Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study:
Improved Inflammatory Bowel Disease Treatment by Reducing Unsafe Corticosteroid Use

1. Summary of the impact

The University of Liverpool (UoL) research identified corticosteroid treatment for more than 3 consecutive months as a risk for serious sepsis in Crohn's disease and an indicator of poor practice; there are 115,000 Crohn's disease patients in the UK. Following this, national audits of Inflammatory Bowel Disease (IBD), also under UoL leadership, showed reduction in inappropriate long term steroid from 46% of Crohn's disease patients in 2006 to 21% in 2010. These audits led to widespread adoption of National Service Standards for the Care of Patients with IBD. Death and hospital readmission rates for IBD patients were subsequently significantly reduced.

2. Underpinning research

Corticosteroids have for >50 years been the initial therapy in most patients with Crohn's disease yet they have been shown to have no useful maintenance effect (Benchimol EL et al Cochrane Database Syst Rev 2009 CD002913) and do not induce mucosal healing or improve the long-term natural history of the disease (Vermeire S et al Aliment Pharmacol Therap 2007;25:3-12). They do however provide rapid symptomatic relief. The Liverpool researchers have for over ten years been at the forefront of research demonstrating a likely pathogenic role for bacteria in Crohn's disease pathogenesis [2-7] and had therefore been concerned that steroids were often used inappropriately at too high a dose and for too long and that patients were coming to harm as a result. Several clinical trials have been initiated from Liverpool to assess alternative treatments such as enteral nutrition and antibiotics [8-10 plus 2 investigator-led trials ongoing]. At the time the Liverpool study of steroid use and sepsis in Crohn's disease was undertaken (2002) there had been little quantification of the safety of corticosteroid usage in this group of patients. The study was designed to assess possible associations between corticosteroid usage and serious sepsis occurring in non-operated patients with Crohn's disease (separate research elsewhere had identified corticosteroid usage as a risk for post-operative sepsis in abdominal surgery).

A retrospective case-control study was performed in 432 patients attending the Royal Liverpool University Hospital with Crohn's disease (the 94% of the IBD database for whom adequate documentation could be retrieved) to compare possible risk factors with incidence of serious intra-abdominal sepsis occurring in non-operated patients [1]. This study was performed between 2002 and 2004. The study was led by Prof Jonathan Rhodes (UoL throughout) with NHS Consultant colleagues Drs Keith Leiper and Anthony Ellis (both Hon Senior Lecturers) and Professor Anthony Morris (Honorary Professor) together with NHS clinical trainees Drs Anurag Agrawal and Shireen Durrani. It showed that systematic corticosteroid use was associated with increased rates of intra-abdominal or pelvic sepsis in patients with perforating Crohn's disease (odds ratio 9.03; 95% CI 2.40-33.98) and patients with relapsed active disease (unadjusted odds ratio 9.31; 95% CI 1.03-83.91). Further, patients receiving higher corticosteroid doses (i.e. 20mg/day or more of prednisolone) or receiving steroids for more than three months experienced higher rates of sepsis compared to those receiving lower and/or shorter duration therapy (odds ratio 5.41; 95% CI 1.02-28.79). This is important because abdominal and pelvic sepsis are potentially life-threatening conditions.

3. References to the research

1. Agrawal A, Durrani S, **Leiper K**, **Ellis A**, **Morris AI**, **Rhodes JM**. Systemic corticosteroid therapy increases risk for intra-abdominal or pelvic abscess in non-operated Crohn's disease. Clinical Gastroenterology and Hepatology. 2005;3:1215-1220. PMID: 17229216. Citations: 31 Impact Factor: 6.648

2. **Martin HM, Campbell BJ, Hart CA, Mpofu C**, Nayar M, Singh R, Englyst H, Williams HF, **Rhodes JM.** Enhanced Escherichia coli adherence and invasion in Crohn's disease and

colon cancer. Gastroenterology 2004;127:80-93. Citations: 229 Impact Factor: 6.648

3. **Mpofu CM, Campbell BJ, Subramanian S, Marshall-Clarke S, Hart CA, Cross A, Roberts CL, McGoldrick A, Edwards SW, Rhodes JM**. Microbial mannan inhibits bacteria killing by macrophages: a possible pathogenic mechanism for Crohn's disease. Gastroenterology 2007;133:1487-98. Citations: 30 Impact Factor: 12.821

4. **Subramanian S, Roberts CL, Hart CA, Martin HM, Edwards SW, Rhodes JM, Campbell BJ.** Replication of Colonic Crohn's Disease Mucosal Escherichia coli Isolates within Macrophages and Their Susceptibility to Antibiotics. Antimicrob Agents Chemother. 2008;52:427-34. Citations: 30 Impact Factor: 4.565

5. **Roberts CL, Keita AV**, Duncan SH, O'Kennedy N, Söderholm JD, **Rhodes JM, Campbell BJ.** Translocation of Crohn's disease *E. coli* across M-cells*:* contrasting effects of soluble plant fibres and emulsifiers. Gut 2010;59:1331-9. Citations: 20 Impact Factor: 10.732

6. Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, **Campbell BJ**, Abujamel T, Dogan B, Rogers AB, **Rhodes JM**, Stintzi A, Simpson KW, Hansen JJ, Keku TO, Fodor AA, Jobin C. Intestinal Inflammation Targets Cancer-Inducing Activity of the Microbiota. Science. 2012;338:120-3. Citations: 65 Impact Factor: 31.027

7. **Prorok-Hamon M, Friswell MK, Alswied A, Roberts CL, Song F, Flanagan PK, Knight P**, Codling C, Marchesi JR, **Winstanley C, Hall N, Rhodes JM, Campbell BJ.** Colonic mucosa-associated diffusely adherent afaC+ Escherichia coli expressing lpfA and pks are increased in inflammatory bowel disease and colon cancer. Gut. 2013 Jul 11. [Epub ahead of print]. Citations: 1 Impact Factor: 10.732

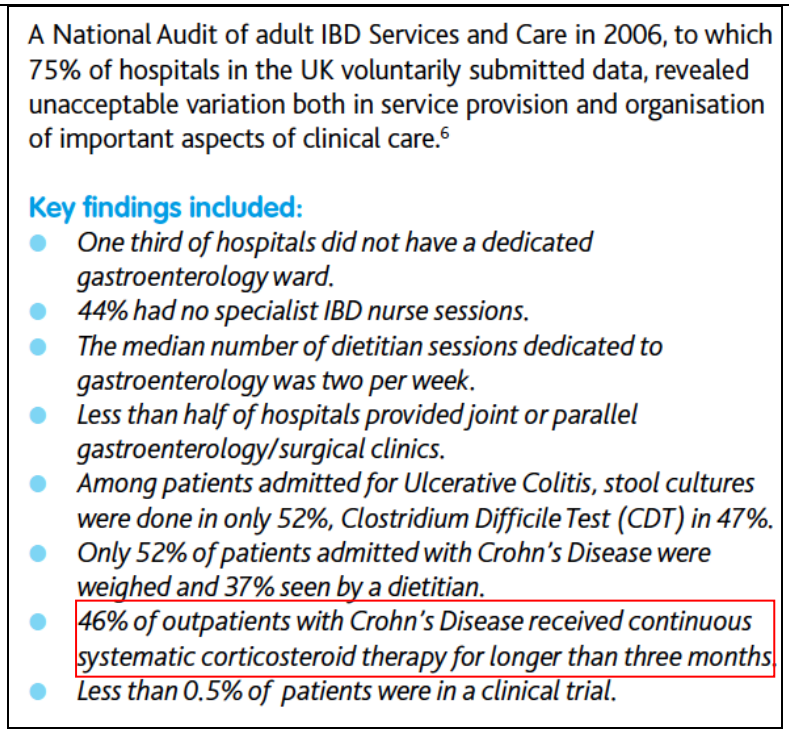
8. **Leiper K,** Woolner J, Mullan MMC, Parker T, van **der Vliet M, Fear S, Rhodes JM,** Hunter JO. A randomised controlled trial of high versus low long chain triglyceride whole protein feed in active Crohn's disease. Gut 2001;49:790-794. Citations: 37 Impact Factor: 10.732

9. **Leiper K, Martin K, Ellis A, Watson AJ, Morris AI, Rhodes JM.** Clinical trial: randomised placebo-controlled study of clarithromycin in active Crohn's disease. Aliment Pharmacol Ther. 2008;27:1233-9. Impact Factor: 4.548

10. **Leiper K, Martin K, Ellis A, Subramanian S, Watson A J, Christmas SE, Howarth D, Campbell F, Rhodes JM.** Randomised placebo-controlled trial of rituximab (anti-CD20) in active ulcerative colitis. Gut 2011;60:1520-6. Citations: 17 Impact Factor: 10.732

4. Details of the impact

The research attracted much international interest (e.g. it was presented internationally (e.g. one of 11 highlighted plenary papers at the 2006 American Gastroenterology Association; 15,000 delegates). Influenced by this research and anticipating probable variations in quality of care for patients with IBD, the British Society of Gastroenterology (BSG) asked Rhodes to initiate a national IBD audit. The first round of this UK IBD audit, led in 2006 by Dr Keith Leiper (Hon Senr Lecturer UoL) and funded by the Health Foundation, revealed widespread variation in quality of care, including inappropriate use of long term corticosteroid therapy in Crohn's disease [13]. This, along with other aspects of unacceptable care, is shown in Figure 1.



A National Audit of adult IBD Services and Care in 2006, to which 75% of hospitals in the UK voluntarily submitted data, revealed unacceptable variation both in service provision and organisation of important aspects of clinical care.[6]

Key findings included:

- *One third of hospitals did not have a dedicated gastroenterology ward.*
- *44% had no specialist IBD nurse sessions.*
- *The median number of dietitian sessions dedicated to gastroenterology was two per week.*
- *Less than half of hospitals provided joint or parallel gastroenterology/surgical clinics.*
- *Among patients admitted for Ulcerative Colitis, stool cultures were done in only 52%, Clostridium Difficile Test (CDT) in 47%.*
- *Only 52% of patients admitted with Crohn's Disease were weighed and 37% seen by a dietitian.*
- *46% of outpatients with Crohn's Disease received continuous systematic corticosteroid therapy for longer than three months.*
- *Less than 0.5% of patients were in a clinical trial.*

Figure 1: Extract from the Executive Summary of the IBD Standards [3; page 5]

The 2006 audit identified that the annual cost to the NHS for IBD including ulcerative colitis and Crohn's disease was £720m based on an annual cost of £3,000 per patient. As the incidence rate continues to rise with an estimated one person in 200 affected, this presents a significant and growing disease burden.

The audits were conducted with the engagement of the BSG, Royal College of Physicians, Association for Coloproctology, British Society for Paediatric Gastroenterology and Hepatology and the patient organisation Crohn's and Colitis UK. These key partnerships led to voluntary hospital participation in the first audit round of 75% and included 2,353 Crohn's disease patients, by the third round this had risen to 3,122 Crohn's disease patients. These engagement mechanisms have provided a pathway for the influence of the clinical and policy making community leading to significant improvements in clinical practice in the UK for the benefit of patients.

The UoL research led to the recognition of "steroid usage for more than 3 consecutive months" as a key indicator of poor practice in Crohn's disease management in the UK IBD Audit. The UoL led UK IBD Audit in turn led to the publication (launched at House of Lords) in 2009 of National Standards of Care for Patients with Inflammatory Bowel Disease agreed jointly by the Association of Coloproctology of Great Britain and Ireland, the British Dietetic Association, British Society of Gastroenterology, British Society of Paediatric Gastroentrology, Hepatology and Nutrition, National Association for Colitis and Crohn's disease (now Crohn's and Colitis UK), Primary Care Society for Gastroenterology, Royal College of Nursing [3].

The national standards were adopted by the Healthcare Commission in England as part of the Annual Health Check to identify risk. The importance of the work on corticosteroids is demonstrated by it being one of only two indicators for Crohn's disease outpatient treatment ([12] page 21).

These national standards together with the programme of audits have had considerable impact. The proportion of patients with Crohn's disease in the UK-wide IBD audit who had received corticosteroids inappropriately for more than 3 consecutive months has fallen from

46% to 38% to 21% in the three consecutive rounds of the IBD audit to date (2006, 2008, 2010 [4]). The three audit rounds to date have been accompanied by substantial improvements in outcomes as highlighted in a Lancet Editorial as: "For adults with ulcerative colitis, significant improvements in the third audit included reductions in the rate of deaths (0.8% in 2010 vs 1.7% in 2006) and readmissions (33.6% vs 51.1% respectively). For adults with Crohn's disease, improvements included a non-significant reduction in the rate of deaths (0.8% in 2010 vs 1.3% in 2006)" [11]. There are also financial savings arising from the reduced rate of sepsis and hospital admissions.

The 2010 audit further showed that, 12 out of 15 key indicators of adult IBD care showed statistically significant improvement over the period 2006-2012, as did 10 out of 12 indicators of Crohn's disease care.

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

11. Lancet editorial. Inflammatory bowel disease audited. Lancet 2012;379:868 http://download.thelancet.com/pdfs/journals/lancet/PIIS0140673612603766.pdf

12. IBD standards document. (2009) http://www.ibdstandards.org.uk/uploaded_files/IBDstandards.pdf

13. IBD UK Audit 1st, 2nd and 3rd round results via RCP website: http://www.rcplondon.ac.uk/projects/ibdaudit.