is a function of lax infection control policies, incomplete health care provider or patient adherence to these protocols, or exposure through patient-to-patient interactions outside the clinic remains difficult to assess. Even a case of negligent infection control policies does not change the balance of considerations for the transplant program regarding candidate risk and benefit. It does, however, have significant moral implications for the bronchiectasis program, which is charged with protecting patients within the health care environment. Relatedly, the CF team's failure to respond appropriately to a *B cenocepacia* outbreak with a review of its infection control policies or consideration of postexposure prophylaxis has moral implications for its program.[16] However, as with the source of infection, failing to control the infection should not change the overall balance of considerations for the transplant team—specifically, the imperative to focus on balancing risks and benefits in the care of a patient.

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Editor's Note

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Conflict of Interest Disclosure

Author disclosed no conflicts of interest.

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