Institution: Newcastle University

Unit of Assessment: UoA-1

Title of case study: How better risk stratification for lung transplant has benefitted cystic fibrosis patients

1. Summary of the impact

Lung transplants represent the last hope for cystic fibrosis patients with end-stage lung disease. However, since the mid-1990s, other than in large research centres, some cystic fibrosis patients were not offered this treatment because of the variable and often poor outcome of surgery. This patient group carried a difficult to treat bacterial infection caused by the *Burkholderia* genus. In 2001 researchers in Newcastle published findings that demonstrated that one particular species, *Burkholderia cenocepacia*, was responsible for the poor outcomes and that other species of *Burkholderia* were not as dangerous. This finding was incorporated into international guidelines and since 2008 most transplant centres worldwide have adopted a risk stratification approach to listing patients for transplant. Consequently, more than 30 people per year worldwide now get transplants that would otherwise have been denied.

2. Underpinning research

Key Newcastle University researchers

Professor Paul Corris and Dr. Anthony De Soyza originated the research: Corris then acted as De Soyza's doctoral supervisor. Professor Gould developed the microbial repository and provided input to study design and analysis. Professors Dark and Fisher contributed to analysis, and, with Corris and Gould, the clinical service. All worked jointly between Newcastle University and the Newcastle upon Tyne Hospitals NHS Trust.

Background

The condition: Cystic fibrosis is an inherited condition, affecting both sexes, that has an impact on many systems in the body, but respiratory problems are the most common cause of illness and death. The incidence of cystic fibrosis in the UK is around 1 in 2,500 newborns per year. The Cystic Fibrosis Trust report that around 10,000 people in the UK live with the condition. In end-stage cystic fibrosis, often the only viable means of prolonging a good-quality life is by transplanting both lungs with healthy donor organs.

Transplantation: The International Society for Heart and Lung Transplantation reported that 178 centres worldwide conducted 3,519 lung transplants in 2010 (the latest full year for which there are data). Of these, 620 were cystic fibrosis patients (17% of total). The British Transplantation Society estimated that on average around 9 out of 10 people will survive for at least a year after a transplant and 5 out of 10 will survive for at least five years.

Infection: Worldwide, it is reported (R5 and Boussaud et al 2008 PMID: 18408050) around 5 – 10% of cystic fibrosis patients become colonised with a bacterium known until recently as *Burkholderia cepacia* (around 500 patients in the UK). Such infection was, and remains, difficult to treat and can cause the clinical syndrome of necrotising pneumonia with associated septicaemia. This is life threatening. From the early 1990s, centres worldwide reported that cystic fibrosis lung transplant patients with *Burkholderia cepacia* infection had variable and generally worse outcomes compared to patients without the pathogen. Consequently, many centres stopped transplanting such patients.

By the late 1990s, research revealed a complex of nine different, closely related, species of bacteria. These included *Burkholderia cepacia, Burkholderia multivorans* and *Burkholderia cenocepacia.* '*Burkholderia cepacia* complex' infections continued to be a contra-indication for transplant in most centres worldwide.

Research in Newcastle

One strand of research in Newcastle focussed on risk stratification for lung transplant in cystic fibrosis patients. Approximately 20 lung transplants for cystic fibrosis are conducted per year at

Newcastle; the highest by volume in the UK. Many more patients are, of course, referred but a number of factors are taken into account before listing a patient for transplant. The number of transplants is limited by donor lung availability.

In 2001, Newcastle researchers published the first results (R1) which showed that one particular species in the *Burkholderia* complex, *Burkholderia cenocepacia,* was associated with poor outcome of transplantation in cystic fibrosis patients. This was confirmed by studies in North Carolina and France. In 2003, De Soyza and Corris reviewed the then-current state of knowledge (R2) and drew the conclusion that accurate identification of the particular *Burkholderia* species carried by each patient was important, as the weight of evidence suggested that patients without the dangerous *Burkholderia cenocepacia* species could be transplanted successfully.

Newcastle researchers published an '*important first step*' (Editorial comment, http://ajrccm.atsjournals.org/content/170/1/6) in 2004, identifying factors underlying the virulence of the dangerous *Burkholderia cenocepacia* (R4). In 2010, Newcastle researchers published a retrospective study (R5) of their experiences of lung transplant in 216 cystic fibrosis patients over 20 years. They noted that 22 patients had confirmed pre-operative *Burkholderia* complex infection, with 12 of these being *Burkholderia cenocepacia*. Nine of these *cenocepacia*-infected recipients died within the first year; however patients infected with other *Burkholderia* species had significantly better outcomes, with post-transplantation survival comparable to other transplant recipients with cystic fibrosis.

3. References to the research

(Citations as at July 2013, key Newcastle researchers in bold.)

R1. **De Soyza A**, McDowell A, **Archer L, Dark JH**, Elborn SJ, Mahenthiralingam E, **Gould K**, **Corris PA**. *Burkholderia cepacia* complex genomovars and pulmonary transplantation outcomes in patients with cystic fibrosis. *Lancet* 2001 Nov 24, 358(9295): 1780-1. doi:10.1016/S0140-6736(01)06808-8. **Cited by 93.**

R2. **De Soyza A and Corris PA**. Lung transplantation and the *Burkholderia cepacia* complex. *The Journal of Heart and Lung Transplantation* 2003, 22(9): 954-8. doi:10.1016/S1053-2498(03)00024-X. **Cited by 21.**

R3. **De Soyza A, Ellis CD, Anjam Khan CM, Corris PA and Demarco de Hormaeche R.** *Burkholderia cenocepacia* lipopolysaccharide, lipid A and proinflammatory activity. *American Journal of Respiratory and Critical Care Medicine* 2004, 170: 70-7. doi: 10.1164/rccm.200304-592OC. **Cited by 35.**

R4. **De Soyza A**, Morris K, McDowell A, Doherty C, **Archer L**, Perry J, Govan JR, **Corris PA, Gould K.** Prevalence and clonality of *Burkholderia cepacia* complex genomovars in UK patients with cystic fibrosis referred for lung transplantation. *Thorax* 2004, 59(6): 526-8. doi: 10.1136/thx.2003.010801. **Cited by 28.**

R5. **De Soyza A, Meachery G, Hester KL, Nicholson A, Parry G, Tocewicz K, Pillay T, Clark S, Lordan JL, Schueler S, Fisher AJ, Dark JH, Gould FK, Corris PA**. Lung transplantation for patients with cystic fibrosis and *Burkholderia cepacia* complex infection: a single-center experience*. The Journal of Heart and Lung Transplantation* 2010, 29(12): 1395-404. doi: 10.1016/j.healun.2010.06.007. **Cited by 22.**

Key funding

Wellcome Trust, *The Role of Genomovars in B.Cepacia Proinflammatory Activity* 01/10/2001 to 30/09/2003, £111,442.00.

The Newcastle upon Tyne Hospitals NHS Charities, *Studies of Host Epithelial Cell-Pathogen Interactions in Cystic Fibrosis Patients Infected with Burkholderia Cepacia,* 01/04/2005 to 31/03/2006, £38,620.00.

Higher Education Funding Council for England: New Blood Senior Lectureship, Dr. Anthony De Soyza, 2007-12; £300,000

4. Details of the impact

Lung transplants represent the last hope for cystic fibrosis patients with end-stage lung disease. By demonstrating that colonisation of the airways with the majority of the closely related *Burkholderia* species of bacteria does not adversely affect the outcome of lung transplant, Newcastle research has resulted in many seriously ill young people now being offered transplants that had previously been considered too risky. The mean survival rate for these patients is as good as that of non-infected patients. In a situation where median lifespan is around 37 years, good-quality lifespan post-transplant can exceed five years (EV a).

Approach to patient treatment in major research centres

As noted above, in the 1990s most centres stopped listing cystic fibrosis patients for transplant if they had any *Burkholderia* infection because of the risk to the patient's life. However, some large research centres, including Newcastle and centres in France, the US, Canada and Australia, continued to consider for transplant patients colonised by these bacteria. Since 2001, all patients in Newcastle have been assessed for risk posed by *Burkholderia* infection by ensuring that those carrying the dangerous *Burkholderia cenocepacia* infection are identified (R1).

If the dangerous *Burkholderia cenocepacia* was found then a revised pre- and post-transplant treatment protocol was implemented. Over time the protocol changed as virulence factors were identified (R4) and researchers sought to improve results for their patients. In 2008, the continued poor outcomes for these patients, even with the amended treatment, led Newcastle and most of the other centres finally to stop transplanting patients with the dangerous *Burkholderia cenocepacia* (see R5). Nonetheless, patients with non-*cenocepacia* infections continued to be transplanted during this period (1990s-2008), but only in the large research-active centres.

The significance of the Newcastle findings (R1-R4), especially the good outcomes for patients with non-*cenocepacia* infection, has been disseminated widely through professional networks and via the guidelines of the International Society for Heart and Lung Transplantation, of which Corris was an author (EV b).

Guidelines into practice

The publication of the International Society for Heart and Lung transplantation guidelines in 2006 brought Newcastle research findings to the attention of transplant centres worldwide. Transplant centres that had stopped listing patients with any *Burkholderia* infection for transplant began to revise their policies after 2008. The Medical Director of the Texas Transplant Centre confirmed,

> '*Implementation of the recommendations suggested, with risk stratification in 2008, led to significant and meaningful changes, not only in our clinical practice, but for the rest of the North American Continent in lung transplantation.*' (EV c)

Further evidence of the Newcastle approach to risk stratification affecting global practice has come from a number of organisations. The President of the International Society for Heart and Lung Transplantation has confirmed that:

> '*Since the ISHLT guidelines were published the majority of transplant centres have, to the best of my knowledge, implemented them in practice. Hence it is fair to say that the current local, and International, policy and clinical practice in relation to lung transplantation of cystic fibrosis patients has largely been informed by the Newcastle research.*' (EV d)

The President of the European Cystic Fibrosis Society in 2013 confirms:

> '*The incorporation of* [Newcastle] *research findings into the ISHLT Guidelines, and the subsequent implementation of risk stratification by the majority of transplantation centres in the past 5 years has led to significant changes in clinical practice throughout Europe. This stratification of* B. cenocepacia *patients, who have very poor outcomes compared to patients with* B. multivorans *and other species, has ensured that the precious resource of transplanted lungs are directed effectively.*' (EV e)

The Chair of the Association of Lung Transplant Physicians UK has also confirmed that '*Most if not all European Transplant centres*' stratify patient risk based on Newcastle's research and noted:

> '*This important finding has been instrumental in informing listing and organ allocation practices in an era of continuing critical donor organ shortage to ensure better use of this scarce resource and effective transplantation in people with Cystic fibrosis. Having previously been denied access to transplantation, many cystic fibrosis patients with non-cenocepacia infection have since undergone successful surgery.*' (EV f)

While work continues to help patients identified as having *the dangerous Burkholderia cenocepacia*, the Newcastle findings have largely benefited cystic fibrosis patients with non-*cenocepacia Burkholderia* complex infections. The Newcastle research paper from 2010 (R5) highlighted the success of transplanting such patients and this data (disseminated widely in abstract form from 2008, the year the paper was first submitted to the journal) has proved influential. The President of the International Society for Heart and Lung Transplantation has confirmed that,

> '*The ISHLT registry does not record infection data stratified by organism, however studies by ISHLT members revealed the prevalence of* Burkholderia *complex species among cystic fibrosis patients on transplant lists to be around 10%. Just under half of these will be colonised by* Burkholderia *species other than* B. cenocepacia*. Consequently it would be reasonable to conservatively estimate that more than 30 patients (adults and children) worldwide per year now receive transplants who would otherwise not have been listed, the majority of those who could benefit.*' (EV d, EV g)

5. Sources to corroborate the impact

EV a. Data on post-transplant survival obtained from International Society for Heart and Lung Transplantation registry. Summary available in the *Journal of Heart and Lung Transplantation* 2012, 31(10): 1073-97. Hard copy available on request. DOI: 10.1016/j.healun.2012.08.004

EV b. The 2006 *International Guidelines for the Selection of Lung Transplant Candidates* are available at http://www.sciencedirect.com/science/article/pii/S1053249806002518. DOI: 10.1016/j.healun.2006.03.011 The guidelines have been cited in 412 papers relating to both research and clinical practice.

EV c. Correspondence from the Medical Director of the Texas Transplant Centre is available and he has agreed to be contacted to discuss matters further.

EV d. Correspondence from the President of the International Society for Heart and Lung Transplantation is available and he has agreed to be contacted to discuss matters further.

EV e. Correspondence from the President of the European Cystic Fibrosis Society is available.

EV f. Correspondence from the Chair of the Association of Lung Transplant Physicians UK is available.

EV g. Details of the manner in which this estimate was reached are available on request and the President of the International Society for Heart and Lung Transplantation has agreed to be contacted to discuss this calculation.