Institution: Queen Mary University of London

Unit of Assessment: A1 (Clinical Medicine)

Title of case study: Enteral nutrition in childhood Crohn's disease

1. Summary of the impact

Corticosteroids are the traditional mainstay of treatment for inflammatory conditions but their side effects are often severe, especially in children. Professor MacDonald's team researched alternatives to corticosteroids in childhood Crohn's disease. With Nestlé they developed a polymeric, milk-based formula feed (Modulen IBD) that was highly effective in inducing clinical remission. NICE guidance have changed to reflect these findings. The treatment is now first-line therapy for childhood Crohn's in UK and the rest of Europe and recommended in clinical guidelines in USA. We estimate that across Europe alone, 13,000 new cases of childhood Crohn's annually will be spared steroid therapy as a result of this work.

2. Underpinning research

Nutritional therapy tackles one of the main problems of paediatric Crohn's disease, namely undernourishment leading to growth retardation and delayed puberty, which may be more troublesome and stigmatising than the disease itself. The concept of "gut rest" using amino-acid based elemental diets has shown promise for Crohn's disease since the 1980s. Its scientific basis lies in changes in gut microflora. Early elemental diets, such as Flexical (based on hydrolysed casein) were unpalatable, had low energy content and had to be given by nasogastric tube.

In the early 1990s, the role of T cells and cytokines as mediators of gut damage in Crohn's disease were identified, principally by MacDonald's research team at Queen Mary. Working with Nestlé, they hypothesised that one of the company's infant milk formulas, called AL110, which contains the immunosuppressive cytokine TGFβ2, might help dampen gut inflammation in Crohn's disease. Importantly, AL110 was palatable. They tested AL110 versus Flexical as a primary therapy in a small group of children with Crohn's disease and found that both were highly effective clinically, dramatically reducing T cell and macrophage derived cytokines from inflamed mucosae [1, 2] along with histological and clinical remission and a catch-up growth spurt in growth-retarded children [3].

MacDonald's team developed and tested a more concentrated formulation of the product in larger samples of children with newly-diagnosed Crohn's; 90 per cent achieved rapid clinical remission along with histological improvement and reduction in pro-inflammatory cytokines [4,5].

Based on these data, Nestle made the new product (CT3211) in a variety of flavours and marketed it as Modulen IBD in the summer of 2001. Modulen IBD is now available as a concentrate at 1.5 Kcal/ml, so that 1 litre contains 1500 calories.

3. References to the research

1. **Breese EJ**, Michie CA, **Nicholls SW**, **Murch SH**, **Williams CB**, **Domizio P**, **Walker-Smith JA**, **MacDonald TT**. Tumour necrosis factor-alpha producing cells in the intestinal mucosa of children with inflammatory bowel disease. *Gastroenterology* 1994; 106:1455-1466.
2. **Breese EJ**, Michie CA, **Nicholls S**, **Williams CB**, **Domizio P**, **Walker-Smith JA**, **MacDonald TT**. The effect of treatment on the frequency of lymphokine-secreting cells in the intestinal mucosa of children with Crohn's disease. *Alimentary Pharmacology and Therapeutics* 1995; 9:547-552.
3. **Beattie RM**, Schiffrin EJ, Donnet-Hughes A, Huggett AC, **Domizio P**, **MacDonald TT**, **Walker-Smith JA**. Polymeric nutrition as the primary therapy in children with small bowel Crohn's disease.

Alimentary Pharmacology and Therapeutics 1994; 8: 609-15.

4. **Fell JM**, Paintin M, Donnet-Hughes A, Arnaud-Battandier F, **MacDonald TT**, **Walker-Smith JA**. Remission induced by a new specific oral polymeric diet in children with Crohn's disease. *Nestlé Nutritional Workshop Series Clinical Performance Programme* 1999; 2:187-96.
5. **Fell JM**, Paintin M, Arnaud-Battandier F, **Beattie, RM**, Hollis A, Kitching P, Donnet-Hughes A, **MacDonald TT**, **Walker-Smith JA**. Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. *Alimentary Pharmacology and Therapeutics* 2000; 14: 281-9.

4. Details of the impact

4a: Laboratory studies led directly to a series of clinical trials in humans.

Following on from the initial studies undertaken at Queen Mary by Prof MacDonald's team, further comparisons between enteral nutrition and corticosteroids were carried out. Heushkel and colleagues summarised 5 other studies that showed that enteral nutrition was as effective as steroids in inducing remission in paediatric Crohn's disease [6]. In 2006, these results were confirmed in an Italian study [7]. Since then pediatric gastroenterologists have accepted the efficacy of enteral nutrition, and more recent studies have focussed on the type of enteral nutrition [8], partial enteral nutrition [9], and fractionated versus continuous feeding [10].

4b: Change in clinical guidelines and policy in UK

The use of enteral nutrition as primary therapy for paediatric Crohn's disease was adopted in 2008 in the guidelines of the British Society for Paediatric Gastroenterology, Hepatology and Nutrition [11]; this recommendation was reinforced in 2010 [12]. It is recommended by leading opinion leaders as the primary choice for patients presenting with Crohn's disease and a degree of malnutrition [13]. Consultative NICE guidelines published in October 2012 are strongly supportive of enteral therapy in paediatric Crohn's disease.

For example, paragraph 1.4.2 of the consultative NICE guidelines states: *"Enteral nutrition is currently widely used as first-line therapy in children and adolescents to facilitate growth and development."* Paragraph 4.3 states: *"Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for: children in whom there is concern about growth or side effects, and young people in whom there is concern about growth."* [14]

4c: Change in clinical guidelines beyond UK

European guidelines changed in 2006 to recommend enteral nutrition as first line therapy in children with Crohn's disease [15].

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition issued new guidelines in 2012 recommending enteral nutrition as first line induction of remission therapy for paediatric Crohn's disease [16].

4d: Change in clinical practice worldwide

In Sweden, 96% of paediatric IBD units now use enteral nutrition for Crohn's disease, and 65% use exclusive enteral nutrition as primary therapy [17]. Overall in 2003, 62% of European gastroenterologists used enteral nutrition to treat Crohn's disease in children [18], and it is likely that the figure is even higher now, although no recent European data are available. Exclusive enteral nutrition is now being used in Australia [19].

In a survey of the use of enteral nutrition in Europe, North America and the Asia-Pacific region, 89% of units used enteral nutrition and polymeric formulae, and by far the majority used two products, Modulen IBD or the lactose free equivalent, Elemental 208 [20].

4e: The change in practice produced a change in patient outcomes

About 20 per cent of children with Crohn's disease treated with long-term low dose steroid treatment have growth failure. After cessation of steroids, 70 per cent do not show catch up growth

[21]. In a two-year follow up of 109 children treated with Modulen IBD, weight and BMI improved markedly during follow up [22]. Height catch-up growth was bimodal, with those patients who responded clinically showing catch-up growth but those who did not, remaining short [22]. In addition, children with Crohn's disease have a markedly impaired quality of life [23]. Exclusive treatment with Modulen IBD improves their quality of life [24].

An estimated 17,000 new cases of Crohn's disease occur in children across Europe annually, so a conservative estimate is that as a result of our early research, at least 13,000 children a year are being spared steroid therapy.

5. Sources to corroborate the impact

6. Heuschkel R, Menache CC, Megerian JT, Baird AE. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. *Journal of Paediatric Gastroenterology and Enteral Nutrition* 2000; 31: 8-15.
7. Canani RB, Terrin G, Borrelli O et al. Short-and long-term therapeutic efficacy of nutritional therapy and corticosteroids in paediatric Crohn's disease. *Digestive and Liver Disease* 2006; 38: 381-387.
8. Ludvigsson JF. Elemental versus polymeric enteral nutrition in paediatric Crohn's disease: a multicentre randomised trial. *Acta Paediatrica* 2004; 93: 327-35.
9. Johnson T, Macdonald S, Hill SM, Thomas A, Murphy MS. Treatment of active Crohn's disease in children using partial enteral nutrition with liquid formula: a randomised controlled trial. *Gut* 2006; 55: 356-61.
10. Rubio A, Pigneur B, Garnier-Lengliné H et al. The efficacy of exclusive nutritional therapy in paediatric Crohn's disease, comparing fractionated oral vs continuous enteral feeding. *Alimentary Pharmacology and Therapeutics* 2011; 33: 1132-39.
11. British Society for Paediatric Gastroenterology, Hepatology and Nutrition Guidelines 2008 http://bspghan.org.uk/documents/IBDGuidelines.pdf
12. Sandhu BK, Fell JME, Beattie RM et al on behalf of the IBD Working Group of the British Society of Paediatric Gastroenterology, Hepatology, and Nutrition. Guidelines for the Management of Inflammatory Bowel Disease in Children in the United Kingdom. *Journal of Pediatric Gastroenterology and Nutrition*. 2010; 50: S1-S13.
13. Heuschkel R. Enteral nutrition should be used to induce remission in childhood Crohn's disease. *Digestive Diseases* 2009; 27: 297-305.
14. NICE guideline on management of Crohn's disease, October 2012 http://www.nice.org.uk/nicemedia/live/13936/61002/61002.pdf
15. Lochs H, Dejong C, Hammarqvist F et al. ESPEN Guidelines on Enteral Nutrition. *Gastroenterology* 2006; 25:260-74.
16. Critch J, Day AS, Otley A et al on behalf of NASPGAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition). Use of enteral nutrition for the control of intestinal inflammation in pediatric Crohn disease. *Journal of Pediatric Gastroenterology and Nutrition* 2012; 54: 298-305.
17. Grafors JM, Casswall TH Exclusive enteral nutrition in the treatment of children with Crohn's disease in Sweden: a questionnaire survey. *Acta Pediatrica* 2011; 100: 1018-22.
18. Levine A, Milo T, Buller H et al Consensus and controversy in the management of pediatric Crohn's disease: an international study. *Journal of Pediatric Gastroenterology and Nutrition* 2003; 36:464-466.
19. Day AS, Stephenson T, Stewart M, Otley AR. Exclusive enteral nutrition for children with Crohn's disease: use in Australia and attitudes of Australian pediatric gastroenterologists. *Journal of Paediatrics and Child Health* 2009; 45: 337-41.
20. Whitten KE, Rogers P, Chee KY et al. International survey of enteral nutrition protocols used in children with Crohn's disease. *Journal of Digestive Diseases* 2012; 13:107-112.