Institution: Queen's University Belfast

Unit of Assessment: 1

Title of case study: Improved management of airway disorders in children

1. Summary of the impact

Research led by Professor Shields and colleagues at Queen's University Belfast has resulted in changes in the treatment of children with cough and wheezing disorders and has been a major contributor to International Asthma and Cough Guideline statements.

Wheezing affects up to one third of children. Research studies that demonstrated that viral induced wheezing (VIW) or isolated cough were not associated with persistent airway inflammation led to a change in recommendations for anti-asthma therapy, such that the use of high dose inhaled corticosteroids (ICS) was no longer recommended in such cases. Furthermore, the dangers of very high dose ICS were better recognized and the upper recommended dose of steroids for use in treatment of classical childhood asthma was reduced accordingly.

2. Underpinning research

The research programme led by Shields aims to determine the type of airways inflammation which underlies childhood wheezing and cough. Shields is an academic respiratory paediatrician working at the Royal Belfast Hospital for Sick Children and Queen's University Belfast (Professor of Child Health). First, Shields and his colleagues developed and reported an ethically acceptable, safe and feasible method for obtaining bronchoalveolar lavage (BAL) lung samples from children purely for research purposes. BAL samples were obtained from children who were already subjected to the risks of anaesthesia for elective surgery[1]. This provided the first accurate normal data as a comparator to allow the study of airways inflammation in children with stable asthma, viral induced wheezing (VIW) and isolated coughing.

They were then able to demonstrate that children with allergic asthma had evidence of persisting inflammation in the bronchi between asthma attacks, whereas children with VIW and chronic cough did not. This suggested that inhaled corticosteroid treatment, which dampens down allergic airways inflammation, was inappropriate in children with VIW and isolated chronic cough as these show no airways inflammation[2,3]. The Tucson epidemiology birth cohort study had already in 1988 suggested that splitting wheezing children into at least two separate phenotypes should be considered. Adult biopsy studies had shown that bronchial inflammation persists between exacerbations BUT whether this was the same in asthmatic children and/ or children with VIW could not be determined easily and ethically in children.

When this clinical research work started, children with non-allergic Viral Induced Wheezing (VIW) and non-specific cough were treated for asthma, often with high doses of inhaled corticosteroids (ICS) and in the 1990s this was considered safe. However, Shields' research demonstrated that the children with VIW did not have persistent airway inflammation and thus were being treated inappropriately with ICS. Subsequent randomised controlled trials performed by many others have supported the finding that ICS were not beneficial in these circumstances. Furthermore, the doses of ICS in clinical use had escalated well above those initially recommended. In a pivotal case series[4], Shields identified potentially very serious complete adrenal suppression and growth failure in children on very high dose ICS. He then showed that monitoring growth in children (which was already done at primary and secondary care clinics) did not adequately predict adrenal insufficiency[5]. This work highlighted the problems with the use of high dose inhaled corticosteroids. Following this and the work of others (who reported similar cases of adrenal suppression), national and international asthma guidelines (examples listed in section 5) have reduced the recommended maximal ICS dose for children and have added warnings about adrenal suppression.

Shields and his colleagues were also able to demonstrate that in allergic asthma the degree of lower airways inflammation correlated closely with a simple non-invasive breath test measurement, Fractional Exhaled Nitric Oxide (FeNO)[6]. An elevated FeNO was highly predictive for the presence

of airways inflammation in children. This finding has been an important stimulus for companies (e.g. Aerocrine) to develop handheld FeNO monitoring devices for general use. These devices are also important in managing asthma and other airways disorders in adult patients as outlined in another Impact Case study (Difficult-to-treat Asthma in Adults).

3. References to the research

1. *Clin Exp Allergy* 1996, 26; 799-806. Investigating paediatric airways by non-bronchoscopic lavage: normal cellular data. LG Heaney, EC Stevenson, Gillian Turner, IS Cadden, R Taylor, MD Shields and M Ennis.
   This paper describes sampling methodology to obtain BAL in normal healthy children overcoming ethical and safety issues, and for the first time allowing true normal data to become available for comparisons with disease states.

2. *Clin Exp Allergy* 1997, 27: 1027-1035. Bronchoalveolar lavage findings suggest two different forms of childhood asthma. EC Stevenson, Gillian Turner, LG Heaney, B Shock, R Taylor, T Gallagher, M Ennis and MD Shields.
   This paper has been cited 274 times and has been described as 'seminal'. It was the first to show that children with allergic asthma had persistent eosinophilic inflammation whereas children with viral induced wheeze did not and that lumping the 2 conditions together as asthma was wrong.

3. *Eur Resp J* 2000, 16:1109-1114. Chronic cough in children: bronchoalveolar lavage findings. PS Fitch, V Brown, BC Shock, R Taylor, M Ennis and MD Shields.
   This paper described that children with chronic non-specific cough and no wheezing did not have persistent eosinophilic airways inflammation and were different from asthma.

4. *Lancet.* 1996 Jul 6;348(9019):27-9.Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. Todd G, Dunlop K, McNaboe J, Ryan MF, Carson D, Shields MD. *This paper(cited 146times) was the first to highlight the potentially very serious risks of high dose ICS especially with Fluticasone Propionate which at the time was considered the safest ICS for children.*

5. *Arch Dis Child* 2004; 89: 713-716. Monitoring growth in asthmatic children treated with high dose inhaled glucocorticosteroids does not predict adrenal suppression. KA Dunlop, DJ Carson, HJ Steen, V McGovern, J McNaboe and MD Shields.
   This paper highlighted adrenal suppression occurring in children on high dose inhaled corticosteroids and reported that simply measuring linear growth at the clinic was not a reassuring monitor for the presence of adrenal insufficiency.

6. *Thorax* 2002,57: 383-7. Exhaled nitric oxide (ENO) correlates with airway eosinophils in childhood asthma T J Warke, PS Fitch,V Brown, RA Taylor, JDM Lyons, M Ennis, MD Shields.
   This paper was the first to show that the non-invasive measurement ENO was diagnostically accurate for the presence of allergic airways inflammation in children.

Research grants facilitating this research

National Asthma Campaign. "Underlying chronic inflammation in different forms of childhood asthma" 1994/5, £25,250. MD Shields, M Ennis.

N Ireland Chest Heart Stroke Association. "Can a simple blood test reflect the airways inflammation in children with asthma" 1995/6, £40,350. MD Shields, M Ennis.

National Asthma Campaign. "Investigation into the role of cytokines. T cell subsets and viruses in childhood asthma". 1997/9, £131421. M Ennis, MD Shields, Johnston.

R&D Office, DHSS (NI). "Exhaled nitric oxide for monitoring airways inflammation in asthmatic

children". Research Training Fellowship, Dr Tim Warke, 1999/2001 (£84,639)

R&D Office, DHSS (NI) R&D Office, DHSS(NI).
A] "Pathophysiology of childhood asthma" 2002/5, circa £800,000. MD Shields, L Heaney, M Ennis
B] "Genetic signature severe RSV disease" 2007/12, circa £1m. U Power, L Heaney, MD Shields

4. Details of the impact

Shields' research has had three major impacts on the treatment of children with asthma and virally induced wheezing as described below. First, it generated guidance to separate these two groups for appropriate treatment; secondly it reduced the risks associated with high dose inhaled corticosteroid treatment and thirdly it helped to advance the development of simple hand-held monitoring equipment.

Impact 1: Improved targeting of inhaled corticosteroids in children by modification of the guidelines for practitioners.

The research work by Shields at Queen's University Belfast showed that it was wrong to group children with VIW and chronic non-specific cough as having asthma and in need of ICS treatment. Early guidelines defined asthma in children as 'Cough and/or wheezing …' and this emphasis on cough as the leading symptom resulted in many children with isolated cough being treated for asthma. In Australia ICS was the commonest used medication for children with isolated cough and almost 13% had experienced steroid side-effects. Shields' research has provided the underpinning evidence that children with non-allergic VIW and children with isolated chronic coughing would be unresponsive to ICS and hence the steroid side effects can be avoided in these children. This has changed the emphasis in national and international asthma and cough guidelines for children[1,2] and the chair of the Diagnosis section of the BTS Asthma Guideline stated that "this research brought about a paradigm shift in the approach to childhood asthma"[3]. It is now recommended that VIW should be distinguished from allergic asthma and that both VIW and non-specific isolated cough indicate a low probability of an asthma diagnosis. ICS are no longer recommended for these conditions. This change in clinical practice and the recommendations now means that fewer of these children are exposed to unnecessary ICS. Shields now chairs the Pharmacology Section of the BTS/SIGN Asthma Guidelines and the Cough in Children Guidelines (BTS).

Impact 2: High doses of ICS are no longer recommended and used for childhood asthma

In the 1990s ICS therapy was considered safe. Data from the Scottish General Practice Research Database show that very high dose ICS (> 800 mcg/day) prescriptions for asthmatic children >5 years of age quadrupled from 1.1% in 1992 to 4.6% in 2004. Not only were children with VIW and isolated coughing inappropriately treated with ICS but the doses of ICS had escalated. The pivotal case series published in the Lancet identified complete adrenal suppression and growth failure in children on very high dose ICS[4]. In addition it was shown that monitoring growth in children (which was done at primary and secondary care clinics) did not predict the potentially serious adrenal insufficiency[5]. The previous recommendation for monitoring growth as the tool for identifying inhaled steroid side-effects (adrenal insufficiency) was clearly inadequate. Following this and the work of others, national and international asthma guidelines have reduced the recommended maximal ICS dose for children and have added warnings about adrenal suppression. Thus while the British Thoracic Society Asthma guidelines in 1997 suggested children on Step 3 (poor asthma control despite treatment with 400 mcg/day of ICS) should be treated with 800 to 2000 mcg daily of ICS, this recommendation changed and after 2008 clear statements were made suggesting Step 3 was up to 400 mcg daily of ICS and those requiring greater than 800 mcg per day should be under specialist respiratory paediatric care[5].

Impact 3: Simple handheld exhaled nitric oxide devices are now available for monitoring airways inflammation in practice

Shields' research also showed that breath Fractional Exhaled Nitric Oxide (FeNO) correlates well with the extent of allergic airways inflammation. A high FeNO value of a child attending an asthma clinic may mean the child is not adhering to ICS treatment or he/she needs the ICS treatment escalated. Even as late as 2006 FeNO measurement was limited to large research centres

because the equipment was bulky and expensive. Manufacturers had the technology for portable equipment but needed further evidence that FeNO measurement was likely to have clinical benefit, and so would be widely adopted, before committing to commercially producing handheld units.

Shields and his colleagues provided the underpinning evidence that the FeNO breath test correlated closely with bronchoalveolar lavage eosinophilia in childhood asthma[6]. This was used as a key piece of evidence by the manufacturer (Aerocrine) supporting the development of their product – the handheld NIOX Mino FeNO monitoring device. This key reference is also used as supporting the diagnostic accuracy and use of FeNO in children in the official American Thoracic Society Clinical Practice Guideline. The Co-Chair from the ATS Guideline Committee has clearly acknowledged this impact when he comments that "the work by MD Shields has made a major contribution to FeNO monitoring in childhood asthma with special emphasis on facilitating moving FeNO from a research tool to clinical practice" (reference letter in box 5).

5. Sources to corroborate the impact

1] ***Airways inflammation in children (cough and wheeze)***

1. **Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report** The European Pediatric Asthma Group, Allergy 2008, 63(1): 5-34
2. **Definition, assessment and treatment of wheezing disorders in pre-school children: an evidence based approach**. Eur Resp Society Taskforce, Eur Resp J 2008; 32(4): 1096-1110.
3. The Chair of 'Asthma diagnosis' section – BTS/SIGN British Guideline on the Management of Asthma (Thorax. 2008 to 2013: May;63 Suppl 4:iv1-121.) *makes a pertinent quote regarding the work therein 'represented a seminal contribution to a paradigm shift in our thinking about childhood asthma and one that continues to be relevant to today's research agenda'*
4. **Guidelines for Evaluating Chronic Cough in Pediatrics**, American College Chest Physicians Evidence-Based Clinical Practice Guidelines
5. **British Thoracic Society Guidelines "Recommendations for the assessment and management of cough in children" (**Thorax 2008; 63 Suppl 3: iii1- iii15.). *MDShields chaired and wrote the BTS Cough guidelines for children that have now been translated into Spanish and Polish. They are widely quoted and form the basis of websites for both patients and doctors.*
   Examples include:
   a. http://www.patient.co.uk/doctor/Chronic-Cough-in-Children.htm for parents
   b. http://healthguides.mapofmedicine.com/choices/map/cough_in_children1.htm for doctors. {This Map of Medicine was published in Apr 2012}
   c. http://www.uptodate.com/contents/approach-to-chronic-cough-in-children
6. '**An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FE_{NO}) for Clinical Applications'**. http://www.thoracic.org/statements/resources/respiratory-disease-adults/feno-document.pdf
7. http://www.aerocrine.com/Global/pdf/Scientific%20Backgrounder%202007/SBVI.pdf

2] ***Problems with high dose ICS***

The publications (**Ref 6** and Lancet 1996, 348, 9019; 27-29) identifying adrenal suppression with high dose ICS and the finding that monitoring linear growth fails to predict adrenal suppression form underlying evidence for statements in the BTS asthma guideline and the Global Initiative for Asthma (***GINA***) guidelines, http://www.ginasthma.org/guidelines-gina-report-global-strategy-for-asthma.html