Institution: University of Nottingham

Unit of Assessment: UoA1

Title of case study:
Improving the safety of aminoglycoside antibiotics in cystic fibrosis

1. Summary of the impact

Research from the University of Nottingham on aminoglycoside antibiotics in cystic fibrosis (CF) has changed clinical practice and improved patient safety internationally. There are over 70,000 people with CF worldwide. Most require frequent and prolonged intravenous courses of aminoglycoside antibiotics (which can cause kidney damage) to treat chronic lung infection with *Pseudomonas aeruginosa*. This infection may lead to respiratory failure and death. Our research has influenced national and international guidelines, and changed practice, such that once-daily aminoglycosides (less toxic to the kidneys) are now used. We have also stopped the use of gentamicin, in favour of less toxic aminoglycosides.

2. Underpinning research

Professor Alan Smyth was awarded an honorary appointment with the University of Nottingham in 1996 and became a full time university employee (Senior Lecturer) in 2004. He is based in the School of Medicine and is the co-ordinating editor of the Cochrane Cystic Fibrosis and Genetic Disorders Group (http://cfgd.cochrane.org/our-contributors). This role has been supported by the School and has allowed Professor Smyth to publish a number of systematic reviews (six published and one in progress).

The publication of the initial systematic review [1] of once versus multiple daily dosing with aminoglycosides in cystic fibrosis (CF) showed that there were few trials looking at the optimal dosing regimen and insufficient statistical power to say if one regimen is better. This Cochrane Review was a key factor in Professor Smyth obtaining a grant (£404,464 from the UK CF Trust, awarded 1999) for the definitive clinical trial – the TOPIC trial.

This UK multicentre trial was conducted between 1999 and 2004, and was the largest clinical trial in CF ever conducted in the UK, with 244 participants. Professor Smyth and Professor Alan Knox (also School of Medicine, University of Nottingham) were co-principal investigators. The trial showed that a once daily regimen in CF patients, using the aminoglycoside antibiotic tobramycin, was equally effective and less toxic to the kidneys than traditional three times daily dosing [2].

Professor Smyth went on to undertake a national survey of cases of acute kidney injury (AKI) in patients with CF [3]. This showed that the incidence risk of AKI was between 5 and 11 cases / 10,000 CF patients / year. The median age of presentation was 10 years and the incidence of AKI in children with CF was found to be 100 times greater than in the general population. The genetic defect of CF is not thought to affect the kidneys and so the cause of this increased incidence is likely to be treatment. Indeed, 88% of individuals who developed AKI had received an aminoglycoside shortly beforehand. These episodes were not trivial – over half of the patients required dialysis, for an average of 8 days [3].

To investigate this link further, Professor Smyth's group performed a case control study of AKI in CF [4]. The team collected data from 55 of 56 CF centres in the UK. This showed that the use of gentamicin, but not tobramycin, was associated with a significantly increased risk of acute kidney injury.

Finally, Professor Smyth has collaborated with colleagues in the US to conduct a registry-based study of chronic kidney disease [5]. This study showed that every year, on average, 2.3% of people with CF develop chronic kidney disease, and that the risk doubles with every decade increase in age. This is a particular problem for patients with severe lung disease who may require a lung transplant, where kidney damage greatly reduces the rate of successful transplant.

3. References to the research

[1] **Smyth AR**, Bhatt J. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. Cochrane Database Syst Rev. 2012:Issue 2. Art. No.: CD002009. [Update of Cochrane Review 1st published in 2000].
http://dx.doi.org/10.1002/14651858.CD002009.pub4

[2] **Smyth A**, Tan KHV, Hyman-Taylor P, Mulheran M, Lewis S, Stableforth D, et al. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis - the TOPIC study: a randomised controlled trial. Lancet. 2005;365:573-578.
http://dx.doi.org/10.1016/S0140-6736(05)17906-9

[3] Bertenshaw C, Watson AR, Lewis S, **Smyth A**. Survey of acute renal failure in patients with cystic fibrosis in the UK. Thorax. 2007;62:541-545.
http://dx.doi.org/doi:10.1136/thx.2006.067595

[4] **Smyth A**, Lewis S, Bertenshaw C, Choonara I, McGaw J, Watson A. Case-control study of acute renal failure in patients with cystic fibrosis in the UK. Thorax. 2008;63:532-535.
http://dx.doi.org/doi:10.1136/thx.2007.088757

[5] Quon BS, Mayer-Hamblett N, Aitken ML, **Smyth AR**, Goss CH. Risk Factors for Chronic Kidney Disease in Adults with Cystic Fibrosis. Am J Respir Crit Care Med. 2011;184:1147-1152.
http://dx.doi.org/doi:10.1164/rccm.201105-0932OC

Grants

£404,464 Smyth A. **T**obramycin **O**nce-daily **P**rescribing **I**n **C**ystic fibrosis (**TOPIC** trial). Cystic Fibrosis Trust (project number: PJ467) 1999-2004.

4. Details of the impact

Change in practice

Since 2008, our findings have informed clinical practice guidelines nationally [a] and internationally [b]. Both sets of guidelines recommend the use of once daily aminoglycosides. The UK guidelines also advise that intravenous gentamicin should not be used. Our national survey, conducted in the UK in 2002, showed that once daily aminoglycosides were used by only 17% of UK CF centres [c]. By 2013, once daily aminoglycoside usage had risen to 86% [d]. Out of 22 CF Centres reporting a change in aminoglycoside dosing interval, 20 cited our work as a reason for changing from three times daily to once daily, and 9 cited the 2009 UK guidelines [d]. Similar studies in Australia have shown an increase in once daily dosing from 54% in 1999 [e] to 88% in 2009 [f]. The Director of the Adult CF Centre in Queensland (also a senior author on references [e] and [f]), has stated that the majority of the increase seen in Australia is attributable to our work [g]. There are no recent surveys from the US, but a once daily regimen is recommended in US guidelines [b]. In 2006, 30% of UK CF centres were still using gentamicin. Following the publication of our case control study in 2008, and the resulting recommendation in UK guidelines against gentamicin in 2009, gentamicin is no longer used as a first line aminoglycoside in any UK CF centre [d]. Of 12 centres who have stopped using gentamicin, 10 have cited our work as the reason for changing their practice [d]. Similarly, our work has been instrumental in the switch from gentamicin to tobramycin in Australian CF Centres [g].

Beneficiaries

The beneficiaries of this impact are:

- People with CF – who, because of the switch from gentamicin to tobramycin, are now at reduced risk of acute kidney injury (AKI) - a serious treatment related complication.
- People with CF having lung transplantation – who may avoid chronic kidney disease, which confers a much worse outcome from lung transplantation and greater costs [h].
- Clinicians who care for CF patients – who can deliver effective care without compromising safety.
- Those who commission health care – who can pay for an intervention which is no more expensive but which has a lower risk of AKI. This complication requires expensive and resource intensive management (dialysis). The cost of dialysis for AKI in CF is around £3,500 per patient and over half of patients with AKI require dialysis.

The cost savings of preventing AKI with a simple strategy of once daily aminoglycoside dosing and avoidance of gentamicin are therefore considerable.

Dissemination

We have disseminated these findings beyond conventional pathways, such as presentations at international conferences, publication in the peer reviewed literature and incorporation into guidelines. Our group have pioneered an innovative approach of engaging with the patient community, to share the findings of research in the CF field. Dr Matt Hurley (University of Nottingham, School of Medicine) has set up CF Unite [i] - a web based public engagement programme (Wellcome Trust People Award 2012, £29,624). CF Unite allows patients to have a dialogue with researchers. This is achieved without the need for people with CF to meet in person (with a risk of cross infection). Dialogue is through:

- lay summaries of research published on the website
- webcasts (and archived recordings) of conventional scientific meetings
- bespoke web conferences for patients and their families
- real-time online dialogue between patients, scientists and clinicians.

Lay summaries of the research described in Section 2 have been uploaded to the CF Unite website. Feedback from users of CF Unite has been very positive; for instance, *'I am very grateful for the opportunity to hear from these experts. Something that would otherwise be unavailable to me'* [j]. Since set-up in 2012, CF Unite has had around 10,700 visits from over 6,500 individuals (one third using mobile devices) [j].

Through our research on aminoglycosides, and our drive to set up CF Unite, we have changed clinical practice, improved the treatment of cystic fibrosis and empowered the CF community to become more informed about their condition. We plan to use CF Unite to actively seek the advice of patients in the design of clinical research and to encourage research participation.

5. Sources to corroborate the impact

[a] Antibiotic Treatment for Cystic Fibrosis. Report of the UK Cystic Fibrosis Trust Antibiotic Group. London: UK Cystic Fibrosis Trust; 2009. (See Section 6.7 'Recommendations'.)
https://www.cysticfibrosis.org.uk/media/82010/CD_Antibiotic_treatment_for_CF_May_09.pdf

[b] Flume PA, Mogayzel PJ, Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, et al. Cystic Fibrosis Pulmonary Guidelines: Treatment of Pulmonary Exacerbations. Am J Respir Crit Care Med. 2009;180:802-808. (See page 805.)
http://www.atsjournals.org/doi/pdf/10.1164/rccm.200812-1845PP

[c] Tan KHV, Hyman-Taylor P, Mulheran M, Knox A, **Smyth A**. To the editor: Lack of concordance in the use and monitoring of intravenous aminoglycosides in UK cystic fibrosis centers. Pediatr Pulmonol. 2002;33:165.
http://dx.doi.org/10.1002/ppul.10036

[d] Smyth AR, Campbell EL. Prescribing practices for intravenous aminoglycosides in UK Cystic Fibrosis Clinics: a questionnaire survey. J Cyst Fibros. 2013:Submitted.

[e] Phillips JA, Bell SC. Aminoglycosides in cystic fibrosis: a descriptive study of current practice in Australia. Intern Med J. 2001;31:23-26.
http://dx.doi.org/10.1046/j.1445-5994.2001.00010.x

[f] Soulsby N, Bell S, Greville H, Doecke C. Intravenous aminoglycoside usage and monitoring of patients with cystic fibrosis in Australia. What's new? Intern Med J. 2009;39:527-531.
http://dx.doi.org/10.1111/j.1445-5994.2008.01787.x

[g] Letter of support from Professor Scott Bell, Director of the Adult Cystic Fibrosis Centre Team, The Prince Charles Hospital, Brisbane; and also Professor at the University of Queensland.

[h] Arnaoutakis GJ, George TJ, Robinson CW, Gibbs KW, Orens JB, Merlo CA, et al. Severe acute kidney injury according to the RIFLE (risk, injury, failure, loss, end stage) criteria affects mortality in lung transplantation. J Heart Lung Transplant. 2011;30:1161-1168.
http://dx.doi.org/10.1016/j.healun.2011.04.013

[i] CF Unite website: http://cfunite.org

[j] Email correspondence from Dr Matthew Hurley, Clinical Research Fellow, The University of Nottingham.