

Institution: Queen's University Belfast
Unit of Assessment: 1
Title of case study: Improvements in clinical assessment and management of Difficult-to-treat Asthma in Adults
<p>1. Summary of the impact</p> <p>Heaney's research at Queen's University Belfast on difficult-to-treat asthma (or simply "difficult asthma" - DA) patients has led to changes in clinical management guidelines and a drive to co-ordinate and commission specialist services nationally for DA patients. It has also led to the establishment of a UK Multi-centre National Clinical Network and Patient Registry (Centres listed in Section 5). DA patients have persistent symptoms and frequent exacerbations despite being on high dose asthma therapy. DA patients (10% of the asthmatic population) have significant morbidity and carry a high risk of asthma death. Their clinical assessment has been optimised to ensure proper management of both their asthma and non-asthma related conditions.</p>
<p>2. Underpinning research</p> <p>Heaney's research has focused on patients with difficult to control asthma (10% of the asthmatic population, totalling circa 500,000 people), who have significant disease-related morbidity. It is estimated that 50 - 80% of asthma deaths occur in this group. In many cases patients are given increasing doses of medication for asthma rather than considering additional underlying factors that may be at play. Heaney's research programme has successfully established multi-disciplinary systematic clinical assessment to characterise patients with difficult-to-treat asthma, providing major benefits in identifying the precise cause for persistent symptoms and the role of non-asthma related co-morbidities in this population^{1,2}. This precise clinical phenotyping of patients prevents the inappropriate escalation of asthma therapy by the targeted management of underlying conditions such as chronic dilation of the bronchi and dysfunctional breathlessness.</p> <p>Of course great strides have been made by others in establishing underlying mechanisms of asthma over the years, but this clinical research importantly demonstrated in 2009 that 35% of patients referred to a Difficult Asthma Service were non-adherent, or inconsistent, in their use of inhaled anti-inflammatory treatment, and that this was associated with poor clinical outcomes for these patients. This has now also been extended to other specialist centres³. Identification of non-adherence is essential in order to prevent the inappropriate escalation of patients onto complex and expensive treatments. In order to deal with this aspect of patient management, the group developed a clinical test which uses directly observed inhaled steroid therapy in parallel with tests that measured to what extent daily exhaled nitric oxide (FeNO suppression test) was suppressed in the patients to identify non-adherence in this population⁴. As outlined in the Impact Case "Improved management of airway disorders in children", this test is useful in managing children with asthma but it also can identify which patients are suitable for the new expensive and complex biological antibody therapies. The tests are currently extended for use in other specialist clinical centres and to include the use of remote telemonitoring technology.</p> <p>A key component of this research has been the development of the National Severe Asthma Patient Registry which was established by Heaney in 2007 (British Thoracic Society Severe Asthma Network – see Section 5) centred at Queen's University, which provides a unique research and clinical infrastructure to move away from the 'one size fits all' approach to treatment in severe asthma. Research in the Registry has produced a series of important publications on patients with severe asthma^{5,6}.</p>
<p>3. References to the research</p> <p>1. Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, Gamble J. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol Thorax 2003;58:561-</p>

Impact case study (REF3b)

566. *Cited 113 times.*

This paper established systematic multi-disciplinary as a clinical model to assess and manage difficult to control asthma.

2. **LG Heaney**, DS Robinson. Severe asthma treatment: need for characterising patients. *Lancet*. 2005 Mar 9;365(9463):974-6. *Cited 108 times*
This paper presented data from 2 Centres (Belfast and Royal Brompton) with similar clinical outcomes and emphasised the multi-factorial nature of difficult asthma and the utility of systematic multi-disciplinary assessment.
3. Gamble J, Stevenson M, McClean E, **Heaney LG**. The Prevalence of Non-adherence in Difficult Asthma. *American Journal Respiratory Critical Care Med*. 2009 Nov 1;180(9):817-22.
This seminal paper was published in the number 1 ranked respiratory journal (2010 Impact factor 10.2) and has already been cited 114 times in less than 4 years.
This paper demonstrated the high prevalence of non-adherence with high dose inhaled therapy in difficult asthma and additionally poor adherence with systemic steroids (prednisolone).
4. McNicholl D, Stevenson M, McGarvey LPA, **Heaney LG**. The utility of fractional exhaled nitric oxide suppression in the identification of non-adherence in difficult asthma. *Am J Respir Crit Care Med*. 2012 Dec 1;186(11).
This paper presented the first 'objective' functional test for non-adherence to inhaled steroids by using the degree of steroid response to an inflammatory biomarker (FeNO).
5. **Heaney LG**, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM on behalf of the British Thoracic Society Difficult Asthma Network. Refractory asthma in the UK – cross-sectional findings from a UK Multicentre Registry. *Thorax* 2010 Sep;65(9):787-94.
This paper described detailed clinical phenotypic features in patients with refractory asthma across the UK.
6. Joan Sweeney, Chris E Brightling, Andrew Menzies-Gow, Rob M Niven, Chris C Patterson, **Liam G Heaney**, on behalf of the British Thoracic Society Difficult Asthma Network. Clinical management and outcome of refractory asthma in the UK – follow-up data from the British Thoracic Society Difficult Asthma Registry. *Thorax* 2012
This paper described clinical outcomes in patients with refractory asthma managed in Specialist Centres across the UK.

Grant funding supporting clinical assessment and mechanisms of difficult asthma

1. 2012 – 2014 – *Multi-centre validation of FeNO suppression testing to identify non-adherence in difficult asthma* – Glaxo Smith Kline European Clinical Centre of Excellence - £150,000
2. 2012 – 2014 – *Lebrikizumab in Severe Asthma* – Chief Investigator for multi-centre study delivered via British Thoracic Society Network – Roche UK, BTS Network Support funding - £556,875
3. 2011 – 2015 - *The Regulatory Importance of SOCS molecules in Th2 immune responses and disease*. Medical Research Council (Johnston, Kissenpfennig, Heaney) - £409,462
4. 2012 – 2013 – *Biomarkers for steroid resistance in refractory asthma* Genentech Inc USA – \$150,000
5. 2011 – 2014 - *Developing and validating a biomarker for non-adherence to inhaled steroid treatment in difficult asthma* – NI Chest Heart & Stroke Association £90,281
6. 2011 – 2013 – *European Framework 7 funded Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling (AirPROM)* – Work package 1 co-lead - €72,852
7. 2011 – 2013 – *Health Economics of Refractory Asthma; a multi-Centre UK analysis* – Glaxo Smith Kline - £119,876
8. 2011 – 2014 – *Take control of asthma: improving stakeholders' understanding of poor medication adherence in difficult asthma and the utility of a targeted management strategy*, HSC R&D Office Knowledge Transfer Programme - £99,986

Impact case study (REF3b)

9. 2010 – 2011 – *Pilot study of treatment of depression in refractory asthma* – Asthma UK - £49,258.
10. 2010 – 2015 — *AUGOSA – genome wide screen in refractory asthma in the UK* - data analysis for National Registry Medimmune UK £50,000.
11. 2009 – 2011 – *Novel biomarkers of non-adherence in difficult asthma* – unrestricted research grant - Glaxo Smith Kline - £100,000
12. 2008 – 2011 *The use of fractional exhaled nitric oxide (FeNO) and induced sputum in the identification of non-adherence in difficult to control asthma*. Asthma UK and NI Chest Heart and Stroke Association £166,282.
13. 2007 – 2010 *Pilot Funding for British Thoracic Society National Difficult Asthma Registry* – (£90,000) unrestricted Research Grants from Glaxo Smith Kline, Astra Zeneca and Novartis UK.
14. 2004 – 2009 *Evaluation of an individualised menu driven nurse led programme to improve adherence in difficult asthma*. R&D Office 2004, MPhil Fellowship £86,727

4. Details of the impact

Patients with difficult to control asthma (10% of the asthmatic population, ca 0.5 million in the UK) have significant symptoms and morbidity and are at a high risk of asthma death. This population currently represents a significant economic burden with estimates suggesting that they consume up to 50 - 60% of NHS spend on asthma totalling over £1 billion per annum, indicating that such appropriate management is likely to generate significant cost savings.

Several conditions that cause respiratory symptoms might co-exist in asthmatic patients, leading to an apparent failure to respond to asthma therapy and a significant impact of Heaney's work is that systematic evaluation has been shown to identify additional or alternative diagnoses in just over a third of the DA cases. In routine clinical practice, asthma management guidelines advocate escalation of asthma treatment to achieve symptom control. However, if the diagnosis of asthma is incorrect, or more commonly, if one of several other conditions, which frequently co-exist with asthma is present, this escalation in therapy does not improve symptoms. This often leads to treatment side-effects, particularly with systemic steroid treatment. Systematic clinical assessment shifts the focus from asthma therapy escalation and identifies and manages these conditions including smoking and chronic obstructive pulmonary disease (COPD), allergic bronchopulmonary aspergillosis (ABPA) and bronchiectasis, rhinosinusitis, vocal cord dysfunction, gastro-oesophageal reflux, allergen, aspirin, or occupational sensitisation, systemic disease (e.g., thyroid disease, vasculitis), psychological factors and poor adherence as well as socioeconomic factors. In all of these conditions, identification and explanation or treatment of the condition causing the symptoms, rather than more asthma therapy, is a more appropriate strategy, and in many cases will lead to symptomatic improvement.

The non-adherence research programme in DA at Queen's identified for the first time the significant scale of this problem (up to 50% of subjects referred to tertiary care DA services are non-adherent). Non-adherence to asthma treatment is associated with poor healthcare outcomes including recurrent hospital admission, increased risk of ventilation for life-threatening asthma, poor asthma-related quality of life, high symptom scores and excessive use of nebulised reliever medication. The reasons for this pattern of behaviour are complex, and include denial, medication and disease beliefs and secondary gain (secondary gain is where an individual gains a real or perceived benefit from being ill). Thus the precise reason for lack of medication adherence determines how the problem should be addressed. Practical barriers, such as forgetting medication or poor inhaler technique, can largely be solved by practical solutions. With perceptual barriers, such as denial or an erroneous belief that the medication is causing harm, a different approach is required to manage what is essentially a perceptual problem. This illustrates the importance of an individualised 'menu-driven' approach to address non-adherence.

Heaney is Director of the Northern Ireland Regional Difficult Asthma Service, managing all NI complex tertiary referrals and as a consequence patients in NI have benefited as a result. This

Impact case study (REF3b)

ground breaking translational research programme has been implemented in Northern Ireland¹ and is fully funded by the NHS. A Difficult Asthma programme was included in the Respiratory Framework Standards for Respiratory Care in NI in 2007² and in 2013 a similar standard has subsequently been incorporated into the NICE Asthma Standards (NICE Asthma Quality Standard 11 – Difficult Asthma)³. In providing a unique research and clinical infrastructure to move away from the 'one size fits all' approach to treatment in severe asthma there has been a significant paradigm shift away from the more traditional 'medical' model of treatments of patients towards a more social and holistic approach.

Multi-disciplinary optimised clinical assessment has informed best practice in International Asthma Guidelines (Global Initiative for Asthma [GINA 2009]⁴, Spanish Asthma Guidelines [SEPAR 2005]⁵, BTS/SIGN Asthma Guidelines 2011 which apply to UK, Australia and New Zealand). The major impact of Heaney's work is exemplified in the recent Consultation document for Specialist Centrally Commissioned Severe Asthma Services⁶ in the NHS in England which builds further on this multi-disciplinary assessment model (4 of the 9 references to underpin this document are from Heaney and the UK Registry). This document supports the development of specialist regional DA services using a systematic multi-disciplinary assessment model and when commissioned, these Centres will be required to input data into the Registry. The National Registry is also hosting the UK Bronchial Thermoplasty Registry for NICE⁷ which will provide long term data capture on the use of this technique within the UK and will provide a unique resource in the future to inform questions about longer term efficacy and safety of this technique.

5. Sources to corroborate the impact

1. Respiratory Framework NI - [http://www.dhsspsni.gov.uk/rsf - asthma in adults.pdf](http://www.dhsspsni.gov.uk/rsf_-_asthma_in_adults.pdf)
2. British Thoracic Society / Scottish Intercollegiate Guidelines Network: British Guideline on the Management of Asthma: A national clinical guideline- <http://www.brit-thoracic.org.uk/guidelines/asthma-guidelines.aspx>
3. NICE Asthma Standards – Difficult Asthma - <http://publications.nice.org.uk/quality-standard-for-asthma-qs25/quality-statement-11-difficult-asthma#source-guidance-11> Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol. 2010 Nov;126(5):926-38.
4. Global Initiative for Asthma - Global Strategy for Asthma Management and Prevention - www.ginasthma.org/uploads/users/.../GINA_Report_2011.pdf
5. Recommendations of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). Guidelines for the Diagnosis and Management of Difficult-to-Control Asthma. Arch Bronconeumol. 2005;41(9):513-23.
6. National Health Service Commissioning Board - Central Commissioning of Severe Asthma <https://www.engage.commissioningboard.nhs.uk/consultation/ssc-area-a/>
7. National Institute for Health and Clinical Excellence - Bronchial thermoplasty for severe asthma (IPG419) - <http://www.nice.org.uk/nicemedia/live/12774/55435/55435.pdf>

Clinical Centres in the British Thoracic Society Difficult Asthma Network* include:

Belfast City Hospital; Wythenshawe Hospital, University Hospital of South Manchester; Glenfield Hospital and Institute for Lung Health, Leicester; Royal Brompton Hospital, London; Birmingham Heartlands Hospital; Southampton General Hospital; Freemans Hospital, Newcastle; Nottingham City Hospital; Gartnavel General Hospital, Glasgow; Stobhill Hospital, Glasgow

* Other clinical centres are currently engaging through the thermoplasty programme and central commissioning plan and being established to enter data into the Patient Registry.