Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Positive Impact of Non-invasive Ventilation on Survival in Duchenne Muscular Dystrophy and Related Neuromuscular Disorders

1. Summary of the impact (indicative maximum 100 words)

Duchenne muscular dystrophy (DMD) is the commonest muscular dystrophy, affecting 1 in 3600 male births and 0.02% of the population. Ventilatory failure is an inevitable consequence; if untreated median survival is 20 years of age. Once a raised daytime arterial carbon dioxide level (hypercapnia) occurs, only 10% of patients survive one year. Imperial College researchers found that the introduction of non-invasive ventilation (NIV) when hypercapnia ensues extended one and five year survival to 85% and 73% respectively. Further, an Imperial-led randomised controlled trial showed NIV initiated at the time of nocturnal hypoventilation, before daytime hypercapnia, improves physiological outcomes. This management is now standard practice worldwide.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College researchers:
Professor Anita K Simonds, Professor of Respiratory and Sleep Medicine, NIHR Respiratory Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust (1990-present)
Professor Francesco Muntoni, Professor of Paediatric Neurology (1995-2008).

Professors Simonds and Muntoni developed a NIV support programme to improve outcomes in DMD and related inherited neuromuscular disorders. NIV delivers respiratory support to the patient's breathing via a mask which is applied externally to the nose or nose and mouth, rather than by an invasive tube to the lungs or tracheostomy. DMD is caused by defects in the dystrophin gene and causes generalised progressive weakness of the limb, respiratory and cardiac muscles from early childhood. Prior to Professor Simonds' and Muntoni's work, DMD patients in the UK were not routinely offered ventilatory support and so died prematurely in their late teens or early 20s. Elsewhere in Europe they were offered invasive tracheostomy ventilation in a staged approach. Professor Simonds collaborated with Professor Muntoni in 1994 to jointly recruit patients to the respiratory research programme.

In a consecutive cohort of 23 DMD patients with daytime hypercapnia, (this was the largest consecutive series managed with NIV at the time,) Professors Simonds and Muntoni demonstrated that NIV used at night as the sole ventilatory method increased one year survival to 85% and five year survival to 73% (from previous 1 year survival of 10%). Arterial blood gas tensions were normalised and the findings indicated that quality of life, using NIV measured by the Short Form-36 generic tool, was equivalent to individuals with non-progressive conditions. This study also demonstrated a plateau in survival confirming an impact on the progression of underlying muscle process. Published in 1998, this was the first demonstration that NIV alone could extend survival significantly (1).

This cohort study was followed by a randomised controlled trial on NIV to control nocturnal hypoventilation in DMD and other muscular dystrophies and myopathies so as to determine the correct time to initiate NIV in the natural history of the disease. Patients were diagnosed at Hammersmith Hospital and underwent respiratory assessment, sleep studies and initiation of NIV at the Royal Brompton Hospital, with subsequent joint hospital follow-up. The trial showed that the introduction of NIV at the time of nocturnal hypoventilation before the development of daytime hypercapnia reduced uncontrolled ventilatory decompensation and improved nocturnal blood gas tensions and health related quality of life (2).

3. References to the research (indicative maximum of six references)

(1) Simonds, A.K., Muntoni, F., Heather, S., & Fielding, S. (1998). Impact of nasal ventilation on

survival in hypercapnic Duchenne muscular dystrophy. *Thorax*, 53, 949-952. DOI. Times cited: 149 (as at 22nd October 2013 on ISI Web of Science). Journal Impact Factor: 8.37

(2) Ward, S., Chatwin, M., Heather, S., & Simonds, A.K. (2005). Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. *Thorax*, 60, 1019-1024. DOI. Times cited: 93 (as at 22nd October 2013 on ISI Web of Science). Journal Impact Factor: 8.37

International recognition of research:
A Simonds was awarded the Margaret Pfrommer Medal of American College of Chest Physicians (ACCP) and delivered the keynote Margaret Pfrommer Lecture: Recent Advances in Respiratory Care of Neuromuscular disease. Seattle, USA 2006. Published as below:
Simonds AK (2006). Recent advances in respiratory care for neuromuscular disease. *Chest*, 130, 1879-1886. DOI

Key funding:
- Breas Medical (1998-2003; £225,000), Principal Investigator A. Simonds, Role of NIV in patients with neuromuscular disease.

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

Impacts include: health and welfare, public policy and services, practitioners and services
Main beneficiaries include: patients, NHS, health service practitioners, international guideline bodies

DMD is the most common muscular dystrophy worldwide, and the most lethal, affecting 1:3600 male births and 0.02% of the population. It leads to gradual loss of muscle function, ambulatory ability, chronic ventilatory failure and eventual death. With no known cure, median survival is 20 years of age if left untreated.

Research at Imperial College paved the way for NIV to be the treatment of choice in managing ventilator failure, rather than invasive tracheostomy ventilation or a combined non-invasive/invasive approach. The Duchenne Standards of Care guidelines (the major international evidence based consensus document), produced in 2010, indicate that NIV should be standard treatment, specifying that tracheostomy is indicated only if a patient cannot successfully use non-invasive ventilation [1]. These Standards were formally approved under the NHS Evidence Accreditation Scheme, provided by NICE, in 2011 [2]. An Australia consensus statement in 2008 supports the use of NIV in children with Duchenne's, using the findings of Professor Simonds and colleagues as the supporting evidence [3].

The British Thoracic Society guidelines (2012) for the respiratory management of children with neuromuscular weakness state that NIV should be the first line treatment for children in acute respiratory failure [4; see page 6]. In addition, rather than waiting for daytime ventilator failure to develop, NIV is now initiated at the onset of symptomatic nocturnal hypoventilation [4; see page 19]. This has impacted on all patients with DMD and related neuromuscular disorders as NIV is now offered to all patients, resulting in prolonged survival and improved aspects of quality of life (well-being, energy/vitality and social functioning). The research has therefore translated into a real life therapy.

The 2011 Canadian Thoracic society guidelines on the use of home mechanical ventilation, using the research evidence described above to inform the recommendations, stipulate that nocturnal NIV should be offered to patients with diurnal hypercapnia or where there is documented evidence of nocturnal hypercapnia and the symptoms of hypoventilation are present [5]. Professor Simmonds and colleagues' 2005 randomised controlled trial is the only recent randomised controlled trial included in the underlying evidence used to inform these guidelines (the other is from 1994).

Practitioners and services:

The NHS Commissioning Board has recently consulted on their Complex Home Ventilation service, which outlines the use of NIV for various neuromuscular disorders. This service specification consultation document (2013) illustrates how specialist centres will assess the respiratory and medical needs of patients with progressive neuromuscular disease associated with respiratory failure such as Duchenne muscular dystrophy, that have complex care requirements that may necessitate multi-disciplinary input [6]. The provision of such services will increase the positive effects on survival observed in patients receiving NIV therapy.

Information for patients has also been produced by Professor Simonds at the request of the Muscular Dystrophy campaign to inform patients about the causes of breathing difficulties and the available treatment options, informed by research evidence [7]. Action Duchenne is a patient created charity that functions to inform patients and carers of ongoing research findings and to raise funds for research. Examples of the dissemination of research findings by patients can be seen via the Duchennepedia [8].

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

[1] Duchenne Standards of Care:
Bushby, K., Finkel, R., Birnkrant, D. J., Case, L. E., Clemens, P. R., Cripe, L. (2010). Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *Lancet Neurology*, 9, 177-189. DOI. (See panel 1 on page 182)

[2] Accreditation of Duchenne Standards of Care in 2011 (http://www.muscular-dystrophy.org/get_involved/campaigns/campaign_news/4490_nice_recognise_rare_condition_for_first_time). Archived on 22nd October 2013.

[3] Ventilatory support at home for children. A consensus statement from Australasian Paediatric Respiratory Group (Feb 2008). Archived on 22nd October 2013:
http://www.thoracic.org.au/documents/papers/aprghomeventilationguideline.pdf

[4] Hull, J., Aniapravan, R., Chan, E., Chatwin, M., Forton, J., Gallagher, J., Gibson, N., Gordon, J., Hughes, I., McCulloch, R., Russell, R.R., & Simonds, A. (2012). British Thoracic Society Guideline for Respiratory Management of Children with Neuromuscular Weakness. *Thorax*, 67, 1-40. DOI
http://www.brit-thoracic.org.uk/Portals/0/Guidelines/Resp%20Mgt%20Children/thoraxjnl_67_Suppl_1_completeissue.pdf

[5] Home mechanical ventilation (HMV): A Canadian Thoracic society Clinical Practice Guideline. HMV for patients with other muscular dystrophies and myopathies (2011). *Can Respir* J, 18 (4), 211-212. http://www.respiratoryguidelines.ca/sites/all/files/2011_CTS_HMV_Guideline.pdf. (Archived on 22nd October 2013).

[6] NHS Commissioning Board Service Specification for Complex Home Ventilation where non-invasive ventilation in Duchenne muscular dystrophy and other disorders is accepted practice to be commissioned as cited in:
NHS Commissioning Board Service Specification A3d1 Respiratory: Complex Home ventilation 2013

[7] Information for patients outlining these approaches to help breathing have been produced at request of Muscular Dystrophy campaign for their website and users. (Archived on 22nd October 2013).
http://www.muscular-dystrophy.org/how_we_help_you/publications/1923_making_breathing_easier

[8] Duchennepedia http://www.actionduchenne.org/duchennepedia (Archived on 22nd October 2013)
http://www.actionduchenne.org/duchennepedia/article/277/the-quiet-revolution. (Archived on 22nd October 2013)