

## Impact case study (REF3b)

<p><b>Institution:</b> University of Cambridge</p>
<p><b>Unit of Assessment:</b> UoA1</p>
<p><b>Title of case study:</b> Transforming the management of Cystic Fibrosis patients infected with Nontuberculous mycobacteria</p>
<p><b>1. Summary of the impact</b> (indicative maximum 100 words) Infection of patients with cystic fibrosis (CF) with the multidrug-resistant Nontuberculous mycobacteria (NTM), <i>Mycobacterium abscessus</i>, has rapidly increased over the past decade and currently affects 5-10% of CF patients worldwide. Our work has identified two possible mechanisms by which <i>M. abscessus</i> infection rates may be increasing: chronic azithromycin therapy may predispose individuals to infection through inhibition of autophagic-killing of mycobacteria; secondly, there is frequent person-to-person transmission of <i>M. abscessus</i> despite conventional infection control measures. This research has had a direct impact on how CF is treated, and has influenced infection control guidelines throughout the UK.</p>
<p><b>2. Underpinning research</b> (indicative maximum 500 words) Dr Andres Floto (Principal Investigator; Cambridge Institute for Medical Research &amp; Department of Medicine, 2008-current).</p> <p>Floto and colleagues used a number of complementary approaches to study the link between long-term azithromycin use by adults with CF and <i>M. abscessus</i> infection. An epidemiological analysis of CF patients attending Papworth Hospital from 2003 to 2008 showed that azithromycin use was strongly associated with <i>M. abscessus</i> infection (Renna et al 2011). Furthermore, they demonstrated by <i>ex vivo</i> analysis of primary human macrophages that concentrations of azithromycin achieved during therapeutic dosing blocked autophagosome clearance, by preventing lysosomal acidification, thereby impairing autophagic and phagosomal killing of <i>M. abscessus</i> (Renna et al 2011). They also studied the effect of azithromycin treatment in vivo in mice exposed to <i>M. abscessus</i> and showed that animal treated with this agent developed chronic infection and more severe inflammatory lung damage (Renna et al 2011). These findings emphasized the essential role for autophagy in the host response to infection with NTM, and revealed why chronic use of azithromycin may predispose to mycobacterial disease, and highlighted the dangers of inadvertent pharmacological blockade of autophagy in patients at risk of infection with drug-resistant pathogens.</p> <p>In a separate publication (Bryant et al 2013), Floto and colleagues performed whole genome sequencing and antimicrobial susceptibility testing on 168 consecutive isolates of <i>M. abscessus</i> from 31 patients attending an adult CF centre between 2007-2011. In parallel, they undertook detailed environmental testing for NTM and defined potential opportunities for contact between patients both in and out of hospital using social network analysis. This study revealed for the first time that <i>M. abscessus</i> could be transmitted from patient-to-patient through an indirect, most likely aerosol route, and that transmission events occurred frequently despite rigorous implementation of national standards of infection control.</p>
<p><b>3. References to the research</b> (indicative maximum of six references) Renna M, Schaffner C, Brown K, Shang S, Tamayo MH, Hegyi K, Grimsey NJ, Cusens D, Coulter S, Cooper J, Bowden AR, Newton SM, Kampmann B, Helm J, Jones A, Haworth CS, Basaraba RJ, DeGroot MA, Ordway DJ, Rubinsztein DC, <b>Floto RA</b>. Azithromycin blocks autophagy and may predispose cystic fibrosis patients to mycobacterial infection. <i>J Clin Invest</i>. 2011. 121:3554-63.</p> <p>Bryant JM, Grogono DM, Greaves D, Foweraker J, Roddick I, Inns T, Reacher M, Haworth CS, Curran MD, Harris SR, Peacock SJ, Parkhill J, <b>Floto RA</b> (2013) Whole-genome sequencing to identify transmission of <i>Mycobacterium abscessus</i> between patients with cystic fibrosis: a retrospective cohort study. <i>Lancet</i>. 2013 May 4;381(9877):1551-60.</p>

#### 4. Details of the impact (indicative maximum 750 words)

This research has identified two important reasons why infection rates of *M. abscessus* are increasing in patients with CF, namely predisposition to infection through azithromycin therapy and person-to-person transmission of infection.

This work has impacted on patients with Cystic Fibrosis in the UK and internationally, their families and the health professionals who care for them by: a) increasing understanding of how people acquire *M. abscessus* infection; b) changing the way azithromycin is used to treat patients with Cystic Fibrosis; c) driving changes to how CF patients are cared for and protected from cross-infection within hospital and at home and d) changing how air ventilation systems are designed in Cystic Fibrosis centres, such as the planned unit in new Papworth Hospital.

The finding that long-term azithromycin therapy impairs host immunity to NTM was widely discussed within the CF community (1,2), the media (3) and at CF conferences (4) has led to the following specific changes in guidelines for clinical practice to ensure safer use of this drug (1,5):

- increased the frequency of sputum sampling for NTM in CF and non-CF patients receiving long term azithromycin
- patients with previous or current NTM infection should not receive azithromycin apart from as a component of multidrug treatment regimens
- Azithromycin should not be used as a component in treatment regimens for macrolide resistant NTM infection.

The finding that person-to-person transmission of *M. abscessus* occurs frequently amongst patients with Cystic Fibrosis was widely disseminated by national (BBC; ref 6) and international (7-10) media organisations and the UK CF Trust (11).

Since these transmission events occurred through indirect spread and despite national standards of infection control, there is concern that urgent changes to cross-infection protocols are required (11).

This research has already led to changes in infection control at Papworth Hospital (12):

- Individuals with *M. abscessus* infection now wear a surgical mask at all times within the hospital buildings except when in a ward side room or a clinic room and are nursed in a negative pressure single room separate from the CF ward;
- staff with structural lung disease are advised against working with these individuals;
- staff caring for NTM infected patients now wear protective clothing when performing aerosol-generating procedures and room and equipment cleaning policies have been changed

This work has also led to changes in the design of the Cystic Fibrosis centre within the new Papworth Hospital building to ensure all rooms have balanced ventilation allowing negative pressure isolation for individuals with *M. abscessus*.

#### 5. Sources to corroborate the impact (indicative maximum of 10 references)

1. <http://www.cff.org/treatments/Therapies/Respiratory/Azithromycin/>

2. <http://www.osservatoriomalattierare.it/fibrosi-cistica/1152--fibrosi-cistica-luso-di-azitromicina-predispongono-i-pazienti-ad-infezioni-da-micobatteri>

3. <http://medicalxpress.com/news/2012-04-autophagy-self-eating-good.html>

4. NACFC 2012 Orlando Florida Azithromycin pro/con debate Prof Lisa Saiman and Prof Kors van de Ent [http://www.officiumroma.it/Doc\\_Info\\_files/News%20dal%20NACF%20Meeting%20-](http://www.officiumroma.it/Doc_Info_files/News%20dal%20NACF%20Meeting%20-)

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5. Papworth Hospital Adult Cystic Fibrosis Unit Protocols for management of Nontuberculous Mycobacterial infection (**Published June 2013**)
6. BBC Radio 4 Today programme April 1<sup>st</sup> 2013; BBC Radio Cambridgeshire Breakfast programme April 1<sup>st</sup> 2013; <http://www.bbc.co.uk/news/health-21965088>
7. <http://www.healio.com/infectious-disease/emerging-diseases/news/online/%7B45939DC7-8055-44A5-9990-F21B26E001A2%7D/Patient-to-patient-transmission-of-M-abscessus-common-in-cystic-fibrosis>
8. <http://www.sciencedaily.com/releases/2013/03/130329090307.htm>
9. <http://www.medscape.com/viewarticle/781727>
10. <http://ntmnews.com/index.php/ntm-news-flash/179-emerging-cf-pathogen-is-transmissible>
11. <https://www.cysticfibrosis.org.uk/news/latest-news/lancet-cross-infection-report.aspx>  
<https://www.cysticfibrosis.org.uk/news/latest-news/new-cross-infection-guidelines-taking-shape.aspx>
12. Papworth Hospital Infection Control Policy (June 2013)