BRITISH SOCIETY OF PAEDIATRIC
GASTROENTEROLOGY HEPATOLOGY & NUTRITION

WINTER MEETING
January 23rd - 25th 2008

Botley Park Hotel and Golf Club
Southampton
SO32 2UA

Sponsorship: We wish to thank the following sponsors for their generous support:

BRITISH SOCIETY OF PAEDIATRIC
GASTROENTEROLOGY HEPATOLOGY & NUTRITION
Dear Colleagues

We would like to welcome you to Southampton and to the Winter Meeting of the BSPGHAN.

We have made clinical practice the main focus of the meeting covering a wide variety of topics across all three of the society’s specialist areas including global malnutrition, obesity, surgical practice and the interface between paediatric and adult specialist practice. We have been fortunate to attract top quality speakers and hope you will enjoy the sessions. Good clinical practice comes from quality research and we are pleased to have Professor Sally Davies to talk on research in the modern NHS.

We were pleased to have more than 50 abstracts submitted and hope you will enjoy the plenary abstract and poster sessions.

We are grateful for all the practical help we have had with the organisation of the meeting. We have had considerable support from the BSPGHAN council. Sue Protheroe’s help has been invaluable organising the abstract adjudication and advising on the postgraduate programme including the introduction of trainee case presentation.

We are also grateful for the support of industry without which it would be difficult for a meeting like this to go ahead.

Carla Lloyd, as part of the organising committee has been invaluable

Mark Beattie
On behalf of the Organising Committee

ORGANISING COMMITTEES

Winter Meeting Organising Committee
Dr Mark Beattie
Mr Mervyn Griffiths
Dr Nadeem Afzal
Mrs Carla Lloyd

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Dr Sue Protheroe
Dr Richard Russell

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Dr Sue Protheroe (chair)
Dr Sue Beath
Dr Richard Russell
Mr Mervyn Griffiths

Social Committee
Mr Mick Cullen
Dr Richard Russell

Wednesday 23rd January 2008 - Postgraduate Course

10.00 - 10.30 Registration and Coffee

Chair: Dr Sue Protheroe and Mr Mervyn Griffiths

Session One : Theme Therapeutic Options in Inflammatory Bowel Disease

10.30 - 11.00 Cochrane Methodology with specific reference to Inflammatory Bowel Disease
Dr Tony Akobeng - Consultant Paediatric Gastroenterologist, Manchester

11.00 - 11.30 New Therapeutic Approaches in Inflammatory Bowel Disease
Dr Ronald Brenner, Birmingham

11.30 - 12.30 Case presentations with Panel Discussion

11.30 - 11.45 Azathioprine: Friend or Foe?
Presenter: Dr Sherina Ross
S Ross, S Rajwal, J Sugarman, S Davison, S Picton, P McClean. St. James’s University Hospital, Beckett Street, Leeds, LS9 7TF

11.45 - 12.00 Crohn’s disease presenting as gastric outlet obstruction
Presenter: Dr Sabarinathan Logathan
Logathan S, Casson D
Alderhey Children’s Hospital, Liverpool.

12.00 - 12.15 Diagnostic and management dilemma in a case of Inflammatory bowel disease
Presenter: Dr Viswa Sivaramakrishnan
VM Sivaramakrishnan, S Protheroe
Department of Paediatric Gastroenterology
Birmingham Children’s Hospital, Birmingham, United Kingdom

12.15 - 12.30 Pre-pouch ileitis after colectomy in paediatric ulcerative colitis
Presenter: Dr Wael El-Matary
Carrie Slater, Safwat Girgis+, Hien Huynh, Wael El-Matary
Division of Pediatric Gastroenterology, Hepatology and Nutrition, Stollery Children’s Hospital and +Department of Pathology, University Hospital, University of Alberta, Edmonton, Canada

12.30 - 13.30 Lunch

Chair: Dr Jane Hartley and Dr Jenny Gordon

Session Two : Theme Liver Transplantation : Update on Transplant Issues

13.30 - 14.00 Case presentation with discussion of the long term complications of transplantation.
Dr Venkatesh Karthik - Specialist Registrar, Leeds

14.00- 14.30 Organ donation issues
Professor Nigel Heathon - Consultant Transplant Surgeon, London

14.30 – 15.00 Update on immunosuppressive agents including the monoclonal antibodies and newer immunosuppressive agents.
Dr Sue Beath - Consultant Paediatric Hepatologist, Birmingham

Chair: Dr Steve Woolton and Dr John Puntis

Session Three: Nutritional Assessment of Children with Chronic Disease

15.30 - 16.00 Introduction to Nutritional Assessment
Dr Steve Woolton - Senior Lecturer in Nutrition, Southampton

16.00 – 16.20 Nutritional assessment in Cystic Fibrosis
Mrs Teresa Hannan - Paediatric Dietician, Southampton

Sponsorship: We wish to also thank the following sponsors for their generous support
Thursday 24th January 2008

Registration 9.30 – 12.00

Working Group/Specialist group meetings

Meetings open to all delegates

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Poster session I viewing from 10.30

24th BSPGHAN Meeting

12.00 – 13.00 Buffet Lunch
Poster session I and judging

13.00 – 13.05 Opening and welcome on behalf of the organising committee
Dr Mark Beattie - Consultant Paediatric Gastroenterologist, Southampton

Session I

Chair: Dr Huw Jenkins and Dr Stephen Murphy

13.05 – 13.50 Research opportunities in the NHS
Professor Sally Davies - Director General for Research and Development, Department of Health

13.50 – 15.20 Plenary session I with abstracts from Gastroenterology, Hepatology and Nutrition

13.50 – 14.05 Polymeric versus elemental feeding in newly diagnosed paediatric Crohn’s disease: a single blind randomised control trial
Grogan J, Terry A, Casson D, Daleell AM
Dept. Nutrition and Dietetics, RLCH NHS Trust, Eaton Road, Liverpool L12 2AP

14.05 – 14.20 A prospective audit of liver biopsies in children
SV Karthik1, S Davison1, P McClean1, S Rajwal1, W Ramsden2,
M Stringer1, H Woodley2, J Wyatt3. Children’s Liver and GI unit1, Departments of Radiology2 and Histopathology3, St James’s University Hospital, Leeds, UK.

14.20 – 14.35 UK regional paediatric HPN data suggest a national underestimate in service requirements
A.R. Barclay1, C.E. Paxton1, J. Livingstone2, D. Hool3, F. Munro4, P. Gilles1, D.C. Wilson1, 5. Departments of Paediatric Gastroenterology and Nutrition, 2Dietetics, 3Pharmacy and 4Surgery, Royal Hospital for Sick Children, Edinburgh, EHP 1UL, 5Child life and Health, University of Edinburgh, EHP 1UW

14.35 – 14.50 Feasibility of confocal laser endomicroscopy in the diagnosis of paediatric gastrointestinal disorders: the first human studies
Venkatesh K1, Hursthouse DP2, Cohen M3, Evans C3, Tiffi N4, Delaney PS, Thomas S5, Taylor C1, Aboutaleb A1, Kieslich R5, Thomson M1 1Centre for Paediatric Gastroenterology, Sheffield Children’s NHS Foundation Trust, Sheffield, United Kingdom 2Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield, United Kingdom 3Department of Histopathology, Sheffield Children’s NHS Foundation Trust, Sheffield, United Kingdom 4Department of Histopathology, Royal Hallamshire Hospital, Sheffield, United Kingdom 5OCTscan, Melbourne, Australia. 6I. Med. Klinik und Poliklinik, Johannes Gutenberg University of Mainz, Mainz, Germany.

14.50 – 15.05 Impact of an improved national paediatric donor organ allocation policy for children waiting for intestinal transplantation (ITx)
Giovannelli M1, Gupple GL1, Pocock P3, Loyd C1, McKiernan P1, Richards S4, Sharif K1, Mizra DP2 Liver Unit, Birmingham Children’s Hospital, 2Liver Unit, Queen Elizabeth Hospital, 3UK Transplant, Bristol, 4Transplant Co-ordinator, Queen Elizabeth Hospital

15.05 – 15.20 Small bowel histology in screening identified vs symptomatic children diagnosed with coeliac disease
Srinivasan S, Rowal D, Spray C5, Ramani P* Dept of Paediatric Gastroenterology, Bristol Royal Hospital for Children and Dept of Histopathology *, United Bristol health Care NHS Trust, Upper Maudlin Street, Bristol, UK

15.20 – 15.45 Tea

Session II

Chair: Professor Bhu Sandhu

15.45 – 16.30 WHO Feeding children with malnutrition
Professor Anne Ashworth Hill, London

16.30 – 17.15 Nutrition in the 21st century
Professor Alan Jackson - Professor of Nutrition, Southampton

17.30 – 19.00 Annual General Meeting

20.30 Reception

21.00 – late Conference dinner and entertainment with the band EMD
Friday 25th January 2008

Breakfast symposium sponsored by Nutricia

Cow's Milk Allergy

Chair: Dr Martin Brueton

8.00 – 8.15 Update on European Protocol for Cow’s Milk Allergy
Dr Martin Brueton - Consultant Gastroenterologist, Chelsea and Westminster

8.15 – 8.35 Practical Management of Cow’s Milk Allergy Patients
Jonathan Hourihane

8.35 – 8.55 Prebiotics in Infancy – a two year follow up
Dr Serfac Arslanoglu - Centre for Infant Nutrition, Macedonio Melloni Hospital, Milan

Session III

Chair: Dr Sally Mitton and Dr John Fell

9.00 - 9.45 Management of Ulcerative Colitis
Dr Simon Travis - Consultant Gastroenterologist, Oxford

9.45 – 10.15 Modern Management of Gastroschisis
Mr David Burge - Consultant Paediatric Surgeon, Southampton

Session IV

Sponsored by Children’s Liver Disease Foundation

Chair: Dr Patricia McClean and Dr Nadeem Atal

10.15 – 10.45 Adolescent Liver Disease
Dr Mark Wright - Consultant Hepatologist, Southampton

10.45 – 11.15 Outcome of Liver Disease in Childhood
Professor Anil Dhawan, Consultant Paediatric Hepatologist, King’s College Hospital, London

11.15 – 11.45 COFFEE

Poster Session II Viewing

Session V

Chair: Dr Ulrich Baumann and Dr Justin Davis

11.45 – 12.15 Metabolic syndrome
Dr Julian Shields - Consultant Paediatric Gastroenterologist, Bristol

12.15 – 12.45 Bariatric Surgery
Mr James Byrne - Consultant Surgeon, Southampton

12.45 – 13.30 BUFFET LUNCH
Poster Session II and judging

Session VI

Chair: Professor David Candy and Dr Mike Bisset

13.30 – 15.00 Plenary abstract session II

13.30 – 13.45 Stable isotope probing of the gut microbiota can link bacterial activity to diversity across varying media, timeframes and bacterial species.
A R Barclay1, L T Weaver1, D J Morrison2 1Division of Developmental Medicine, 2SUERC, University of Glasgow, Glasgow, United Kingdom
How Cochrane Systematic Reviews Guide Therapy in IBD: Maintaining Remission in Crohn’s Disease

Tony Akobeng, Booth Hall Children’s Hospital, Manchester, UK

Background: Systematic reviews of randomised controlled trials (RCTs) are considered to be evidence of the highest level in the hierarchy of research designs evaluating effectiveness of interventions. Systematic reviews allow us to take account of the whole range of relevant findings from research on a particular topic, and not just the results of one or two studies. Systematic reviews can be used to establish whether scientific findings are consistent and generalisable across populations, settings, and treatment variations, or whether findings vary significantly by particular subgroups.

Aim: In this presentation, I will talk about the general principles of systematic reviews and meta-analyses and briefly talk about the work of the Cochrane collaboration in general and the Cochrane IBD review group in particular. I will discuss the important role that Cochrane systematic reviews play in helping to promote understanding of the current evidence on existing interventions for maintaining remission in Crohn’s disease (CD) and discuss interventions on which there are Cochrane reviews. Where no Cochrane review was available on an intervention, relevant RCT’s will be briefly mentioned.

Methods: The Cochrane Library and Medline (Pubmed) were searched for level 1 evidence on specific interventions. Search terms included “Crohn’s disease or synonyms”, “remission or synonyms” and the names of specific interventions.

Results: Azathioprine, infliximab and adalimumab are effective at maintaining remission in Crohn’s disease. Natalizumab is also effective but there are concerns about its potential association with progressive multifocal leukoencephalopathy. Long term enteral nutritional supplementation, enteric-coated omega-3 fatty acids and intramuscular methotrexate may also be effective but the evidence on these is based on relatively small studies. The available evidence does not support the use of oral 5-ASA agents, corticosteroids, anti-mycobacterial agents, probiotics or ciclosporin as maintenance therapy in Crohn’s disease.

Conclusions: A better understanding of the evidence base of existing interventions for maintaining remission in CD could result in the use of treatments which are more likely to lead to improved patient outcomes.

New Therapies in Crohn’s Disease

Ronald Bremner, Specialist Registrar in Paediatric Gastroenterology, Birmingham

Crohn’s disease is characterised by an ongoing inflammatory response in the absence of an obvious trigger. Laboratory, genetic and clinical studies have added to the understanding of the mechanisms of this immune dysregulation. Interactions between the innate and adaptive immune system at the mucosal level appear central to pathogenesis, directing the polarisation of lymphocytes towards the Th1/Th17 phenotypes. The multilayered defence within the gut and systemic immune system provides many potential targets for therapy.

Since infliximab, several other specific anti-TNF therapies have been developed. These include adalimumab and certolizumab-pegol. Adalimumab is a fully human monoclonal anti-TNF antibody, with efficacy similar to infliximab in anti-TNF-naïve subjects for induction and maintenance of remission. Efficacy is less, but still significantly better than placebo in those unresponsive or intolerant of infliximab. Certolizumab-pegol can be given monthly and appears more effective in those patients with raised inflammatory markers. Reports of hepatosplenic lymphoma after exposure to infliximab have highlighted long-term safety issues with biological therapies.

There are preliminary data suggesting efficacy of agents directed against other pro-inflammatory mediators, including interleukins 6 and 12, interferon-? and MAP kinases. Anti-inflammatory IL-11 and inhibitors of leucocyte adhesion have shown only moderate clinical benefit. Other strategies under investigation include methods to stimulate the innate immune defence systems at the mucosal level using probiotics, prebiotics or non-pathogenic helminths.

Trials examining the “top-down” approach to treatment compared to traditional “step-up” management strategies are reviewed.
Azathioprine. Friend or Foe?
S Ross, S Rajwai, I Sugarman, S Davison, S Picton, P McClean.
St. James’s University Hospital, Beckett Street, Leeds, LS9 7TF.

Azathioprine is an effective treatment for steroid dependent Inflammatory Bowel Disease (IBD). Recently concerns emerged in regard to long term risk of neoplasia in patients with IBD treated with azathioprine or its metabolite, 6-mercaptopurine.

To date, studies have been inconclusive in confirming any association between azathioprine and haematopoietic malignancies. This risk is deemed insignificant and does not preclude the use of azathioprine and/or 6-MP in the treatment of IBD, especially in young patients where cancer risk is at a minimum.

We report an unusual case of EBV associated lymphoproliferative disease in a fifteen year old boy who was initially diagnosed with Crohn’s disease at the age of ten. His disease activity was initially mild but proved to be difficult to control three years into his diagnosis when he persistently required systemic steroid to induce and maintain remission. This prompted treatment with azathioprine, with a maximum dose of 3mg/kg/day.

Eighteen months later, he presented with bilateral painless cervical lymphadenopathy. Initial blood investigations showed pancytopenia but normal biochemistry. EBV IgM, IgG and PCR were positive with titres in excess of 100,000 copies/ml. Lymph node biopsy was consistent with EBV associated B-cell lymphoproliferation and immunohistochemistry was CD20+. Bone marrow examination only showed reactive changes. Chest radiograph and abdominal sonography at presentation were also normal.

Azathioprine was therefore stopped. He deteriorated two weeks later with profluse bloody diarrhoea, hepatosplenomegaly, jaundice and hypoalbuminaemia. Coagulation was deranged with prothrombin time of 46 seconds which corrected with intravenous vitamin K. Antiviral therapy with intravenous ganciclovir was commenced with no response. He continued to deteriorate clinically and biochemically with increasing hepatosplenomegaly, ascites and steady decline in liver and renal functions. Computed tomography of neck, thorax and abdomen showed evidence of large necrotic bilateral cervical lymphadenopathies, bilateral nodular consolidation of lungs, worsening abdominal lymphadenopathy with multiple focal abnormalities of poor echogenicity in the spleen. As a result, antimonials antibody treatment with rituximab and COP chemotherapy (cyclophosphamide, vincristine and prednisolone) were initiated.

His initial response to treatment was poor despite three cycles of rituximab and chemotherapy. He deteriorated further with persistent diffuse per rectal bleeding and eventually had a subtotal colectomy for bowel perforation. Remarkably, he was clinically much improved post bowel resection and EBV titres recurred within a week of finishing. In view of the previous lymphoma there was dilemma about commencing azathioprine. On discussion with the oncologists it was felt that this represented an acceptable risk and it was commenced. Further contrast studies showed featureless duodenum but no evidence of stricture. We faced a dilemma over progression to surgery in view of concerns over the possible involvement of the ampullary region and discrepancy between radiological and endoscopic disease localization. With this uncertainty we proceeded to surgical intervention at which disease distribution was as had been described endoscopically involving D1 only. The on-table surgical dilemma was between stiucturoplasty, balloon dilatation and a Roux-EN-Y gastric bypass. The latter was performed and she has remained well for past 1 year.

Summary:
We present a complex case of Crohn’s disease which presented several dilemmas: there was initial difficulty at distinguishing Crohn’s from relapse of lymphoma, subsequent treatment was ineffective at inducing remission, the decision to start azathioprine in view of previous malignancy was fraught, the anatomy of the stricture was difficult to establish and the optimal surgical procedure was uncertain.
Diagnostic and management dilemma in a case of Inflammatory bowel disease

VM Sivaramakrishnan, S Protheroe
Department of Paediatric Gastroenterology, Birmingham Children's Hospital, Birmingham, United Kingdom

Background:
Classical clinical features of inflammatory bowel disease can be mimicked by infective diseases including tuberculosis. Annual incidence of tuberculosis in children (Asian ethnic group) is 21/100,000, whereas incidence of Crohn’s disease is perhaps 4/100,000.

Case Summary:
A 14 year old British Asian girl presented with pyrexia of unknown origin, bilateral hip and left elbow pain to the Rheumatology team. She did not respond to the anti inflammatory medication. She had a positive Mantoux test and noted to have a family contact of tuberculosis. She had BCG vaccine at birth. Despite a negative synovial biopsy, she was given a 6-month course of antituberculous therapy (ATT) for synovitis with minimal improvement in clinical symptoms.

A gastroenterologist opinion was sought in Oct-06 for intermittent abdominal pain with fever, diarrhoea and arthralgia all of which were present since first seen. She was also noticed to have blood in the stools for 2 months prior to the referral. On examination she had no generalized lymphadenopathy or hepatosplenomegaly. Small bowel contrast studies showed ulceration of distal ileum with irregular mucosa, indistinct ileocaecal valve with caecal involvement. Colonoscopy revealed patchy ulceration in caecum and terminal ileum. Ileocaecal biopsies showed severe, chronic active inflammation in keeping with Crohn’s disease. The biopsy material was negative for acid & alcohol fast bacilli staining and TB cultures were negative. Early morning urine sample for TB was also negative. Management with liquid diet and Mesalazine yielded improvement both clinically and histologically.

Her symptoms recurred within two months and she declined further liquid diet therapy. She was found to be steroid dependant and she has been referred to the surgeons for an opinion regarding ileocaecal resection. She may not be a good candidate for further immune-suppression and certainly would not qualify for infliximab as she has had evidence of exposure to TB infection in the past.

Conclusion:
Our case serves to highlight the difficulties that can be encountered in differentiating Crohn’s disease from tuberculosis. A positive Mantoux could be misleading towards a diagnosis of tuberculosis and false positivity is well recognised when there has been prior tuberculosis contact. Accurate diagnosis is essential prior to any proposed pharmacological and/or immune therapy.

Pre-pouch ileitis after colectomy in pediatric ulcerative colitis

Carrie Slatter, Safwat Girgis+, Hien Huynh, Wael El-Matary
Division of Pediatric Gastroenterology, Hepatology and Nutrition, Stollery Children's Hospital and +Department of Pathology, University Hospital, University of Alberta, Edmonton, Canada

Background:
Colectomy and ileal pouch anal anastomosis (IPAA) is a potentially curative option for patients with ulcerative colitis. A rare, post-operative complication is terminal ileitis, which arises when the ileum is reanastomosed into a non-physiologic environment. Terminal ileitis is well described in adults, but has been poorly documented in pediatric patients.

Aim: To describe our experience of children with ulcerative colitis who developed terminal ileitis following colectomy and IPAA.

Methods and Results: A search of our pediatric inflammatory bowel disease database of patients we are currently following revealed two boys (initially presenting at ages 4 and 9) diagnosed with ulcerative colitis on the basis of clinical presentation, investigations including endoscopy and colonoscopy and biopsies. As they were resistant to medical therapy, including steroids, 5-ASA preparations (oral and rectal), azathioprine, tacrolimus and various antibiotics, they each underwent colectomy with IPAA. Pathological examination of the surgical specimens confirmed the diagnosis of ulcerative colitis.

One year later, both children had recurrence of symptoms, including watery, bloody diarrhoea and weight loss. Several endoscopies and biopsies showed acute on chronic mucosal inflammation, ulceration, friability and granularity in the pouch and up to 50cm into the terminal ileum. Biopsies revealed mixed inflammatory infiltrate rich in eosinophils, plasma cells and neutrophils. No granulomas were seen. Stomach and duodenal biopsies were normal. Both children were diagnosed with pouchitis and terminal ileitis. At present, their symptoms are well controlled using 5-ASA preparations in one child and azathioprine in the other.

Conclusion: Development of terminal ileitis after colectomy and IPAA can occur in children with ulcerative colitis. Although every effort should be made to exclude Crohn’s disease as a cause of the terminal ileitis, this unique and poorly defined condition should not be considered to be against the diagnosis of ulcerative colitis. More research is needed to develop a better understanding of the aetopathogenesis of this uncommon condition.
Update on immunosuppressive agents including the monoclonal antibodies and newer immunosuppressive agents.

Dr Sue Beath Paediatric Hepatologist Birmingham Children’s Hospital

Immune suppressants agents have developed from general anti-inflammatory agents such as aspirin and steroids to highly specific molecules targeted on a specific cell type or enzyme system within the immune system. The increasing expansion in indications for organ and tissue transplantation is driving pharmacological innovation rapidly as knowledge about fundamental controls of the immune system begins to emerge.

There are several parallel strategies for controlling the immune system in the context of organ transplantation:

- **Drugs with a wide range of effects mediated via actions on the nucleus ie protein translation and transcription, eg steroids which are effective but have many unwanted effects in addition to attenuation of inflammatory mediators. And inhibitors of purine or pyrimidine synthesis, so called anti-metabolites, e.g. azathioprine, mycophenolate and leucomidone, and which are often toxic to bone marrow.**

- **Drugs acting on specific pathways and sites within the cytosol – extra nuclear actions e.g., tacrolimus and steroids. But such pathways feed into other cellular control systems, thus a cascade of side effects often seen in a dose dependent way e.g. Tacrolimus up-regulates endothelium receptors which is one mechanism whereby arteriolar blood flow including renal arteries is restricted leading to hypertension and renal impairment.**

- **Drugs with a specific receptor-ligand interaction – such simple interactions are often to be found on the cell surface and are particularly suitable for monoclonal antibody blockade – has led to an exponential proliferation in designer antibodies active against a variety of ligands from inflammatory mediators such as TNF to receptors for IL-2 activation.**

- **Nutrionals – the role of omega 6 fatty acids in the production of inflammatory mediators such as prostaglandins & arachidonate opens the possibility of a tolerogenic diet rather than simply a hypo-inflammatory diet.**

Intracellular signaling pathways

Trans-membrane proteins/receptors are the means whereby drugs, viruses, hormones, proteins, fatty acids stimulate or control intracellular pathways. These pathways, in turn, stimulate pathways leading to programmed cell death. How ever, NF-kappa B exerts a more selective form of immune suppression with minimal adverse effects. This has led to numerous monoclonal antibodies active against various cytokines.

Cytokines

Cytokines are important mediators of immune cells and have been the focus of attempts to produce a more selective form of immune suppression with minimal adverse effects. This has led to numerous monoclonal antibodies active against various cytokines.

Macrophages produce a large number of cytokines of which IL-1 (causes the release of prostaglandins, thromboxane and platelet activating factors from inflammatory cells) and TNF-alpha (contributes to synthesis of arachidononic acid and derived mediators including prostaglandins and leukotrienes) and TNF-? (induces synthesis of acute phase proteins by the liver and attacks gastrointestinal epithelium) are important examples. All 3 of these macrophage cytokines are inhibited by cortico-steroids.

Thymocytes also produce cytokines and are often categorized into 2 main types according to cytokine profile: Th-1 which is associated delayed type hypersensitivity including rejection and Th-2 which is associated with more immediate responses including allergy and anaphylaxis. The Th-1 cytokines are IL-2 and IFN? (induces synthesis of acute phase proteins by the liver and attacks gastrointestinal epithelium) are produced by T lymphocytes and is pivotal in the immune response leading to clonal expansion of activated T cells. Cyclosporin and tacrolimus block gene transcription of IL-2 via calcineurin pathways inhibition and NF-kappa B. Sirolimus blocks transcription of IL-2 via the inhibition of the fork pathway. The Th-2 cytokines are IL-4, IL-5, IL-6 and IL-10. IL-10 is produced by Th-2 T lymphocytes and B lymphocytes and it acts on macrophages to down regulate expression of MHC. A viral analogue for IL-10 exists in some viruses eg EBV – may also allow evasion of host immune response by down regulating the MHC molecules on the cell surface. This is in contrast to the effects of IFN? which up regulates MHC expression by epithelial cells. Thus the two type of thymocyte antagonise each others actions to provide a balance within the immune system.

Monoclonal antibodies

The latest range of monoclonal antibodies are humanized and well tolerated, although it is still possible to induce a cytokine release syndrome and repeated use can induce allo-antibodies which reduce the efficacy of the monoclonal antibody. The mechanism of action is one of inhibition either by masking/blocking the cytokine/ cell surface receptor, or by cell destruction via a lytic effect. Monoclonals are often referred to by the cytokine being targeted, or by the cellular immunophenotyping which is a classification based on the cell differentiation receptor. The range of cell receptors, their receptors are shown in the table below.

Table showing Cellular differentiation (CD) receptors and their role in disease and immuno-suppression via monoclonals

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<th>CD receptor</th>
<th>Target</th>
<th>Ligand</th>
<th>Uses</th>
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<tr>
<td>CD 3</td>
<td>1 cell receptor (all T cells)</td>
<td>ATG and Orthocline/OXIT</td>
<td>Pre-transplant depletion therapy; rescue in severe rejection episodes</td>
</tr>
<tr>
<td>CD 4</td>
<td>Subset of T cells (cytotoxic/helper)</td>
<td>receptor for HIV as well</td>
<td></td>
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<tr>
<td>CD 8</td>
<td>Subset of T cells (suppressor)</td>
<td>blocked by basiliximab, also tacrolimus both prevent IL-2 stimulating a proliferating immune response,</td>
<td>used in induction regimens to prevent first episode of rejection, allow lower doses of steroids and calcineurin inhibitors</td>
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<tr>
<td>CD25</td>
<td>IL-2 receptor found on cytokotic 1 lymphocytes</td>
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<tr>
<td>CD 20</td>
<td>carried almost exclusively by nearly all B cells</td>
<td>rituximab attaches to receptor and induces lysis, results in none, or very few, B cells and a deficit in immunoglobulin</td>
<td>used to treat tumours in B cells especially post-transplant lymphoproliferative disease.</td>
</tr>
<tr>
<td>CD 52</td>
<td>Found on most B cells</td>
<td>Alemtuzumab (Aka Campath H1) induces lysis on mainly B cells and some T cells also neutrophils</td>
<td>Pre-transplant depletion therapy, also conditioning before BMT</td>
</tr>
<tr>
<td>CD 29</td>
<td>numerous tissue types</td>
<td>TNF-??</td>
<td>Intiflubam, adalimumab are blocking monoclonal antibodies which bind to active molecule. Elancept has similar effect but is a fusion protein with p75 receptor</td>
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Summary

In organ transplantation, no single immunosuppressive agent is sufficient to achieve induction of tolerance, but the combination of calcineurin inhibitors with antibodies restricting stimulators such as CD28 receptor and low dose steroid have combined to produce a lower frequency of rejection in liver, kidney and small bowel allografts. In the long term, new modalities targeting adhesion of immune cells, and, manipulation of the diet to limit the availability of reactive oxygen species and pro-inflammatory cytokines like arachidonic acid, and, molecules influencing the intracellular signaling pathways especially those connected with fibrosis such as the TNF-ROCK-VEGF pathway, may be available to clinicians to achieve the goal of induction of tolerance and effective treatment of chronic rejection, without unacceptable side effects.
Twenty-five percent of cases of inflammatory bowel disease (IBD) present in childhood with Crohn’s disease being the most common type. A significant feature at presentation is poor nutritional status which may worsen during the clinical course. As a result, poor linear growth can lead to permanent growth retardation and failure to reach predicted adult height. Factors contributing include inadequate intake, malabsorption, altered energy demands and stool losses particularly evident in colitis. Nutrition is therefore central to the medical management of the disease in aiming to induce and maintain remission.

Managing nutritional status and prescribing enteral nutrition (EN) requires assessment of energy requirements. At present, there is very little data published on making accurate predictions of an individual’s energy needs during the course of the disease.

In a study of 40 children newly diagnosed with Crohn’s disease energy intakes exceeded the Estimated Average Requirements (EAR) values for age in 82% of the patients with a median of 117.5% of EAR values (Gavin et al, 2005). The group with ileocolonic disease had the highest intakes compared to isolated small bowel or colonic disease (not statistically significant). In the absence of energy balance studies this study concluded that energy intakes in the range of 100-149% of EAR for age may be required.

In inactive Crohn’s disease a study (Hart et al, 2005) compared measured versus predicted energy expenditure in 23 patients. Resting energy expenditure (REE) was measured with indirect calorimetry and compared with predicted basal metabolic rate (BMR) using the Schofield equation. Total energy intake was compared with EAR values. Results showed that REE was higher than predicted BMR values ranging from 79%-136%. Total energy requirements (TEE) ranged from 72%-163% of EAR values. Conclusions made were that the Schofield equation and EAR values are unreliable in predicting energy requirements in inactive Crohn’s disease and may result in underestimating their true energy needs.

More reliable methods of assessing nutritional requirements are needed on the changing requirements throughout the disease process which also accounts for growth and changes in body composition.
For many patients with cystic fibrosis (CF) and pancreatic insufficiency, good nutritional status can be achieved by taking a high calorie diet with an adequate use of pancreatic enzyme replacement therapy (PERT). However, suboptimal growth in some children with CF can remain a problem. As malnutrition in CF is linked to poorer pulmonary function, reduced survival and quality of life, prevention of malnutrition is essential.

Poor weight gain and growth observed in some children with CF suggests a chronic negative balance between energy intake and energy expenditure. To plan effective malnutrition prevention and treatment interventions, an understanding of energy balance is needed. Energy balance depends on the following contributing factors: energy intake, energy expenditure, energy loss in stool due to maldigestion and malabsorption, and energy storage for tissue accretion.

Energy intakes of CF patients may be affected by several factors, including recurrent vomiting from coughing, gastroesophageal reflux, chronic respiratory infections and psychosocial stress. In CF children, energy intakes are often not able to meet the clinical demands of the disease, particularly during puberty, and hence this age group may require greater nutritional targeting (White et al, 2007).

Clinical practice has shown that energy requirements of patients with CF can vary widely, however it has been estimated that energy requirements can be as high as 120-150% of the Estimated Average Requirement (EAR) for age. This increase in requirement is thought to be attributed to a higher basal metabolic rate as a result of catabolic lung inflammation and increased work of breathing (Levison & Cherniak, 1988). However in the stable CF patient, there are conflicting thoughts as to whether total energy expenditure (TEE) is higher than that of healthy individuals.

TEE of individuals with CF can also be increased by uncontrolled maldigestion and malabsorption despite optimal use of PERT. In 1991, Murphy et al reported that raised stool energy losses may contribute towards an energy deficit sufficient to limit growth in CF. Increased maldigested and malabsorbed dietary nutrients, endogenous secretions and cellular debris, and colonic bacterial micro flora lead to increased stool energy losses. A simple measure of stool lipid losses may not be the most accurate way of assessing the adequacy of PERT, as total energy losses will not be detected. A more novel way of measuring total stool energy loss would be to do a three day stool collection, estimating energy loss from stool weight.

In clinical practice, by accurately assessing the different factors that contribute to energy balance in individuals, this will lead to a more effective way of preventing and treating malnutrition in CF.
Polymeric versus elemental feeding in newly diagnosed paediatric crohn’s disease a single blind randomised control trial

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Introduction Enteral feeds are effective treatment for inducing remission in childhood Crohn’s disease (1, 2) although the mechanism is unknown. Previous studies have shown no benefit of amino acids over whole protein based feed (3, 4) but oral intake may be affected (5) as polymeric formulae (PF) are considered to be more palatable than elemental formulae (EF). We compared our existing treatment EF (Emsogen, SHS International) with a novel PF (Alicalm, SHS International) Parameters measured were: oral and nasogastric tube (NGT) feeding, paediatric Crohn’s disease activity index (PCDAI) and weight (Wt).

Methods Children, aged 5-16 yrs with newly diagnosed small (SB) +/ large bowel (LB) Crohn’s disease. Diagnosis was by endoscopy +/- barium meal and follow through and PCDAI >11. A NGT was inserted during the diagnostic endoscopy. Children were randomised to EF or PF. After commencing feeds via NGT they were given the option to take the feed either by NGT or orally for a total of 6 weeks. Changes in PCDAI, Wt, time to first relapse and treatment preference at first relapse were evaluated. Follow up was for two years.

Results 41 children were recruited EF = 20 (11M, 9F), PF = 21 (14M, 7F). Thirty five (85%) completed the 6 weeks treatment period EF =16 (8M, 8F), PF = 19 (13M, 6 F). Disease distribution was SB +LB disease, EF = 81% PF = 95% or SB disease only, EF=13% PF=5%. One patient (EF) had no evidence of SB disease was not withdrawn as was responding to treatment. This study was carried out on an intention to treat basis and four children commenced oral prednisolone during the study period (1EF, 3PF). These children had PCDAI scores at entry in the upper quartile for this population (>42.5). These children are not classified as remissions. Outcomes for those children in remission with feeds are shown below.

<table>
<thead>
<tr>
<th>Feed</th>
<th>Remission</th>
<th>Reduction in PCDAI score at 6Wks</th>
<th>Required NGT for wks</th>
<th>WZ Score at 6wks</th>
<th>WZ Score at 0wks</th>
<th>Wt Gain (Kg)</th>
<th>Time to first relapse days</th>
<th>% using feed at first relapse</th>
<th>No relapse score at 2yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>14/16</td>
<td>7% (14/15)</td>
<td>29 (50)</td>
<td>87%</td>
<td>-0.96 (-3.9 - +2.0)</td>
<td>-0.39 (-3.4- +0.3)</td>
<td>3.63 (3.9)</td>
<td>187 (63-288)</td>
<td>90%</td>
</tr>
<tr>
<td>PF</td>
<td>15/19</td>
<td>7% (15/16)</td>
<td>29.8 (10-47.5)</td>
<td>94%</td>
<td>-0.91 (-2.5 - +2.7)</td>
<td>-0.28 (-1.6- +0.8)</td>
<td>4.58 (2.9-1)</td>
<td>157 (53-256)</td>
<td>70%</td>
</tr>
</tbody>
</table>

Discussion Only two children chose to take all their feed orally (1PF, 1EF). There was no significant difference in remission rates between the two groups EF = 87%, PF = 79% (P=0.05). Wt Z scores were significantly improved within each group (p <0.001). Time to first relapse was between 2 and 10 months, however 33 % (EF) and 38 % (PF) of children in this study had not relapsed by 2 years. Uptake of feed for future relapse did not differ between groups and overall 20/24 (83%) of the children who relapsed recommenced enteral feeds.

Conclusion This study has shown that in the treatment of paediatric Crohn’s, EF and PF have similar remission rates, weight gain, relapse rates and need for NGT feeding. Remission rates in this study were higher than many other reports within the literature. Wt gain was significant implying good adherence to the treatment and may be explained by our practice of using NGT’s as standard. Furthermore, in our unit this does not seem to inhibit re-uptake of feeds at relapse as has been cited in other studies (5, 6).

References

ABSTRACTS FOR PRESENTATIONS

MAIN MEETING

Research opportunities in the NHS

Professor Sally C. Davies, Director General, Research and Development, Department of Health.

In March 2006, the government launched the National Institute for Health Research (NIHR) to provide the framework through which we can position, manage and maintain the research, research staff and infrastructure of the NHS in England. The aim is to enable the NHS to become an organisation that supports outstanding individuals (both leaders and collaborators) working in world-class facilities (both NHS and university), conducting leading-edge research focused on the needs of patients and the public.

Through the NIHR we seek to include all professionals who have a role in conducting and enabling health research in England, and to engage patients increasingly in the identification, design, recruitment to and dissemination of research projects.

To play our part well and have an impact across the range of research requires careful assessment of need and quality of research design and process. We are also supporting the effective translation of research results into health practice.

Over the time that the Department of Health has been responsible for R&D in the NHS we have built up effective partnerships and relationships with many stakeholder groups. We will build on this strength by increasing our engagement with patients and the public and, working through the UK Clinical Research Collaboration to foster deeper and more productive links with key stakeholders.
Since June 2000, consecutive children were prepared for liver biopsy according to a standard protocol. Indications for prophylactic antibiotics were immunosuppression, biliary obstruction or to prevent endocarditis. General anaesthesia (GA) was preferred. For percutaneous Biopsies, ultrasound was used to select site at time of biopsy, or to guide insertion of needle (US guidance). Needle type was that preferred by the operator. Children post-Bx were observed in hospital overnight. Bx tissue was examined for diagnosis and adequacy.

RESULTS: Between June 00 and Oct 07, 539 Biopsies were performed in Children (M:F 262:277) of median age 5.7y (9 days-18.3y) and weight 20.2kg (1.9-112). Of these 142 (26%) were Infants <1 year, including 58 aged <3 months. 186 (35%) were liver transplant recipients (LT). Biopsies were given in 311 (58%) and blood products in 59 (11%). All but 4 received GA. The operator was a radiologist in 243 (45%), paediatrician in 292 (54%), trainee 24%, consultant 30%, and paediatric surgeon in 4. Biopsy approach was transjugular in 9, the remainder were percutaneous. Needle types used were spring-loaded devices: Temno (18G) in 379 (72%) and Biopercut (16G) in 3, and Jamshidi aspiration (17G) in 136 (26%). Both Temno and Jamshidi were used together in 12. Of 515 Temno or Jamshidi Biopsies, site was US localised in 372 (72%) and US guided in 129 (25%). A similar proportion of LT had a Jamshidi biopsy (30%) or Temno biopsy (70%) compared to those with native liver (Jamshidi 24%, Temno 74%; p=0.22). Similarly there was no difference between LT and native liver groups in use of US guidance v localisation (p=0.13).

Complications occurred in 22/539 Biopsies (4.1%); 15 (2.8%) were deemed major (1 pre Bx, 14 post Bx) and 7 (1.3%) minor. Major complications were respiratory arrest pre Bx (1), bile leak (2) sepsis (4), bleeding requiring transfusion (2) and embolisation (1), cardio-respiratory compromise (4) and pneumothorax (1). Minor complications requiring no intervention were local pain/discomfort (4) and localised bleeding (3). The incidence of post-Bx complications did not differ in those with US guidance v localisation (6% v 3.4%; p=0.19) or according to needle type: Jamshidi 2/136 (1.5%) v Temno 17/379 (5%); p=0.07. There was no difference in complication rates in those age <3 months or in Infants <1 year compared to older children. However, complication rates were higher in LT than native liver (6.5% v 2.8%; p=0.04). Of 539 Biopsies, 3 did not undergo histological assessment (1 each for copper, microbiology and enzyme analysis). 12/536 (2.2%) were inadequate for diagnosis (8 insufficient; 4 no liver tissue). Inadequate tissue was more likely from Jamshidi than Temno Biopsies (6.1% v 1.3%; p=0.02). Of 524 adequate for diagnosis, fragmentation was more likely in Jamshidi Biopsies than Temno Biopsies (19.4% v 4% p=0.0001). Adverse event (complication post-Bx and/or inadequate tissue) occurred in 32 Biopsies (5.9%). There was no difference according to needle type (Jamshidi 6.6% v Temno 6.1% p=0.84).

CONCLUSION: Complication rate overall was 4.1%, and did not differ according to either needle type or mode of US use. Complications occurred more frequently in LT recipients. Infants, including those aged <3 months were not at increased risk. Although Jamshidi needle biopsies were more likely to be fragmented and/or inadequate, the overall performance (complications and/or inadequate tissue) did not differ from the Temno needle.
Feasibility of confocal laser endomicroscopy in the diagnosis of paediatric gastrointestinal disorders: the first human studies

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Background and aims
Confocal laser endomicroscopy is a recent development which enables surface and subsurface imaging of living cells in vivo at x1000 magnification. The aim of the present study was to evaluate the feasibility and utility of the confocal laser endomicroscope (CLE) in the description of normal gastrointestinal mucosa and in the diagnosis of gastrointestinal disorders in children in comparison to histology.

Methods
Forty one patients (18 female) median age 10.9 years (range 0.7 to 16.6 years) with suspected or known GI pathology underwent oesophagogastrroduodenoscopy (OGD) (n=31) and/or ileocolonoscopy (IC) (n=29) with CLE using sodium fluorescein and acriflavine as contrast agents. Histologic sections were compared with same site confocal images by 2 experienced paediatric and GI histopathologists and endoscopists respectively.

Results
Duodenum and ileum were intubated in all but one patient undergoing OGD and IC respectively. The median procedure time for OGD was 16.4 minutes (range 7-25 minutes and for IC was 27.9 minutes (range 15-46 minutes). A total of 4386 confocal images were compared with 132 biopsies from the upper GI tract from 33 procedures and 4250 confocal images were compared with 184 biopsies from the ileo-colon from 30 procedures. Confocal images were comparable to conventional histology both in normal and in pathological conditions such as oesophagitis, H pylori gastritis, coeliac disease inflammatory bowel disease, colonic heterotopia and graft versus host disease.

Conclusion
Confocal laser endomicroscopy offers the prospect of targeting biopsies to abnormal mucosa thereby increasing diagnostic yield, with consequent reduction in number of biopsies taken, with the potential decreased burden on the histopathological services, and associated cost savings.

Impact of an improved national paediatric donor organ allocation policy for children waiting for intestinal transplantation (ITx)

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Background: The availability of grafts continues to be a major problem in intestinal transplantation (ITx). In UK prioritisation of paediatric organ allocation was changed in November 2004, to improve donor availability for ITx, which was now considered the first priority after super-urgent liver transplantation.

Aims: To evaluate the effect of change in prioritisation of the paediatric donor organ allocation in the pre and post 11/2004 and its impact on the recipient population.

Methods: Data regarding paediatric donor organ availability and allocation was accessed from the national transplant database. Recipient demographics were recorded from the liver unit database. Statistical analysis was performed by SPSS.

Results: Table 1: Demographics of paediatric donor population within UK

<table>
<thead>
<tr>
<th></th>
<th>01/2001 to 10/04</th>
<th>11/2004 to 12/04</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total donors (mean donors per year)</td>
<td>117 (44.6%)</td>
<td>72 (33.3%)</td>
</tr>
<tr>
<td>Median donor: recipient ratio</td>
<td>2.14</td>
<td>2.16</td>
</tr>
<tr>
<td>Graft allocated for superurgent livers</td>
<td>24 (14%)</td>
<td>15 (20.8%)</td>
</tr>
<tr>
<td>Number of available liver small bowel donors</td>
<td>147</td>
<td>57</td>
</tr>
<tr>
<td>No consent for small bowel retrieval</td>
<td>31 (21%)</td>
<td>14 (24%)</td>
</tr>
<tr>
<td>Small bowel not offered</td>
<td>94 (63%)</td>
<td>15 (26%)</td>
</tr>
<tr>
<td>Small bowel offered</td>
<td>22 (15%)</td>
<td>28 (48%)</td>
</tr>
<tr>
<td>Small bowel not retrieved</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Small bowel retrieved</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 2: Transplant activity between 2001 to 2006

<table>
<thead>
<tr>
<th></th>
<th>01/2001 to 10/04</th>
<th>11/2004 to 12/04</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referrals for paediatric transplant</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>Waiting list deaths</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Number transplanted</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Median time to transplant in days</td>
<td>69.5</td>
<td>85</td>
</tr>
<tr>
<td>No of isolated ITx</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Median time to isolated ITx in days</td>
<td>153.5</td>
<td>215</td>
</tr>
<tr>
<td>Number of combined liver and intestinal transplant (LITx)</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Median time to LITx in days</td>
<td>64.5 days</td>
<td>74.5 days</td>
</tr>
</tbody>
</table>

Discussion: There was a reduction in overall paediatric organ donation. Increasing awareness about ITx has resulted in more number of small bowel organs being offered, although this has been associated with an increased in referrals for transplantation. Since the allocation sequence has changed there has been an increase in number of ITx being performed however the waiting list mortality remains high particularly for children under 10 kg. Disappointingly, isolated bowels not offered/utilised in paediatric donors allocated for super-urgent liver transplants represents a pool yet untapped.

Conclusion: The prioritisation of national paediatric donor allocation favouring ITx has resulted in an increased number of procedures, without an impact on waiting list mortality, especially for small children.
Small bowel histology in screening identified vs symptomatic children diagnosed with celiac disease

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Objectives: The prevalence of Coeliac Disease (CD) is about 1% in the general population. Greater prevalence exists amongst certain high risk groups who are being increasingly identified by screening. We aimed to study comparative histology on small bowel biopsies of screening identified paediatric subjects with symptomatic controls diagnosed with CD based on the hypothesis that screening identified subjects may have milder changes on intestinal biopsy.

Methods: Small bowel biopsies of screening identified children diagnosed with CD were compared with samples from age matched symptomatic controls. Objective measurement of Villous height/ Crypt depth (V/C) ratios and Marsh grades were used to compare biopsies by a single blinded histopathologist. Results were compared using the Mann Whitney u test (non parametric) and further by comparing histological differences between each subject - control pair using the Wilcoxon Matched -Pairs Signed- Ranks test.

Results: The study group consisted of nineteen children diagnosed following screening for CD and had no bowel symptoms. 14 were insulin dependent diabetics, four had first degree relatives with CD and one was a child with Turner’s syndrome. The median age of the group was 8.73 years (1.86 – 16.93). 18 of the 19 children in this group had significant elevation of Anti Endomysial antibodies. The subject who was negative was Ig A deficient. The age matched control group consisted of 19 children as well. The Median age of this group was 8.68 years (2.1-16.3). All of them were anti endomysial antibody positive. The V/C ratios of the symptomatic group compared to the screening identified group was not significantly different (p = 0.75). Similarly, the Marsh grading scores were not significantly different between the two groups (p = 0.99). Mann Whitney U test. Comparing each age matched pair of screening identified to symptomatic children, neither the V/C ratios (p = 0.76), nor the Marsh grading scores (p = 1) was significant. (Wilcoxon Matched Pairs Signed- Ranks test).

Conclusions: There were no significant histological differences between biopsies obtained from screening identified children and those symptomatic with CD.

WHO feeding children with malnutrition

Ann Ashworth, Emeritus Professor Community Nutrition
London School of Hygiene and Tropical Medicine

Severe malnutrition is accompanied by reductive adaptation which is a physiological process aimed at conserving energy and prolonging life. This process alters the functioning of every system, organ and cell, and these changes must be taken into account when prescribing treatment, otherwise mortality is very high. Treatment is divided into two phases – a short stabilisation phase and a longer rehabilitation phase. Feeding during the stabilisation phase aims to halt catabolism, correct electrolyte imbalance and micronutrient deficiencies, repair the metabolic machinery and gut function, get rid of oedema, and restore appetite. Feeding is oral and/or nasogastric (not parenteral), with small, frequent, low-protein, low-lactose feeds. Target intakes are maintenance amounts of energy and protein (i.e. 100kcal/kg/d and 1-1.5g protein/kg/d for young children). Na is restricted and additional K (4mmol/kg/d) and Mg (0.6mmol/kg/d) are given to correct electrolyte imbalance. Additional Zn (2mg/kg/d), Cu (0.3mg/kg/d), vitamin A, folic acid and multivitamins are required to correct micronutrient deficiencies and repair antioxidant defences. Iron is withheld. Modified milk feeds containing 75 kcal, 0.9g protein and 1.3g lactose/100ml are recommended.

In the rehabilitation phase the aim is to restore lost tissue, which requires high intakes of energy and protein (150-220kcal/kg/d and 4-6g protein/kg/d). The transition to the rehabilitation diet is controlled for 3 days to avoid the refeeding syndrome and then the diet is given freely and frequently to maximise intake. The energy and protein contents of the rehabilitation diet should be at least 100kcal and 2.9g protein/100ml.

Adherence to the WHO guidelines reduces mortality rates substantially and improves weight gain at low cost.
Nutrition in the 21st century

Professor Alan Jackson, Professor in Human Nutrition, Southampton

One major challenge for the 21st century will be determined by how well we are able to manage the extremes, simply captured as wealth and deprivation. The divisions within society, once seen as differences between countries or cultures, are now evident as major differences within society, where the gap between great opportunity and no opportunity is wider than ever. Seemingly simple solutions are ignored, and although policy is said to be evidence based, the available evidence is not used to inform critical behaviours. Too often we know what to do, but fail to put that knowledge into effective practice. Thus, for children, the reasonable aspiration of achieving the reality of the Millennium Development Goals is as challenging as ever. Poor growth and development during early life lay the foundation for a lifetime of lost opportunity, but effective breastfeeding and desirable weaning remain an illusory ambition. The backward linkages to good nutrition before and during pregnancy challenge our very concept of how best to ensure and enable young people to grow and mature with responsibility. Freedom of choice has to be associated with better choice, allowing some risk, but fostering better ability to learn from indirect experience are critical abilities acquired during early life. Poor nutrition at every stage links to poor development and less desirable judgement and social behaviour. The current nutritional intake of many young people is extremely poor and will require novel, creative approaches if improvement is to be achieved without unreasonable constraint. The aspiration to achieve health at all ages is based fundamentally on the need to ensure normal growth during infancy and childhood. The responsibility this places on individuals and society as a whole challenges the core of our values and aspirations.

Current therapy of ulcerative colitis and ECCO guidelines

Simon Travis DPhil FRCP
John Radcliffe Hospital and Linacre College, Oxford

The goals for managing acute ulcerative colitis are objective evaluation of disease activity, induction of remission, prevention of relapse and treatment of complications.

Evaluating activity Simple activity indices (1) should guide clinical practice, because it is easy to underestimate severity. A paediatric disease activity index has been developed (2).

Inducing remission topical treatment is appropriate initial treatment for distal disease, but if symptoms persist for a fortnight, then decisive treatment is usually appreciated by the patient. Corticosteroids have been the mainstay, although high dose aminosalicylates (adult dose >4g/d mesalazine) are an alternative for symptoms not interfering with daily activity. Infliximab is an option for persistently active UC refractory to conventional therapy in outpatients, but only 24% of (adult) patients are in steroid-free remission at 6months (3). Severe colitis, defined as a bloody stool frequency >6/day with any one of a tachycardia (pulse >90bpm), temperature (>37.8oC), anaemia (Hb <10.5g/dL), or raised ESR (>30mm/hr) is an indication for intensive intravenous treatment. Ciclosporin 2mg/kg or infliximab 5mg/kg are appropriate as rescue therapy for non-responders to intravenous steroids; debate continue about which is best (4). National (UK) figures indicate that 30% come to colectomy on that admission and objective criteria for predicting the need for colectomy have been validated. The timing of colectomy is the most important decision that a physician is called on to make, in conjunction with the patient and surgical colleagues. This needs particularly careful contingency planning in children.

Maintaining remission Mesalazine (2-4g/d) continues to be first-line therapy (5). Steroids have no place in maintaining remission. Criteria for azathioprine include patients after a severe relapse of ulcerative colitis, early relapse after steroids (dose <15mg/d, or within 6 weeks of stopping), and those needing a second course of steroids within a year. Infliximab (5mg/kg every 8wk) maintains remission in a proportion (34.7% at 12 months, vs 16.5% controls, p=0.001) (3).

Conclusion Therapeutic decisions should have a strategy, aimed at navigating the patient around relapses and through to sustained remission. Good management depends on clinical skills, compassion and care of the individual as well as on pharmacists.

References
The modern management of Gastroscisis

D M Burge, Consultant Paediatric Surgeon, Wessex Regional Paediatric Surgical Unit, Southampton

The modern management of gastroscisis requires a multidisciplinary specialist team conversant with all the problems associated with this abnormality. Gastroscisis is now the most common congenital abnormality requiring surgery in the neonatal period and is virtually always detected on prenatal ultrasound scan. The incidence has increased three-fold in the last 10 years and it has been estimated that the condition currently costs the NHS in excess of £15 m per year.

Surgical management begins with specialist counseling following the detection of the abnormality, usually at the 20 week anomaly scan and will include plans for surveillance during the pregnancy, induction of labour and postnatal management. Delivery should take place at a regional centre capable of managing the condition. The introduction of regular antenatal assessment from 32 weeks gestation appears to have resulted in a reduction in the 10% late fetal loss rate that used to occur.

Following delivery correction of the abnormality has traditionally involved primary or stage closure of the abdominal wall defect. The commonest new modality of treatment is the use of a preformed silo which prevents the need for surgical closure, ventilation and the complication of compartment syndrome.

Most babies will be home by three to four weeks of age. Until this time they will require experienced management of their intestinal problems, particularly dysmotility, which includes intravenous feeding, the introduction of trophic feeds to stimulate gut function, the management of dysmotility, transition to full feeds in an organized and logical manner and early discharge with close outpatient monitoring.

Some patients will be much more complex particularly those with intestinal atresia, short gut syndrome or prolonged intestinal dysmotility. These patients require an experienced team conversant with the specific intestinal issues encountered. The main challenge to enable their survival is prevention of sepsis and long-term liver damage associated with long term PN. Close monitoring of intestinal microbiology with gut decontamination and measures to prevent and treat line sepsis are needed. Occasionally babies will require intestinal transplantation.

In the majority of babies who achieve early discharge detailed and close outpatient supervision is essential. Many exhibit early faltering growth and may have ongoing intestinal dysfunction particularly with respect to feeding, milk allergy, gastro-oesophageal reflux and constipation.

Outcome in gastroscisis is still generally good with less than 5% mortality. However an additional 5% of patients will require long-term intravenous feeding and 10% will get subsequent surgical complications. Research into the reasons for the increase in incidence is on-going and additional research into the prevention and treatment of the severe dysmotility seen in some cases is required.

**“Adult” liver disease in childhood And “Childhood” liver disease in Adults**

Notes from a joint hepatology clinic

Dr Mark Wright - Consultant (Adult) Hepatologist, Southampton

In this talk I will discuss a number of themes I have identified from the setting up of a joint adult/paediatric hepatology clinic here in Southampton.

Hopefully children with liver disease grow up. Usually their liver disease stays with them. At a simplistic level all liver disease is the same: Prevention/ delay of end stage disease followed by the management of cirrhosis and its complications.

Traditionally they split into 2 categories: Survivors with “paediatric” problems eg. CF, Alpha 1 antitrypsin deficiency, Wilsons, Transplants, Biliary Atresias and those with diseases common to both children and adults eg. CF, IBD and AIH/PSC.

A joint clinic provides an excellent way for these patients to make their transition to adulthood and fulfills a need for an adolescent service. It provides an opportunity for older children and young adults to get to know adult physicians in a familiar environment. The experience of adult physicians in dealing with more grown up issues such as substance misuse, the beginnings of alcohol abuse, sex (with increasing relevance due to lower ages at 1st intercourse) is also useful. Young people also face issues regarding life insurance and mortgages, employment, relationships and childcare. Often the children of adult patients with “childhood” liver disease require assessment and screening and a joint clinic provides the ideal location for this. There are also important lessons from adult hepatology to be learned in regard to roll out of “tertiary” services and the convenience to patients of a local service.

As with adult disease the growing disease burden from NAFLD, viral hepatits and to a lesser degree alcohol is beginning to impact on paediatric liver services in a major way. The big 3 in adults increasingly have their beginnings in childhood. And identification of which patients will go on to have problems as adults is an important opportunity. I will discuss in detail the issues pertaining to hepatitis C and NAFID in this population.

In the case of HCV, until now it has been generally accepted that children have only historically mild disease. However some will go on to develop severe disease in early adult life. Biopsy studies to date generally show less severe disease but acknowledge that duration of infection is short. It is less clear however that age and duration correlate with degree of damage and HCC and ELSL are reported in older adolescents (albeit rarely). As with adults children who are also overweight have more fibrosis. There are parallels with the concept of “mild” disease in adults who have often only been infected for a short duration. In many ways childhood may possibly be a better time to treat HCV because of higher SVRs than seen in adults, less co-morbid factors, the opportunity to eradicate prior to transmission, better tolerability and good compliance. It is probably also cost effective to treat mild disease in children, not least because less drug is needed. The virus is not going to do away and in most cases will eventually need treatment in adult life. Treatment in Children should become more widespread. It will be necessary to gear up for treatment outside of the current very few centres.

Similarly in HBV a proportion of cases will go on to develop severe disease. Here though the situation is more complex as nearly all are immune tolerant and existing drugs are not effective at this stage. At some point however treatment will be required in a proportion and a transitional paediatric to adult clinic should ensure that there is minimal loss to follow up. Demographic changes mean that we will see more HBV in the future. We have an opportunity to limit the impact of the disease through vaccination, possibly in conjunction with the new cervical cancer vaccinations.

The growing problem of childhood obesity and with it NAFID is going to be another major impact. Often it provides an issue for “reverse” screening as the children attend clinic accompanied by their obese parents who can be sent along to the adult clinic. As treatments for overweight and obesity evolve we will need to be more aggressive in our management of this population.

New areas in paediatrics will be driven by advances in adult medicine such as new drugs and the availability of new tests eg. non invasive liver fibrosis markers.

In conclusion

Paediatric and adult liver diseases will be recognised to be not that distinct from one another. I will discuss how we need to be more aggressive about some of the emerging liver diseases of childhood because they will not go away and will continue to be a problem in adults, storing up trouble for the future.
Diagnostic and therapeutic advances leading to better understanding and outcome of childhood liver disorders

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Last two decades have seen significant advances in the field of paediatric hepatology both in the identification of newer conditions and improved outcome of the known childhood liver disorders. Advances in molecular diagnostics have helped to identify several newer conditions out of the group of idiopathic neonatal hepatitis syndrome like progressive familial intrahepatic syndrome (PFIC). The newer classification of the PFIC based on serum GGT levels and precise defects in bile transporters will be discussed.

Newer drugs have now become available to treat autoimmune liver disease and viral hepatitis. Second part of the talk will focus on impact of liver transplantation on the outcome of childhood liver diseases like improved survival of children with biliary atresia with combined portoenterostomy and liver transplantation. Significantly improved long term survival of childhood liver tumours like hepatoblastoma where survivals with combined chemotherapy and liver transplantation are now in excess of 80% from less than 30% twenty years back.

Survival after liver transplantation continues to improve with current 1 and 5 year survivals in excess of 95% and 85%. This could be attributed to improvement in surgical techniques and new immunosuppressive agents. However long term complications of transplantation like de novo autoimmune hepatitis, unexplained chronic hepatitis and issues related to immunosuppressive medication continue to pose risks for long-term health and longevity.

All these advancements have now made it possible for the vast majority of children with liver disease to enter adulthood. This group of children ‘grown ups with childhood liver disease’ is a new breed of patients that poses unique challenges to our adult hepatology colleagues. Better coordination and establishment of transition services is urgently required to ensure that these gains are real long-term.

Metabolic syndrome in childhood

Dr Julian Hamilton-Shield – Reader in Diabetes and Metabolic Endocrinology: University of Bristol & Bristol Royal Hospital for Children

Metabolic syndrome is a clustering of central obesity, abnormal glucose metabolism, dyslipidaemia and hypertension that is associated with a three-fold increase in cardiovascular risk and five-fold increase in risk of diabetes in adult populations. There have been numerous efforts to define a similar syndrome in childhood and the latest was produced by the International Diabetes Federation (IDF) in 2007. A prerequisite in the definition is that of abdominal/central obesity as visceral obesity is at the basis of metabolic dysfunction. The IDF guidelines are suitable for children aged 10-16 years as it is felt that those below this age should not be defined as having metabolic syndrome per se. The definition requires central adiposity plus two of the following: raised triglycerides ≥ 1.7 mmol/l, HDL-Cholesterol ≤ 1.03, Systolic BP ≥ 130 (diastolic ≥ 85), fasting glucose ≥ 5.6 mmol/l or diabetes. It could be argued that liver dysfunction (raised ALT) associated with fatty liver infiltration could also be a component of the metabolic syndrome as this is becoming increasingly prevalent amongst our obese children.

Estimates of the prevalence of metabolic syndrome in youth have indicated that in some populations (USA) the level may be as high as 12% although European data indicates a lower prevalence. Amongst selected obese populations the level of metabolic dysfunction can almost reach 50% (USA) whilst the levels from two UK cohorts give a prevalence of around 25%. In the majority of children, weight loss or an improvement in BMI SDS is the mainstay of treatment. In a recent study conducted in Bristol, a loss of ≥ 0.5 BMI SDS was associated with a 28% fall in ALT, 46% fall in hsCRP, 27% fall in triglycerides, 10% increase in HDL levels and 27% improvement in insulin sensitivity as estimated by HOMA-IR. In those increasing BMI SDS in the same period, the figures were a 16% increase in ALT, 16% increase in hsCRP, 7% increase in triglycerides and a 21% worsening of HOMA-IR. As metabolic syndrome in childhood predicts adult risk, weight management in youth must be considered a priority.
Bariatric Surgery
Mr James Byrne, Consultant Surgeon, Southampton

There has been a dramatic increase in the prevalence of obesity and morbid obesity amongst both adults and children throughout the Western world over the last thirty years. This presents a major challenge to individuals affected in this way, their families and to society as a whole.

For many adults with morbid obesity, bariatric surgery is the only treatment that delivers sustained significant weight loss. Weight loss in turn leads to either ‘cure’ or marked improvements in weight related co-morbidities and quality of life.

Bariatric surgery in children has been found to be safe and effective provided that they have reached 95% of skeletal maturation and that this surgery is performed within the context of a highly specialist multidisciplinary team that is able to provide not only the appropriate peri-operative environment, but also the appropriate support to both child and family for long term follow up. Laparoscopic adjustable gastric banding and laparoscopic Roux-en-Y gastric bypass have been the most commonly performed procedures in both adults and children. There is no consensus regarding the optimal surgical procedure for children and very careful consideration needs to be given by patient, family and remainder of the team in order to individualise procedure selection to particular circumstances of each patient.

In the United States, approximately 200 procedures were performed annually between 1996 and 2000 in children. Since then there has been a rapid increase in the numbers of procedures per year with 771 procedures recorded in 2003 with no recorded mortality, compared with over 100,000 operations in adults and mortality of 0.2%.

In the US, a national working group maintains a register of all children undergoing surgery, in order to clearly define outcome following surgery in children. At present there is very limited provision of bariatric surgical services for children in the UK, and as these evolve it would clearly be wise to model such a service along the same lines as the US.

Stable isotope probing of the gut microbiota can link bacterial activity to diversity across varying media, timeframes and bacterial species.
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INTRODUCTION: Changes in gut microbial diversity have been observed in chronic diseases such as inflammatory bowel disease (IBD). Culture independent techniques to characterise the metabolic activity of the colonic bacteria may provide insight into their pathogenesis. Stable isotope probing (SIP) is a technique that links bacterial physiology with metabolic activity.

AIMS & METHODS: The aim of this study was to develop SIP as a new method to study human gut microbial metabolic activity. Fresh human faecal homogenates (5% w/v) from a healthy adult volunteer were incubated with 13C urea (99 atom%; 50mg) in four different culture media which varied in electrolyte and substrate support (Medium 1: cornstarch, electrolytes, buffer. Medium 2: oligofructose, electrolytes, buffer. Medium 3: oligofructose, buffer. Medium 4: buffer only). Sequentially samples were removed at 0, 2 and 6 hr. Bacterial total nucleic acids and total RNA for all media and timeframes were precipitated and purified. 16s rRNA probes (Bact 338, Bif 164), which target all bacteria (eubacterial) and Bifidobacteria respectively, were used to extract 16s rRNA from total RNA of enriched samples. A modified gene-capture technique employing oligo-dt paramagnetic capture particles and a unique CA clamp was used to extract 16s rRNA hybridised to complementary probes. 16s rRNA was analysed in the three highest enriched media at 2 and 6 hr. Analysis was performed by liquid chromatography isotope ratio mass spectrometry (LC-IRMS) to determine 13C incorporation.

RESULTS: Total nucleic acids, total RNA and 16s rRNA all were enriched with 13C over time, indicating bacterial sequestration of labelled substrate. In total nucleic acids and RNA greatest 13C enrichments were seen consistently in the media with carbohydrate and electrolyte support (1 and 2). In the three media probed for eubacterial 16s rRNA (bact 338), total RNA and 16s rRNA 13C enrichments were in proportion over the two time-points (enrichment falling at 6 hr in media 1 and 2 but continued to rise in medium 3) (Fig 1). In contrast to eubacteria, Bifidobacterial enrichment continued to rise at 6 hr, and this rise was most pronounced in oligofructose medium (medium 3) (Fig 2).

Figure 1: 13C enrichments of RNA and eubacterial 16s rRNA in media 1-3 at 2 hr, 6 hr.

Figure 2: Comparison of 13C incorporation in eubacterial (bact 338) and bifidobacteria (bif 164) 16s rRNA in two time points in medium 1 (cornstarch) and medium 2 (oligofructose).

CONCLUSION: Sequence-specific 16s rRNA SIP is a new method to determine how changes in microbiota activity relate to changes in microbiota diversity. LC-IRMS analysis of 16s rRNA provides a sensitive technique to detect small changes in 13C incorporation, and combined with the phylogenetic resolution by sequence specific capture technology, 16s rRNA-SIP offers sensitivity and resolution to study multiple bacterial species from a single stool sample. The study of human faecal samples in relapse or remission, and the extension of SIP methodology use in vivo, may be useful ways of exploring the pathogenesis of IBD.
The early stool patterns of young children with autistic spectrum disorder

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Background: There is some evidence that older children with autistic spectrum disorder (ASD) have an increased prevalence of gut symptoms, and it has been hypothesised that a non-specific enterocolitis is associated with the onset of ASD. However it is controversial as to whether gut symptoms are intrinsic to ASD or are secondary to dietary and behavioural changes in these children. We have used prospectively collected data from a large population study to investigate whether gut symptoms in ASD children are (a) concordant with those known to be associated with enterocolitis and (b) preclude the onset of, or as opposed to being a consequence of, autistic behaviour.

Methods: Information on children’s stool patterns and gut symptoms reported prospectively by mothers taking part in the Avon Longitudinal Study of Parents and Children (ALSPAC). Data were collected by questionnaire at 4 weeks and 6, 18, 30 and 42 months of age and the 86 children identified by local health and/or education systems to have special educational provision for ASD were compared with the 12,896 remaining children.

Results: Comparison of the ASD and control group during the first 3.5 years of life showed that their stools did not differ significantly in colour or consistency. The ASD children had similar stool frequency up to 18 months. At 30 and 42 months there was a trend for ASD children to pass more stools (OR 3.73, 95% CI 1.11, 12.6; P = 0.034), although only three children passed more than 4 stools/day. The ASD children did not have a higher frequency of episodes of diarrhoea, constipation, bloody or black stools or abdominal pain.

Conclusions: Analysis of this large, prospective, population based study concluded that during the first 42 months of life ASD children had a stool pattern that is very similar to other children apart for a slight increase in frequency at 30 and 42 months. There were no symptoms to support the hypothesis that ASD children have an enterocolitis.

References
Introduction: Gastroparesis is a chronic condition characterised by delayed gastric emptying in the absence of mechanical obstruction. It is associated with diabetes, gastric surgery, viral infections, anorexia nervosa and certain drugs. Nearly 60% of cases have no known aetiology. Nausea, vomiting and post-prandial fullness are the most common symptoms, and can be treated with dietary modification, and a combination of prokinetic and anti-emetic drugs. In the most severe cases, patients require surgical intervention and supplemental nutrition by post-pyloric feeding. Current treatment focuses on symptom control and nutritional support. Gastric electrical stimulation or gastric ‘pacing’ represents a novel treatment for severe gastroparesis by regulating gastric electrical dysfunction with a neurostimulator. In adults vomiting frequency has been reduced by up to 81% from baseline at 12 months follow-up. There is no published data in children. We describe a 13 year old girl with life-long severe idiopathic gastroparesis who was successfully treated by gastric neurostimulation.

Case: The patient had persistent vomiting since the first few days of life and despite multiple investigations and attempts at therapeutic intervention, continued to vomit up to 15 times a day as a teenager. She was developmentally normal, attended mainstream school and had no other neurological or medical diagnoses. Her bowel habit was normal and her weight stable. Investigations included an upper GI endoscopy aged 10y, which showed mild esophagitis. Barium meal and pH study were normal. Gastric emptying study aged 12y was highly abnormal showing a half-emptying time for liquids of 20mins and solids of 265mins. EGG showed a normal pre-prandial rhythm (71%), but post-prandial tachygastria (28.6%). Provocation meal test did not provide any further information. Psychosocial review over many years had provided supportive care, but had not reduced her symptoms. Disruption to her schooling required extra home tuition and she was at least a year behind in her education. Prior to referral, nasojejunal feeding had been well tolerated; she was able to eat infrequent infant-size portions of solid food without vomiting. However, following a viral illness, she had deteriorated again to vomiting all liquids and solids and was fully jejunostomy feed dependent.

Gastric neurostimulator: The Enterra device (Medtronic) was placed surgically at age 13y and 11m. Oral feeding was slowly re-introduced while anti-emetics were continued. Follow-up at 3, 6 and 9 months showed a gradual reduction in vomiting frequency with increasing settings to 5mA, with a 1 second stimulus every 4 seconds. The patient had no further hospitalisations and gradually increased her oral intake. At present, 16 months after insertion of the device, she has not used her jejunostomy in 4 months, her weight remains stable and she is eating normal meals without vomiting.

Discussion: In carefully selected cases gastric neurostimulation represents a novel treatment for severe gastroparesis. We describe a case of severe idiopathic gastroparesis in a child, resistant to medical and surgical intervention, who responded successfully to gastric neurostimulation. Although complete resolution of symptoms took over 12 months, this intervention has dramatically improved her quality of life.

References

Adalimumab usage in early-onset Crohn’s disease – results of a regional cohort study
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Background and Aim: There is limited data on the use of Adalimumab (human IgG1 monoclonal antibody against TNF: Abbott Laboratories) for induction of remission in patients with chronic and intractable Crohn’s Disease (CD) of early onset. We used our regional cohort of 180 patients to study adalimumab usage, in particular with respect to information on efficacy, safety, dose-escalation and cost data of Adalimumab as rescue treatment in medically-refractory CD.

Methods: Cohort study of 241 patients diagnosed with early-onset (onset <16 years of age) IBD and managed in a UK regional centre over a 10 year period (1997-2007). Within this, we studied those patients with relapsing CD who commenced fortnightly subcutaneous (SC) Adalimumab injections (induction dosage 80 mg then 40 mg fortnightly), having failed to enter sustained remission on maximal immunosuppressive treatment with Azathioprine (AZA), 6-MP and/ or Methotrexate (MTX), and who had been unresponsive or intolerant of Infliximab (IFX), and who had been followed for at least 6 months after commencing Adalimumab (ADA).

Results: Over this 10 year period, 241 patients from a region with a stable population of 1.25 million were managed with early-onset IBD; 159 had CD, 41 received MTX, 23 received IFX and 6 had AZA for >6 months or more.

Case 1: Female with steroid dependent CD from age 8.5 yrs. Failure to enter remission on AZA and Infliximab, with early relapse on MTX. Poor response to further Infliximab. Adalimumab started at age 19.3yrs with remission maintained at week 4. Case 2: Female, with steroid dependent CD from age 5.8yrs. Early relapse on AZA. Primary sclerosing cholangitis (PSC). No response to Infliximab. MTX contraindicated in view of PSC. Adalimumab started at age 18.5yrs with remission maintained at week 13. Case 3: Female with steroid intolerant CD from age 11.1yrs. 6-MP induced neuroleptic sepsis. Poor response to Infliximab necessitating surgery. AZA treatment stopped due to abnormal LFT and 6-MP reintroduced with further Infliximab inducing delayed hypersensitivity reaction. Adalimumab started at age 24.5yrs with remission maintained at week 25. Case 4: Males with steroid resistant CD from age 15.6yrs. No response to Adalimumab. Early relapse on MTX and Infliximab necessitating surgery. AZA restarted with Infliximab inducing delayed hypersensitivity reaction. Adalimumab started at age 21.5yrs with remission maintained at 4 weeks. Case 5: Male with steroid resistant CD from age 11.1yrs. No response to AZA, MTX or Infliximab necessitating colectomy. Adalimumab started at age 15.9yrs with remission induced at 4 weeks, and maintained in remission in steroid-free state. Case 6: Female with steroid resistant CD from age 9.7 yrs. No response to AZA, MTX or Infliximab. Adalimumab started at age 16.7yrs with dosage escalation to weekly therapy and remission induced at 11 weeks, and maintained in remission in steroid-free state.

Summary: 6 patients with severe CD have responded to Adalimumab therapy by entering remission, 5 within 4 weeks of commencement, with no adverse side effects.

Conclusions: These cases have shown that Adalimumab may be effective in inducing rapid remission in young adults who have severe intractable CD of early-onset with multiple relapses, and who have been intolerant of or failed to respond to infliximab. In the short-term it appears to be well tolerated. Dosage increase to weekly scheduling may be required. Further evidence is now needed for the use of Adalimumab fromRCTs in both the induction and maintenance of remission of severe early-onset CD.
Cyclical Vomiting Syndrome

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Cyclical vomiting syndrome (CVS) is a disorder characterised by recurrent severe episodes of nausea and vomiting in an otherwise healthy child. Associated symptoms include abdominal pain, diarrhoea, headache, motion sickness, photophobia, and drooling. The pattern of vomiting is stereotypical for each child. Onset of symptoms is generally in the pre-school years, though diagnosis may be delayed for years with children undergoing numerous investigations in the intervening period.

Retrospective hospital based studies suggest CVS is a rare condition while community-based studies report a prevalence of 2% or higher. An incidence of 3.15 per 100,000 children per year was reported using The Irish Pediatric Surveillance Unit. This was much higher than expected and is similar to the incidence of Crohn’s disease in that population. The reasons for this high prevalence are unclear but confirmation of the incidence rate is needed.

The aetiology of CVS is unknown. Disorders of fatty acid and mitochondrial metabolism, or ion channelopathies have been postulated. The on-off character of the episodes and their typical pattern suggests a latent disorder that when triggered follows the same physiological cascade. CVS is frequently compared with migraine and has been included as a new headache type in the revised International Classification of Headache Disorders (2004). For some children the possibility stress induced symptoms must be considered. A follow-up study of children with CVS reported that vomiting resolved within weeks of diagnosis in 39% of children. In addition over 40% of children reported other somatic symptoms at follow-up regardless of whether vomiting resolved or not. Both these findings suggest that for a proportion of children CVS may have a functional component.

The impact of CVS on the lives of children and their families should not be underestimated. Diagnosis is often delayed and there is no medication which is effective in treating or preventing episodes in all children. Increasing awareness of the condition and further research into the aetiology and most effective therapies are urgently required.
**ABSTRACTS**

**Poster session I**

**Thursday 24th January 2008**

**Pattern of Infliximab Use and Clinical Response in Inflammatory Bowel Disease – single centre experience**

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Introduction: Infliximab is an increasingly used treatment in Paediatric Crohn’s disease (CD) and more recently Ulcerative Colitis (UC) too. However, the regimen for treatment & indications for stopping are unclear. Aim: We sought to review our experience of Infliximab use, clinical response, outcome and side effects in our patients. Methods: Data was collected retrospectively for all patients with inflammatory bowel disease who had received Infliximab from Aug 2002- Sep 2007. Data was collected for disease distribution, indications for infliximab, dose/schedule of infliximab, clinical response, outcome and side effects. Results: 15 patients (10 girls; age range 6-16 yrs) were treated with infliximab, all of whom had CD. All received concomitant immunosuppressives. Indications for infliximab use were refractory disease (n=6); steroid dependence (n=7); fistulising CD (n=3). All received 5mg/Kg per dose as Initial regime. 3 children received a single dose at Induction, 2 of whom remained well with no further doses. One required a second dose because of relapsing symptoms 10 weeks later but had a serious anaphylactic reaction. This was the only adverse incident in our series. 2/3 children with perianal/fistulising disease who received induction at 0.2,6 weeks remain infliximab dependent while 1 became resistant & underwent detorsion/colostomy, 6/10 children with luminal CD induced at 0.2,6 weeks only responded initially but later restarted infliximab because of relapse. 2 are in remission off infliximab, 2 have undergone small bowel (SB) surgery due to strictures and 1 remains infliximab dependent. 4/10 received maintenance treatment for 1 year and 2 have been in remission since stopping for at least 1 year. 1 underwent colonic reassessment for persisting lower GI symptoms and did not have active colonic disease but had developed an anal stricture causing his symptoms. The final patient has recently restarted because of relapsed luminal CD having been maintained previously on IFN because of multiple SB fistulas unresponsive to infliximab. Overall, 7/15 responded to treatment and 8/15 only had partial response or became dependent. 3/8 of these patients required surgery. Conclusion: Approximately, 50 % of our patients were able to stop infliximab without relapsing or requiring surgery. Patients with luminal CD who received maintenance infliximab treatment had a more sustained remission after discontinuing infliximab. Patients with fistulizing or perianal CD were more likely to require surgery. Patients with luminal CD who received maintenance infliximab treatment had a more sustained remission after discontinuing infliximab. Patients with fistulizing or perianal CD were more likely to require surgery. Patients with luminal CD who received maintenance infliximab treatment had a more sustained remission after discontinuing infliximab. Patients with fistulizing or perianal CD were more likely to require surgery.

**The Muscle Bone Unit in Children with Ulcerative Colitis**

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Abstract:

Background: Children with ulcerative colitis (UC) may have poor bone health and low lean mass due to the effects of chronic inflammation and the use of glucocorticoids.

Aims: (1) To describe longitudinal changes in the muscle-bone unit in UC (2) To compare the relationship of lean mass (LM), fat mass (FM), height (HT) with bone mineral content (BMC) in UC and healthy children

Subjects and methods: 19 children with UC (9 M) with repeat DXA scans performed as part of clinical bone health monitoring and 162 healthy school children (mean age 11.6 years, 77 M) recruited from our local area. DXAs were performed using a Lunar Prodigy (GE Medical Systems, Waukesha, Wisconsin, USA) scanner. Total body (TB) and lumbar spine (LS) BMC for children with CD were corrected for ht and LM. TB and LS bone area (BA), LM and FM were corrected for ht based on regression equations generated from the 162 healthy children from. Results expressed as mean (SD).

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**Cumulative Prednisolone dose 6 months before DXA (mg/kg/day)**

| 0.3 (0.4) | 0.1 (0.1) |

* Significantly different from zero (p< 0.05)
** Significantly different from 1st DXA (p< 0.0001)

In healthy children TBBMC showed positive association with LM(r= 0.94,p<0.0001) and FM (r = 0.59,p<0.0001) on univariate analysis. Multiple linear regression analysis showed that LM [co-efficient 0.037, p<0.0001], FM [co-efficient 0.006,p<0.0001] and ht [co-efficient 13.1,p< 0.0001] were significant independent factors associated with TBBMC in healthy children. In UC similarly, TBBMC showed positive association with LM(r= 0.94,p<0.0001) and FM(r = 0.51,p<0.0001) on univariate analysis. Multiple linear regression analysis showed that only LM [coefficient 0.032,p=0.004] was a significant independent factor associated with TBBMC in UC.

Conclusion: Children with UC have relatively narrow bones (bone area), less marked at lumbar spine, which show no improvement with follow-up. Bone mineral content at total body and lumbar spine are inadequate for size (height adjusted) and muscle bulk (lean mass adjusted). When adjusted for lean mass, bone mineral content appears to be lower when adjusted for height. With follow-up only, lean mass adjusted total body bone mineral content showed significant improvement. The relationship between bone mineral content in children with UC and healthy children appear to be similar but fat mass was not associated with bone mineral content in children with UC. Future studies should explore factors affecting the muscle bone relationship in UC including the role of inflammation, glucocorticoid, changes in growth and puberty, nutrition and physical activity.

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<th>Cumulative Prednisolone dose 6 months before DXA (mg/kg/day)</th>
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Traction Removal of Percutaneous Endoscopic Gastrostomies is Safe and Cost Effective

Srinivasan R, Sampath S, Irvine T, Coldicutt P, Dalzell AM
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Abstract:
Background: There are few published data on non-endoscopic removal of Percutaneous Endoscopic Gastrostomy (PEG) devices. We present prospective data acquired for traction removal of PEG’s at a single tertiary Paediatric centre over a five year period.

Materials and Methods: Data were obtained from endoscopy records, computerised hospital patient information systems and case note analysis. The devices used were the Corflo 12 Fr PEG and the Mic-key button 14 Fr and BARD button devices of appropriate length. PEG removal was performed either by traction or by endoscopic removal as clinically appropriate. All procedures were performed under general anaesthesia.

Results: Between the period 2002-2006, 217 children underwent PEG removal. In 166 children PEG’s were substituted with low profile devices and in 49 children PEG’s were removed as they were no longer required for feeding support. In 3 patients PEG to PEG conversion was the preferred option. PEG removals were performed endoscopically in 51 patients and by traction in 166 cases. The median duration between PEG insertion to button conversion was 0.83 years (0.12 - 3.86). Most patients went home on the same day (mode) as PEG removal or conversion to low profile device, range (0 - 9 days).

Complications from traction removal included bumper separation in 2 cases (allowed to pass per rectum, uneventfully), enterocutaneous fistula requiring surgical closure of the stoma in two cases, failure to insert button needing PEG to PEG conversion in one patient and misplacement of button in one case requiring surgical intervention. Disruption of the stoma track or false track creation occurred in two patients undergoing endoscopic removal. We calculated the material cost of scope disinfection (£10) and surgical intervention. Disruption of the stoma track or false track creation occurred in two patients undergoing endoscopic removal. We calculated the material cost of scope disinfection (£10) and surgical intervention. Disruption of the stoma track or false track creation occurred in two patients undergoing endoscopic removal. We calculated the material cost of scope disinfection (£10) and surgical intervention. Disruption of the stoma track or false track creation occurred in two patients undergoing endoscopic removal. We calculated the material cost of scope disinfection (£10) and surgical intervention. Disruption of the stoma track or false track creation occurred in two patients undergoing endoscopic removal. We calculated the material cost of scope disinfection (£10) and surgical intervention. Disruption of the stoma track or false track creation occurred in two patients undergoing endoscopic removal. We calculated the material cost of scope disinfection (£10) and surgical intervention. Disruption of the stoma track or false track creation occurred in two patients undergoing endoscopic removal. We calculated the material cost of scope disinfection (£10) and surgical intervention. Disruption of the stoma track or false track creation occurred in two patients undergoing endoscopic removal. We calculated the material cost of scope disinfection (£10) and surgical intervention.

Conclusion: No mortality or serious morbidity occurred as a result of traction removal of PEG devices. The probable misplacement of a button requiring surgical intervention occurred in one instance. Traction removal of PEG devices is a safe and cost saving procedure in our experience.

References

Gastrointestinal tolerance and convenience of a new ready-to-use paediatric peptide feed.
R Walling1, J Grogan3, K Karmour1, F Court-Brown1, C Davidson1, S Cooke1, R Bolch1, J Sijben2, A Dhawan2
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Abstract:
Introduction: Peptide based enteral feeds may be beneficial for patients with malabsorption disorder. In the UK peptide based formulae are currently limited to adult peptide ready-to-feed, powdered peptide infant (<1y) and powdered peptide 1-6y) formulae. None of these feeds are ideal for children (1-6y). Adult feeds provide excessive, and infant feeds insufficient, amounts of protein and some micronutrients. Furthermore infant feeds provide insufficient energy. When compared to ready-to-use formulae, powdered formulae may have reconstitution risks such as contamination, handling errors and increased time to prepare. Gastrointestinal (GI) tolerance and convenience of a new ready-to-use enteral peptide feed (1 kcal/ml) formulated specifically for children (8-30kg) was assessed in an open label, randomised, controlled, cross-over study.

Method: Eight children (age 3-11y) received either their current feed (CF) or the trial feed (TF). Children were randomised to receive either their current feed (CF) or the trial feed (TF). GI tolerance (nausea, vomiting, abdominal distension, burping, flatulence, constipation, diarrhoea) was recorded daily during weeks 2-4 and weeks 6-8, as well as the number and consistency of bowel motions. Anthropometric measures were assessed at weeks 0, 4 and 8. Feed intake was recorded daily. At the end of week 4 and week 8, parents completed a questionnaire to evaluate the feed convenience and preference.

Results: The TF was well tolerated in 86% of the children that received it (1 dropped out upon crossing over onto the TF). In some cases the TF reduced GI symptom severity and improved stool consistency. Six children gained weight over the 4 week trial period on the TF compared to 2 in the CF group. The average change in weight was +0.5kg (+0.4 - +1.4) during the TF period and +0.03kg (+0.5 - +0.8) in the CF period. On average children received 65 kcal/day (11-175) from the TF compared to the CF. The TF was reported as being easy to use (6/7), convenient (5/7) and time saving (5/7). When asked their preference of the two feeds, 6 parents reported a preference for the TF.

Conclusion: This small trial suggests that a new paediatric, ready-to-use peptide feed was well tolerated in children with varying pathologies. When compared to the more complex current feeding regimens, parents preferred the ready-to-use peptide feed for its convenience and ease of use.

References


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See the text for the abstract and the full text of the paper.
The British Intestinal Failure Survey (BIFS - a registry to record incidence, causes and outcomes of childhood intestinal failure

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Background: IF is a complex, life threatening disorder which requires highly specialised treatment with great variation in outcome. Most patients recover, many require continuing support on home parental nutrition (HPN) and a proportion may require intestinal transplant (ITx). The paucity of information in the UK about incidence and causes and outcome of IF has precluded rational planning of long term clinical services including transplantation.

Aim: To pilot a project prospectively identifying all cases of IF in the UK, defined as parenteral nutrition dependency as an inpatient for 28 days or more.

Subjects and Methods: Prospective evaluation of all children > 16 years of age enrolled through a pilot study set up through the BSPGHAN, involving 7 regional gastroenterology centres. Outcome data (PN dependency; complications; transplantation; death) solicited at 6 monthly intervals.

Results: Between July 2005 and March 2007, 80 infants and children (38m, 42 f) registered. Median age at commencement of PN was 15 days (range from birth to 16 years).

Conclusions: This pilot study has successfully collected national data on children with IF through a cooperative effort on the part of the BSPGHAN representing paediatric gastroenterologists in the UK and with close working relationships with the British Association of Paediatric Surgeons. Maintaining recruitment over time and obtaining follow up data will depend on fostering close links between IF Registry Manager and identified reporters in centres looking after patients with IF.

<table>
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<tr>
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<td>2 days</td>
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Diagnostic paediatric upper gastrointestinal endoscopy can be safely and effectively carried out in a DGH setting: a 10-year single centre experience

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Aims: The aim of this study was to assess whether diagnostic paediatric upper GI endoscopy (DPUGE) could be safely and effectively carried out in a district general hospital (DGH) setting.

Methods: We performed a retrospective case-notes of all patients who underwent DPUGE over a 10 year period from 1995-2005 in a single district general hospital in the Kent region. Demographic data was recorded. Furthermore, the case-notes were interrogated for method of sedation/anaesthesia, endoscopist’s seniority, complication rates and diagnosis.

Results: A total of 380 upper GI endoscopies were performed over the 10 year period with a median of 38 per year (range 34-44). The children undergoing endoscopy had a median age of 10 years (range, 1-16 years). All of the endoscopies were supervised by a single consultant paediatrician. During the first 5 years of the study period, 111 DPUGE were performed under intravenous sedation and 71 under general anaesthesia. During the second 5 years all procedures (198 DPUGE) were carried out under general anaesthesia, under the supervision of paediatric anaesthetist. None of the patients in this study had a serious bleeding episode or other significant complication. 162 patients (42.63%) of patients undergoing DPUGE had abnormal findings on either macroscopic appearance or biopsy assessment.

Summary: This study suggests that appropriately trained paediatric gastroenterologists can safely and effectively carry out DPUGE in a DGH setting where suitable paediatric anaesthetic support and sufficient workload exists.

Conclusion: Diagnostic paediatric upper gastrointestinal endoscopy an efficient tool when performed under general anaesthesia at a DGH. This may reduce the patient burden in terms of travelling time and missed work/school. Close liaison with regional gastroenterology centres in a ‘hub and spoke’ model is vital. This model potentially provides an invaluable adjunct to regional tertiary endoscopic services.
Incidence and long-term outcome of Intestinal Failure Associated Liver Disease (IFALD) in children on Parenteral Nutrition (PN) from the neonatal period.

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Introduction
Children with severe intestinal failure on treatment with parenteral nutrition (PN) are at risk of liver disease. Episodes of sepsis may exacerbate the disease.

Aim
To review incidence and outcome of liver disease in children with intestinal failure from the neonatal period treated with PN for > 12 months who were discharged home and to compare with frequency of sepsis in infancy.

Patients
39 children (17 male, 22 female) born between 1990 and 2002 were reviewed. Aetiology of intestinal failure was short gut in 20(53%), enteropathy in 11(29%) and dysmotility in 7(18%). One child with early-onset microvillous atrophy was excluded.

Methods
Results of serum bilirubin levels were reviewed at 6 and 12 months and 2, 5, 10 and 15 years. Numbers of episodes of sepsis before 12 months of age were calculated.

Results
Incidence of liver disease at 6 months was 52% (7/25 mild [serum bilirubin 50-99umol/L], 6/25 severe [serum bilirubin >100umol/L]). By 12 months only 3% (1/32 cases) had mild and 9% (3/32 cases) severe disease. At 2 years of age 7% (2/26) had mild disease and none severe disease. All 21 cases followed up for 5 years had serum bilirubin < 50 umol/L. 12/13 children had serum bilirubin < 30umol/L by 10 years of age. One child had a temporary rise of bilirubin to 69 umol/L which later returned to <50 umol/L. All 9 children followed up to 15 years had serum bilirubin < 50umol/L. Two children born in 1992 died of liver disease.

The incidence of infection in infancy in 35 children ranged from 0-13 episodes (mean and median 1 episode). There was no clear association between incidence of infection and bilirubin level at 12 months.

Conclusion
Abnormal serum bilirubin levels improve with time in children with intestinal failure treated with intravenous feeding for >6 months and discharged home.

Factors influencing changes in mean corpuscular volume and white blood cell indices in paediatric inflammatory bowel disease treated with azathioprine.

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Aim
1. To describe the relationship between mean corpuscular volume (MCV) and white blood cell indices (WBC) in children with inflammatory bowel disease (IBD) treated with azathioprine.
2. To determine the effect of age, gender, diagnosis, azathioprine dose, thiopurine methyltransferase (TPMT) status, plasma protein level and additional therapy on this relationship.

Method
The Sheffield Children’s Hospital pharmacy database identified all children from April 2002 to April 2007 treated with azathioprine for IBD. Patient demographics, haematological indices, azathioprine dose and other treatment modalities were documented following review of case notes. Baseline data was defined as values occurring within the preceding six months of commencing azathioprine. Data was further collected at time intervals 3-6 months, 6-12 months and 12-24 months post initiation of azathioprine therapy. Non-parametric data was log transformed. Mann-Whitney U test was used for non-parametric data and paired t-test for parametric data. Trends were tested for significance by ANOVA and multiple regression analysis.

Results
The population sample included 97 children with IBD (Crohn’s n=52, ulcerative colitis n=14 and indeterminate colitis n=31). Baseline age, weight, initial azathioprine dose per kg and TPMT levels were similar for each group. Baseline MCV was lower (74.7fl (7.5) vs 79.1fl (6.2)) and final azathioprine dose per kg body weight was higher (2.3mg/kg (0.7) vs 2.3mg/kg (0.7)) in children with Crohn’s compared to other types of IBD. Total WBC and neutrophil count fell steadily within the first six months then plateaued between 6-24 months. Conversely, MCV increased steadily within the first six months of treatment with a plateau between 12 to 24 months. This occurred despite a steady increase in dose per kg of azathioprine from baseline to 24 months (1.75mg/kg (0.7) vs 2.4mg/kg (0.77) respectively). Patients with an elevated MCV at 24 months also had a corresponding elevated MCV value at baseline (p=0.006). TPMT was a poor predictor of MCV and WBC variability (p=0.05, R2=15% ) The relationship between MCV and WBC values (or MCV and TPMT) was not influenced by age, gender, azathioprine dose per kg, infliximab, elemental diet or steroids. The association between MCV and WBC significantly strengthened by including a diagnosis of Crohn’s (p=0.05, R2=21%) and mean plasma protein levels at baseline (p=0.008, R2=58%).

Discussion
This study cohort did not include children that developed severe blood dyscrasias since trends were subject to dose adjustment on clinical grounds. A total of 12 patients had azathioprine discontinued for reasons of hyperamylasaemia, neutropenia, post-surgery and for non-specific symptoms. A further 8 patients had azathioprine dose reduction for hyperamylasaemia, lymphopenia and TPMT status. There was no uniformity in this dose alteration. Our findings suggest that regular blood monitoring especially in the first six months, provides early detection of drug induced marrow suppression. Since indices stabilise by 12 months, frequency of monitoring can be reduced thereafter. Pre-azathioprine therapy factors that are yet unknown may predispose some children to drug induced macrocytosis. Crohn’s is associated with a greater disturbance in blood indices than other forms of IBD. Potentially, plasma protein is an as yet unrecognised pharmacodynamic factor that decreases available free azathioprine.

Conclusion
Factors yet unrecognised, other than TPMT level and dose per kg, may influence children’s response to azathioprine. The rate of plasma proteins needs to be further investigated. There needs to be a consensus on dosage adjustment of azathioprine when faced with potential adverse reactions.
Review of food-related symptoms in children with Crohn's disease following treatment with liquid enteral feeds

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Introduction

Whilst it is well established that liquid enteral feeds can effectively bring Crohn's disease into remission, it is still not clear as to the role that foods play in inducing symptoms.

Aims

To review food related symptoms in children once disease was in remission following treatment with liquid enteral feed (the first line treatment for children presenting to our unit with Crohn's) with or without immunosuppressive treatment.

Patients

All 49 children (24 male, 25 female) aged 5-16 years (mean 15) presenting from 2000-2005 who were treated with liquid enteral feeds were reviewed.

Methods

Paediatric Crohn's disease activity index (PCDAI), site of disease, and indicators of an allergic predisposition (atopy, non-food allergies) and results of blood tests for IgE and specific IgE to foods were recorded.

Children were treated with liquid enteral feed for 6-8 weeks then foods were individually introduced at 3-day intervals.

Results

16 of the 49 children had food related symptoms. Abdominal pain was the most common problem (12 cases). 10 of the 49 were atopic and all 10 had food related symptoms (P 0.000, confidence interval 0.73-1.39). 13/49 had raised total IgE and 3 of 21 positive specific IgE. Foods most commonly causing symptoms were milk products, wheat, egg, soya, potatoes. PCDAI ranged from 0-18 (mean 5.8).

Conclusion

Food-associated symptoms commonly occur in children when re-starting a normal diet after a period of treatment with liquid enteral feed and affected all atopic children in this study. Individual reintroductions of foods with dietitian support are helpful if food-associated symptoms are to be detected and dealt with.

Poster Session II Friday
25th January 2008

Endoscopic cystogastric stenting for pancreatic pseudocysts
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Pancreatic pseudocyst is an uncommon but complicated condition in children. Most cysts are secondary either to trauma or idiopathic pancreatitis. A large proportion of cysts respond to non-surgical management. If a symptomatic cyst is refractory to conservative treatment and does not respond to aspiration most surgeons resort to an internal drainage procedure by fashioning a cystogastrostomy or cystojejunostomy. These procedures are complex operations and carry a significant risk of short and long term morbidity. We have successfully performed endoscopic cystogastric stenting (ECS) for four patients who otherwise would have required an operative cystogastrostomy or cystojejunostomy.

Three patients presented with pancreatic pseudocyst secondary to idiopathic pancreatitis and one was after a traumatic transection of the pancreatic body. Presenting symptoms were recurrent abdominal pain, vomiting, fever and early satiety. The endoscopic procedure was performed using a straight viewing ultrasound gastroscope under fluoroscopic guidance. Median inpatient stay after stent insertion was 72hrs compared to up to 2 weeks after an open operation. In one patient there was inadvertent aspiration of Gall Bladder, managed conservatively. Endoscopic removal of the stent was performed as a day case procedure, after ultrasonic confirmation of the resolution of the pseudocyst, six weeks post stent insertion.

We believe that ECS is a safe and effective technique for the treatment of pancreatic pseudocysts.
Expression of recombinant FOXP3 transcription factor and two isoforms in Escherichia coli

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Background: Profound inflammatory disorders of the gut, skin and endocrine glands occur in the absence of T regulatory lymphocytes. The function of these lymphocytes is largely dependent upon the expression of FOXP3 transcription factor, which is tightly restricted to the subpopulation of CD4+, CD25+, CTLA4+ T cells. Murine knockout, or knockdown models of Foxp3 producing Treg cells develop colitis and rheumatoid arthritis. The long-term aim of this project is to develop a functional assay of FOXP3 and DNA binding. The immediate aim was to engineer E. coli to produce pure, recombinant FOXP3 (wild type and isoforms a and b) and to verify in vitro biological activity of proteins.

Methods: Overproduction of FOXP3 in E. coli was achieved following analysis of the FOXP3 cDNA sequences (for full length and 2 splice variants, a and b). Oligonucleotide primers were designed with unique restriction enzyme sites to facilitate ligation of PCR amplified FOXP3 DNA into pGEX-KG expression vector. Placing the FOXP3 coding sequence downstream of the GST tag allowed the encoded fusion protein to be easily isolated by affinity chromatography. The FOXP3 expression vector was transformed into E. coli BL21 (DE3) for expression trials. Optimization of conditions was assessed on 25 ml cultures. The presence of FOXP3 was detected by western blotting. Once optimized, the scale of the culture was increased. Binding to specific recognition sequences in the IL2 promoter region was tested by electrophoretic mobility shift assays. Isolated FOXP3 was incubated with the target DNA and FOXP3-DNA complexes were detected by electrophoresis and autoradiography. The electrophoretic mobility shift assays were also used to measure kinetics of FOXP3 and isoforms.

Results: Three isoforms of FOXP3 were isolated as GST fusion proteins by affinity chromatography of cell extracts from cultures of recombinant E. coli. After release of the FOXP3 variants from the GST tag by thrombin cleavage, SDS-PAGE analysis and Western blotting suggested that the polypeptides migrated more slowly than would be predicted on the basis of their molecular weights. Further analysis indicated that the full-length FOXP3 protein was present as an aggregate that failed to bind the IL2 promoter. In contrast, the GST-FOXP3 fusion protein was predominantly dimeric and interacted with the IL2 promoter in electrophoretic mobility assays. The GST-FOXP3a and GST-FOXP3b variants also bound at the IL-2 promoter, with GST-FOXP3a exhibiting the greatest binding affinity.

Conclusion: Escherichia coli strains have been created that express FOXP3 proteins. This is an essential step towards developing assays to investigate the mechanisms of FOXP3 function.
IgG antibodies to foods are of no relevance to IgE mediated food allergy

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Aim: IgG food antibodies have been claimed to be important in both enhancement and suppression of food allergies. We hypothesised that food specific IgG antibodies are raised in those known IgE mediated allergy to the same food when compared to children with known allergies to different foods. Thus the aim of this study was to examine the serum concentrations of IgG antibodies to casein, egg and peanut in children with IgE mediated allergy to dairy, egg and peanut.

Methods: Patients with food allergy and controls were recruited from the allergy and paediatric gastroenterology clinics. Controls were children having blood taken in the paediatric gastroenterology clinic with no atopy or inflammatory bowel disease. Total serum IgE and specific IgE and IgG antibodies to casein, egg and peanut using the Pharmacia Unicap system were measured. Medians were compared using the Mann-Whitney-U, test.

Results: A total of 94 children were recruited. 62 had food allergies requiring dietary avoidance (mean age=6 years ), with raised RAST or SPT and/or acute onset within one hour of ingestion. 21 reacted to dairy products, 25 to egg and 27 allergic to peanut. There were 32 controls, with a median age of 11 years. As expected the allergic group had higher total IgG and RAST concentration to casein, egg and peanut than the controls. All three food antibody IgG levels were higher for the food allergy group as a whole than the controls (p<0.05).

However in the food allergic patients there were no significant differences found in the food IgG to which they react (e.g. Casein IgG in dairy allergy) when compared to allergic children without that specific allergy.

Summary: In a group of children with defined food allergies there was no increase in food IgG antibodies in those with reactions to the measured food compared to those without the reaction.

Conclusion: Although food allergic children have higher levels of food specific IgG antibodies than controls, these data suggest that IgG food antibodies in serum are not related to the presence (or absence) of IgE mediated food allergic reactions. Any direct relevance to the pathogenic process remains unlikely.

The Paediatric Feeding Team: Who, Why, What, When & Where
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Aim
To investigate the pattern, patient journey and clinical outcome of both internal and external referrals to the paediatric feeding team at Barts and the London.

Multi-disciplinary feeding teams have been established nationally to manage complex feeding problems in the paediatric population. The compositions of teams are varied. There is very little information on the children who present to these teams as to referral patterns and outcomes. This study was set up to answer these questions for the feeding team based at the BLT.

The BLT feeding team is a regional service that has senior multi-disciplinary input (dietetics, speech and language therapy, gastroenterology and clinical psychology). The team meets once a week for 1 session with 1 clinic per month for new referrals.

Method
In 2004 82 patients were appointed as new referrals. This study reviewed all new patient notes for the year 2004. Of the 82 patients seen in new patient clinics in 2004, 65 sets of medical notes were obtained for review. The equivalent multi-disciplinary notes were reviewed. Notes were reviewed for the 22 month period from January 2004 to October 2005.

Summary
Given the small numbers of each group statistical trends have not been possible. Therefore a description of comparison between the groups is summarised.

Children with vomiting, aspiration and faltering growth tend to be referred earlier. These children were more likely to be referred under the age of 2. Children with selective eating around range or texture tended to be older when referred. Preterm children presented only with vomiting or faltering growth. Children in the faltering growth category were premature and born at earlier gestational ages. Children with aspiration were likely to have disability, children with selective eating around range less so. None of the children with selective eating around range were tube fed.

Children with selective eating around texture had fewer appointments. Children with concerns around aspiration and faltering growth were least likely to attend appointments, whilst those with concerns around selective eating were most likely to attend.

Investigations had 75% positive diagnosis. Children with selective eating around texture were least likely to have investigations (50%) children presenting with vomiting (92%). Children with faltering growth were least likely to have a diagnosis made relating to their feeding difficulties. Ongoing or previous experience of reflux was as likely across all but the faltering growth group. Children with aspiration concerns and faltering growth were most likely to be discharged back to referrer. Overall 35% continued to be seen in clinic at the time of review.

Conclusions
Our team needs to define stricter referral criteria based on types of feeding presentation in order to best utilise the composition of the team. We need to develop a better format for recording information and problem definition to facilitate research and audit. The formulation of the psychological component of feeding problems is poorly developed and acknowledged in medically related feeding problems.
The spectrum of inflammatory bowel disease associated with autoimmune liver disease in the paediatric age range

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Background: Previous studies have suggested a high incidence of inflammatory bowel disease (IBD) in children with sclerosing cholangitis (SC), whilst ulcerative colitis remains the most common form of IBD. Some individuals develop a unique form of IBD, which has been termed ‘PSC-IBD’. This condition is said to more frequently exhibit endoscopic rectal sparing. The clinical features of IBD associated with autoimmune liver disease (AILD) in children have not been well documented. The aim of this study was to characterise the type of IBD and natural history of children diagnosed with both conditions.

Methods: We carried out a retrospective case-notes review of all paediatric patients (aged 18 years or younger) diagnosed with IBD and AILD of our institution between 2001-2006. The biochemical, endoscopic, radiological and histological features of both the liver and the bowel disease were recorded including the auto-antibodies (AAB): antinuclear antibodies, anti-smooth muscle antibodies and liver-kidney microsomal antibodies. A diagnosis of autoimmune sclerosing cholangitis (AISC) was made on the basis of specific cholangiographic changes and/or histological features of acute or chronic cholangitis, in the presence of positive AAB. SC without positive AAB was described as primary sclerosing cholangitis (PSC). All of the patients included in the study had been investigated with ileo-colonoscopy (ICOL). Where the IBD diagnosis preceded the onset of liver disease, endoscopic and histological diagnoses were reviewed. In those individuals, diagnosed at our unit with liver disease first, all patients underwent elective ICOL within 3 months of diagnosis.

Results: Thirty-four children with liver disease and IBD were identified during the study period (62% male). At the time of the diagnosis of liver disease they were a median age of 12 years 3 months (range: 5 yrs - 15yrs 9m). Eighty-eight patients were diagnosed with IBD and AISC during the study period. A further two patients both with ulcerative colitis were diagnosed with autoimmune hepatitis (AIH) with normal cholangiography and no cholangiologic feature demonstrated on liver biopsy. Four patients had endoscopic retrograde cholangio-pancreato-graphy (ERCP) confirmed sclerosing cholangitis associated with IBD without positive ANA or SMA. 2/4 had positive perinuclear anti-neutrophil cytoplasmatic antibodies (pANCA). These children were included as having PSC, and not included in subsequent analysis. Overall 29/30 (96.7%) patients were pANCA positive. Therefore during the study period there were 30 children diagnosed with AILD and inflammatory bowel disease. Of these 21/30 (70%) had ulcerative colitis, 6/30 (20%) had indeterminate colitis and 3/30 (10%) had Crohn’s disease. Of those patients with indeterminate colitis 4/6 demonstrated rectal sparing macroscopically and histologically.

Conclusions: As in the adult population, SC has a strong association with inflammatory bowel disease in children. In the paediatric age range SC seems to be predominantly of an autoimmune aetiology. Whilst ulcerative colitis remains the most common form of IBD in children with AILD, indeterminate colitis is slightly over-represented, and rectal sparing was observed which would be relatively unusual in the wider paediatric non-Crohn’s IBD population. SC without serological autoimmune features (PSC) was a rare event (0.8%) in our series compared to adult studies. In this study patients with AIH have been diagnosed with IBD without any evidence of SC on biopsy or cholangiography. Long-term follow up is necessary to see if the patients with AIH will evolve into SC. It would seem appropriate that all patients with AILD with ERCP or liver biopsy findings suggestive of SC should have a formal ileo-colonoscopy soon after diagnosis, even in the absence of symptoms.

Granulomatous Bronchiolitis Complicating Ulcerative Colitis

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A 6 year old boy presented with a 2 year history of intermittent rectal bleeding, diarrhoea, poor appetite and weight loss. He was initially investigated by the paediatric surgeons with a Meckel’s scan, upper GI endoscopy, limited sigmoidoscopy & laparoscopy - all of which were normal. He has developmental delay and epilepsy. Chromosomal analysis revealed abnormal chromosome 15 and Y chromosome with unbalanced trisomy translocation.

At 5 years of age, he was referred to paediatric gastroenterology team at BRCH because of persistent symptoms. He was admitted for Upper and Lower GI endoscopy. However, he developed severe respiratory illness which was initially treated as infection with macrolides and delayed his endoscopic investigations.

Over the following months he had recurrent attacks of respiratory disease and intermittent rectal bleeding. Extensive investigations ruled out an infective cause of the respiratory illness. Thoracotomy with open lung biopsy revealed granulomatous bronchiolitis with Interstitial lung disease. Upper and Lower GI endoscopy revealed extensive inflammation of the left side of colon, consistent with Ulcerative Colitis (UC) both macroscopically and histologically.

The spectrum of lung diseases in inflammatory bowel disease is very broad. The pattern of respiratory illness tends to be selective to either Crohn’s disease (CD) or UC in the majority of cases. However, there is a degree of overlap. Granulomatous lung disease tends to characterise CD.

This may be the first case of UC with granulomatous and interstitial lung diseases.
Infliximab, panacea or dangerous drug?
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Infliximab is a chimeric anti-TNF monoclonal antibody with potent anti-inflammatory effects. It is highly efficacious in a severe active and fistulating Crohn’s disease. The most commonly reported side-effects are infections (including tuberculosis) and hypersensitivity reactions; there is a small risk of lymphoproliferative disorders. We report a case of young boy with severe Crohn's colitis who developed visual symptoms and seizures post infliximab infusion with abnormal magnetic resonance imaging (MRI) of the brain. This showed extensive high signal abnormalities affecting cerebellar hemispheres, occipital poles, medial parietal lobes and peripheral frontal lobes, characteristic of extensive posterior reversible encephalopathy syndrome (PRES). This rare ‘encephalopathic’ process has been reported in pre-eclampsia, hypertensive encephalopathy or in association with immunosuppressive agents such as cyclosporine A and tacrolimus; to our knowledge an association with infliximab has not previously been reported.

This report emphasises the possibility of serious and unexpected side effects of Infliximab, whilst demonstrating its efficacy in the management of Crohn’s disease. The importance of counselling patients and families regarding the known and unknown side effects of novel interventions is highlighted.

Is There A link Between X-linked Ichthyosis, Blau Syndrome and Crohn’s Disease
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INTRODUCTION
We report on a teenage patient with X-linked Ichthyosis who was diagnosed with Crohn’s disease after being symptomatic and having had positive investigations.
In the literature there has been only one publication describing the possible link of Ichthyosis and Crohn’s disease and only one case report describing Ichthyosis as a very rare skin manifestation in Blau syndrome.

CASE REPORT
We present a fifteen year old Asian boy who was referred to us with a four month history of increased frequency of stools, loss of appetite and weight loss.
He started to have fresh rectal bleeding intermittently in the last month. His systemic examination was normal except generalised ichthyotic skin. His inflammatory markers were high. His colonoscopy both macroscopically and microscopically along with the barium follow through confirmed the diagnosis of Crohn’s disease.

His maternal grandfather, mum’s cousin and maternal uncle all suffer from ichthyosis. His uncle and Mum’s cousin have been diagnosed with non specific colitis. His other two male siblings do not suffer from ichthyosis or inflammatory bowel disease.

DISCUSSION
X-linked ichthyosis is a genetic disorder of keratinization characterized by a generalized desquamation of large, adherent, dark brown scales. The extracutaneous manifestations include corneal opacity and cryptorchidism. X-linked Ichthyosis is a relatively common genetic disorder, affecting approximately 1 in 6000 males with no significant racial or geographical differences. The most common forms of skin eruption in Crohn’s disease are erythema nodosum and pyoderma gangrenosum. In a study of 832 cases of Crohn’s disease, in one patient an association was found with familial ichthyosis. CARD15 gene with a mutation G908R is found to be a factor in common in Crohn’s disease and Blau syndrome. Blau syndrome is a rare condition typically defined by granulomatous arthritis, skin eruption (mainly maculopapular) and uveitis occurring in the absence of lung or other visceral involvement. Only one case has been reported in the literature establishing a link between Blau syndrome and ichthyosis.

CONCLUSION:
CARD15 gene with a mutation G908R is common in Crohn's disease and Blau syndrome. Our patient with X-linked ichthyosis without any other systemic features of Blau syndrome was subsequently diagnosed with Crohn’s disease. His close relatives suffer from Ichthyosis (all males) and some of them also suffer from non specific colitis. Therefore we recommend that further work including genotyping needs to be done to establish a link between X-linked Ichthyosis, Blau syndrome and Crohn’s disease.
Steroid dependent Crohn's Disease in 16-year old boy

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He was first seen in the clinic in April, 2005 at the age of 13.6 years. He had been having abdominal pain in RLQ, diarrhoea, lethargy and loss of weight and appetite. He was anaemic (haemoglobin 9.4) and had high inflammatory markers. His colonoscopy showed pancolitis with ileal involvement. There was a poorly formed granuloma in the biopsy specimen from ileum and chronic inflammation in colonic biopsies. The barium study showed ileal involvement. He was given a course of steroids and his symptoms were settled. He continued with Sulfasalazine.

Five months later (October, 2005), he had a first relapse with bloody diarrhoea and was treated with a course of steroids. Azathioprine was then added. He had another relapse 4 months later, which was treated with steroids. He responded to steroids within a week. Three months later (January, 2006) he had a third relapse and required another course of steroids. When he had fourth relapse in June, 2006, we treated him with Mesalazine enema. His symptoms recurred when enema was stopped and therefore Infliximab was commenced in July, 2006. He responded to Infliximab within a few days. He went on to two monthly IV Infliximab.

In September, 2006, Sulfasalazine was replaced with Pentasa. In December, 2006 he had fifth relapse while he was on regular IV Infliximab. He was treated with a course of steroids. He relapsed again (sixth relapse) in January, 2007 within a few weeks of stopping Prednisolone. He was then treated with Prednemna and IV Infliximab was given a week earlier than scheduled. His symptoms were settled again.

In June, 2007 he relapsed again for the seventh time. IV Infliximab was given earlier. His bloody diarrhoea stopped for a few days but continued to have loose stools. A few weeks later he started passing bloody stools. He became anaemic and his inflammatory markers went up. We repeated colonoscopy in September, 2007 which showed pancolitis up to right hepatic flexure and there was a patchy distribution in ascending colon. He was then given a course of steroids. His symptoms were settled within a week. He is now in remission. His other medications include Azathioprine 2.5mg/kg and Mesalazine 500 mg tds.

In summary, this 16-year old boy who is on regular IV Infliximab infusion for the past one year, has been having relapsing symptoms. Despite a good initial response to IV Infliximab, he is not able to maintain the remission. His colonoscopic appearance after one year of treatment has not improved much. However, he seems to respond to steroids well clinically and he relapses within several weeks of stopping steroids. Our questions are:

1. Why is he relapsing while on IV Infliximab?
2. Is it worth continuing IV Infliximab (he has been on this medication for one year) at the current regime? or
3. Is it worth increasing the dosage of IV Infliximab or
4. Is it worth changing to another biologic agent?

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