

Uncertainties and Conflicting Interests in Lung Transplantation

Some years ago, I worked as a bronchoscopy technician on a lung transplant service. This service maintained a very aggressive post transplant surveillance regimen that was formally connected with the hospital's translational research efforts.

After lung transplantation, patients were seen 9 or 10 times over the course of the first year. They routinely had bronchoscopy, which included a saline flush whereby tissue from the lobe could be collected and then analyzed for signs of infection or rejection. Additionally, patients underwent transbronchial biopsies with the tissue sent to pathology for evaluation of developing allograft rejection. The tissue was also sent to the research labs for collaborative translational studies. Patients also went through a series of breathing tests, thoracic CT scans, and blood draws during their regular check ups.

This aggressive follow-up was not without controversy. Many, probably most, in the field believed it was necessary to detect rejection or infection early so as to intervene rapidly and as effectively as possible. Others felt that these patients should be left alone after transplant unless symptoms actually arose. I recall one transplant group in particular claiming that their center's overall post transplant survival times are just as good as those at centers that use the more aggressive regimen.

I believed that it was an honest question as to whether the aggressive management at my facility was, in fact, providing better patient care. The central problem was that lung graft survival times are less than desired overall and have not changed much over the past decade. More research is needed to better understand and be able to predict and treat episodes of lung allograft rejection before total graft failure occurs and the patient dies. So, it is certainly fair to say that while aggressive management for both clinical and research purposes might have problematically put the patient at an increased risk without immediate personal benefit, transplant knowledge gained through the diligent and extensive collection of clinical and biological data is the only way to better understand the pathology of lung allograft rejection and why some treatments do or don't work. Of course, the most likely beneficiaries of this knowledge will be future patients, not the ones we are currently treating.

The second ethical problem with this research was the collection of lung alveolar tissue by transbronchial biopsy for both clinical and research purposes. This is a procedure that poses serious risks with even the possibility of death. However, the procedure is currently the gold standard for diagnosis of lung allograft rejection. The problem is that while we wanted to take biopsies for both clinical as well as research purposes, sometimes the decision had to be made to skip one or the other because of an occasionally limited ability to obtain tissue.

Multiple biopsies are the gold standard because rejection can be occurring in a portion of the lung not sampled, thus leading to false negatives. But when the tissue samples at a particular visit only go to research and the patient eventually goes into rejection, I have wondered whether we would have caught some of the false negatives sooner had the samples only gone to the clinical lab.

Perhaps there is no ethical solution to these issues because lung transplantation is hardly a perfect science. But there certainly seems to be ample room for ethical reflection on the somewhat conflicting stakes between research and patient care, and the clinical uncertainties that are part and parcel of lung transplantation.

Expert Opinion

One of the problems posed by this dilemma is whether or not it was ethically acceptable to subject transplant patients to a highly aggressive post-transplant regimen of procedures to check for allograft rejection. One might argue, as the dilemma contributor does, that this regimen, which included tests of a purely research as well as clinical nature, might have disposed patients to excessive or unreasonable risk (not to mention the unpleasantness involved). Of those tests that serve a purely clinical value, however, we are of the understanding that “surveillance” bronchoscopies with multiple (i.e., at least 6) transbronchial biopsies for early detection of clinically occult acute rejection are the gold standard worldwide, as the number and intensity of acute rejection episodes are the strongest predictors of subsequent graft dysfunction and patient death.¹ While there may be some investigators who claim equal results without this amount of follow-up, those claims do not seem to represent mainstream transplant understanding and practice. Moreover, our experience with transplant recipients has shown that they very much desire aggressive follow-up. Consequently, we find the author’s argument, i.e., that aggressive clinical follow-up is probably what the standard of care should require, compelling. But what about those tests that are purely of a research nature—the ones where, according to the dilemma contributor, “the likely beneficiaries of this knowledge will be future patients, not the ones we are currently treating”?

If the risk burden of these tests, as measured by the quantity and gravity of adverse events or complaints, is not deemed excessive or unreasonable by the institution’s IRB or office of clinical trials, participants simply must be apprised of their dual role as 1) patients about to undergo transplant and 2) research participants whose post-transplant experiences will be closely monitored for scientific purposes. They must be informed that certain of the tests they experience will not help them personally but will rather help researchers develop better transplant interventions for future patients.

Acknowledging research participation by way of these informed consent considerations suggests that patients be allowed to opt out of them, or that they can rescind their consent at any time. At Emory University, for instance, the physician performing a bronchoscopy for research purposes confirms that the patient has a signed research consent form on file and asks at each visit if the individual still wishes to participate.

The dilemma contributor’s transplant center is having patients fulfill both research as well as clinical roles, which those patients have a perfect right to know about. Indeed, one cannot imagine that the informed consent documents these patients sign would omit that information. Furthermore, one would hope that the various professionals who are seeing these patients are clearly distinguished from one

another as clinicians and investigators. To the extent, however, that many of them, especially physicians, play both roles, conflicts of loyalty can easily occur that could compromise informed consent discussions with patients. It is possible, in other words, that clinician-investigators might pose informed consent conversations in such a way that patients feel they have no choice but to acquiesce to the research studies, or they might not be made sufficiently aware that certain of the tests have no clinical benefit for them. The former is coercive while the latter is deceptive. Both, of course, are unethical.

But the dilemma contributor raises a second problem per his suspicion that biopsied material was occasionally sent only to the research arm of the study and not to the clinic, which might have harmed certain patients who went into rejection. While we will never be able to tell with sufficient confidence whether this investigator's worries are legitimate, it is hard to think that the research protocol in this case as vetted by the institution's IRB would not have stipulated the frequency and amount of tissue that would need to be taken to satisfy both patient protection requirements as well as research objectives. If the actual implementation of the protocol sometimes did not accommodate or satisfy those stipulations, then it is easy to indict a lack of reporting or oversight on protocol adherence as the culprit. Note, also, how this recalls the conflict of loyalty mentioned above: that if a health professional was assigned to care both for the patient's clinical needs as well as collect tissue for research, he or she risks becoming compromised by conflicting demands. (And it would not be terribly difficult to imagine him or her rationalizing a decision that favors research interests, especially if the investigators feel very pressured to collect adequate material.)

Still, an IRB would never allow the participants' personal welfare to be subordinated to their value as research subjects. So, if a conflict ever had to be adjudicated about prioritizing where the patient's tissue would go if it could go to only one place, i.e., to a research lab or a diagnostic lab, morality would dictate the latter over the former.

If the technician observed the clinical care of patients being compromised by the investigators' research interests, he should have reported it. This brings up the question as to whether he didn't think it his job, or that he feared reprisals for doing so, or that he believed that reporting wouldn't make a difference. Ideally, everyone on the research team should feel comfortable bringing up concerns like this, but we know in practice that such "speaking up" can be excruciatingly difficult to do, especially if, as was the case here, the would-be whistleblower is someone without much power. On the other hand, the dilemma contributor might have simply understood his concerns to be nothing more than uncomfortable suspicions that ultimately lacked evidence. This leaves us with the interesting and provocative question as to: At what point does a population like this become "sufficiently" endangered by having their lung tissue go clinically unexamined because, say, it is diverted to research? Until that question is confidently answered, moral reflection over the quality of patient protections, the possibly reckless endangerment of patients, and the design of and adherence to biobanking protocols will remain inconclusive.

1. Dransfield M. **Standardized guidelines for surveillance bronchoscopy reduce complications in lung transplant recipients.** The Journal of Heart and Lung Transplantation, 2004; 23 (1):110 - 114 M .

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