Infections after Transplant: Lessons from the World's First Heart Transplant

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Abstract

Infections in immunosuppressed patients are always a big challenge and even with the best of care, there is a lot of mortality and morbidity. This article describes the experience of Dr Christiaan Barnard and his team during and after the first cardiac transplant of 1967. Relevant points useful for today's clinicians are discussed in detail.

Keywords: Cardiac Transplant, Chest X-ray, Infection, *Pseudomonas*.

Bengal Physician Journal (2019): 10.5005/jp-journals-10100-6102

Infections are one of the main challenges facing clinicians today. In some special situations like post-transplant cases, infection is the main cause of mortality and morbidity. In this context, it would be pertinent to look back at the experience of doctors who performed the world's first cardiac transplant. This is further helped by the fact that Dr Christiaan Barnard, the surgeon responsible for this medical milestone, accurately documented his experience in his later autobiography, one Life. The hematology, microbiology and radiological reports of the patient each day after the transplant are documented in great detail. Thus, this is an invaluable account for posterity and a study of the accounts of this astute clinician is a valuable lesson for doctors even today. This article is mainly based on Dr Barnard's account. Anyone going through the subsequent paragraphs will no doubt have a sense of déjà vu because the scenarios depicted by Dr Barnard more than 50 years ago are still very much relevant.

The first recipient of cardiac transplant was a man named Louis Washkansky. Dr Christiaan Barnard of South Africa was the surgeon who performed this feat, thereby reaching one of the most important milestones in medical history. However, after 18 days, the patient succumbed to illness. The following paragraphs give a brief account of the last days of this patient. It must be remembered that in 1967, this was an uncharted territory. The doctors striving for success had very little evidence to depend upon. Their experience was mainly derived from animal studies. Many of the drugs used at that time were new and their effects were unknown. Interpretation of hematology or radiology reports after transplant was also something new. Thus, each new report brought new challenges and the doctors had to find explanations on their own. In hindsight, some of their decision may seem inappropriate. But at that juncture, they all tried their best and did whatever they thought was right.

Mr Washkansky was given hydrocortisone, prednisolone and azathioprine after the transplant. Also, cobalt irradiation to the heart was given to prevent rejection. On day 5, actinomycin C was further added.

The first 5 days were stormy with frequent cardiac arrhythmias and other organ dysfunction. At this time, Klebsiella was isolated from nostril and rectum during routine surveillance; this was thought to be a colonizer and only gentamycin was added. After that, days 6–10 were stable with no fever and the transplant team was optimistic that the immediate threat of infection had been averted.

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How to cite this article: Paul R. Infections after Transplant: Lessons from the World's First Heart Transplant. Bengal Physician Journal 2019;6(1):15–16.

Source of support: Nil

Conflict of interest: None

On the 11th day post-transplant, the first inkling of trouble was a rise in the WBC count from 15,900 to 29,860/cmm. In the team meeting, it was discussed and at first it was thought that this leukocytosis was due to high dose of steroids. But Dr Reuben Mibashan, the hematologist, had found toxic granular changes in the white cells. Since no source of infection was apparent, the team members agreed that this change could also be due to steroids. The chest X-ray was clear, stool and urine cultures were sterile. Thus, they decided to continue with the same treatment.

On the 12th day, the patient had a shoulder pain and complained of being tired. However, during the evening team meeting, it was seen that the white cell count had dropped and cardiac enzymes had also dropped. So, these were taken as signs of improvement. Routine mouth and nose swab revealed *Klebsiella*, which was again thought to be a colonizer and thus, no new antibiotics were added. Later that evening, the chest X-ray revealed a tiny shadow in the left lung. But Dr Barnard was not sure whether this was a focus of infection or a vascular lesion. The patient developed a slight temperature (98.6° F). They thought the temperature and shoulder pain were due to post-pericardiotomy syndrome. Thus, no change in treatment was done.

The very next day, the whole situation changed. Early morning on day 13, bronchial breath sound was found on the left side. Temperature was still 98.6° F. But over the next few hours, temperature rose to 101.6° F, pulse rose to 100/minute, blood

pressure fell. The morning X-ray showed patches in the left lung and also, lower lobe of the right lung. There was no sputum production and hence, cultures could not be sent in the morning. But after 1 pm, the patient started to cough up rusty sputum. Immediately a sample was sent to the laboratory and pneumococci were found on Gram stain. Penicillin was immediately started. But temperature continued to rise to 102.2° F. By evening, temperature was 103.8° F.

The next morning, the chest X-ray remained the same. But sputum initial culture reports were available and they grew *Klebsiella* and *Pseudomonas*, white cell count fell from 27,390 to 24,600/cmm. They started cephaloridine, in addition to penicillin.

But by the same evening, lung shadows had become denser, although repeat sputum Gram stain showed no pneumococci. From the same night, the patient started to deteriorate, with fecal incontinence and also complained of pain in the chest. On day 15, the patient went into shock with severe dyspnea. Morning X-ray showed increased confluent shadows in both lungs. The peripheral blood smear showed toxic granules and vacuoles in WBCs. Thus, there was sepsis but the transplant team was not sure whether this X-ray finding was infection or transplant lung (immunological lung damage after transplant). So they continued the antibiotics but also increased the immunosuppression. pO_2 dropped from 100 to 70.

On the next day 16, white cell count suddenly dropped from 22,200 to 5,640. Since they had given actinomycin C as immunosuppressant, they could not be sure whether this fall in count was due to the drug or overwhelming sepsis. But they eliminated the actinomycin anyway and decided to give white cell transfusion. By that evening, the patient went into respiratory failure and had to be intubated and ventilated.

On day 17, the sputum again grew *Klebsiella* and *Pseudomonas*. Carbenicillin was added to the therapy. But the white cell count fell further to 2,790. The pO_2 started to fall rapidly and finally the patient had cardiac arrest.

Later at autopsy, both lungs were found to be filled with pus with almost no airspace spared. The transplanted heart, however, was perfect.

As this account makes clear, infection in immunosuppressed patients can spread like wildfire. The tiny speck in chest X-ray one evening progressed rapidly to involve both lungs over next two days and then after two more days, the patient had respiratory failure. Also, any rise of temperature or atypical features like diarrhea in these patients should be taken seriously as this can herald serious infection. For clinicians of today, this is a valuable lesson that infections often have a very small window of opportunity and if this is missed, the patient usually succumbs. Also, the right antimicrobial agent needs to be instituted at the right time. For example, on day 5, the patient grew *Klebsiella*. But instead of giving colistin, they settled for only gentamycin. Probably this was not a correct decision in hindsight. Also, was it the correct decision to increase immunosuppression on day 15? The answer is difficult to gauge because post cardiac transplant lung shadows can be due to both infection and immunological insult. This dilemma is faced by clinicians through the ages.

Infections of the lung can spread quickly and give very little time before respiratory failure supervenes. This is true not only for this particular post-transplant scenario, but in general. *Klebsiella* and *Pseudomonas*, the organisms which wreaked havoc in Louis Washkansky's lung, are ubiquitous in the critical care unit today and the same challenges faced by Barnard and team are faced by critical care physicians today. The question is, was Dr Barnard right in attempting a cardiac transplant in 1967? There is no doubt about his surgical skill but was it wise to do a transplant in an era when antibiotics were still in their infancy? Should he have waited a few more years for more potent antibiotics to be available? It is impossible to answer these questions. Dr Barnard and his team were trailblazers and such people do not wait for circumstances to change. According to Dr Barnard's account, they were acutely aware of the threat of infection and they took all possible measures to counter it.

But, even in modern times, with much better antibiotics, a large number of post-transplant cases are still lost to infection. And many of the infections are the same as faced by Dr Barnard's patient 50 years ago. We are fortunate that Dr Barnard wrote a vivid account of his experience and this account is a good reference point for clinicians.

This historical narrative is thus relevant for today because it teaches a lot of valuable lessons in infection control, post-transplant care and antibiotic strategy.

Lessons to be learnt:

- Even before the rise of temperature, subtle clinical signs like tachycardia or hypotension may herald a serious infection.
- A sudden fall in leukocyte count in sepsis is as bad as a striking rise in count.
- In potential sepsis patients, clinical samples like sputum should be sent for bacteriological study as soon as they are available.
- Post-transplant lung shadows may be due to immunological reaction or infection. The treatments are diametrically opposite. Physicians always have to walk a tight rope.[1]

Reference

1. Barnard C, Pepper CB. One Life. London: George G. Harrap & Co. Ltd.; 1969.