Challenges in the Care of IBD in Patients of All Ages

October 2 – 3, 2013
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Abstracts
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Falk Symposium 190

CHALLENGES IN THE CARE OF IBD
IN PATIENTS OF ALL AGES

London (Great Britain)
October 2 – 3, 2013

Scientific Organization:
A. Levine, Holon (Israel)
A. Forbes, London (Great Britain)
C. Probert, Liverpool (Great Britain)
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Session I

Natural history
Can we predict the high risk patient?

Edouard Louis, MD, PhD
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Inflammatory bowel diseases (IBD) are heterogeneous entities. Both Crohn’s disease (CD) and ulcerative colitis (UC) may present as benign non-progressive disease, as slowly or lately progressive disease or as rapidly severe disease. The relevance of predicting disease course is linked to the importance of tailoring treatment strategies to the individual patient to avoid tissue damage. This is to avoid overtreatment or undertreatment, optimizing the benefit/risk and the benefit/cost ratio. Main outcomes in CD are, the development of stricturing and penetrating complications, including perianal disease, surgical resection, disability and mortality. Main outcomes in UC are colectomy, either linked to chronic active disease, acute severe colitis or colorectal cancer, and mortality. In CD, the strongest predictor of stricturing disease, intra-abdominal penetrating disease and surgical resection is still small bowel location of the disease. Overall, 80% of these patients will develop stricturing and/or penetrating behavior and 65% will have to be operated. The strongest predictor of perianal disease is the colonic and even more strikingly the rectal location of the disease, up to 90% of patients with rectal CD developing perianal disease. Simple clinical characteristics, such as extensive small bowel disease and early age at onset have also been associated with an increased mortality. Anti-microbial and anti-glycan serological antibodies as well as genetic markers such as CARD15 gene variants are associated with the risk of development of complicated disease and surgical resection, but it is still unclear whether they have added predictive value over simple clinical characteristics. Other serological and genetic markers may help in the future to stratify patients. Endoscopic features have only been little studied as far as their predictive value. However, a retrospective cohort study suggests that deep ulcers of the colon covering more than 10% of a colonic segment are associated with a high risk of colectomy. In UC, disease extent is a predictor of the risk of colectomy, colonic cancer and mortality. Young age at onset and early extension of the disease are also predictors of colectomy. Concomitant sclerosing cholangitis is associated with a high risk of colorectal cancer. Some genetic factors, including HLA-DR variants have been associated with the risk of acute severe colitis and colectomy. Whole genome transcriptional analysis of peripheral CD8 lymphocytes seems to be able to identify patients requiring early treatment escalation both in CD and UC. Several attempts have been made to build up complex predictive models integrating both clinical characteristics, serological and genetic markers. They have lead to preliminary promising results. In the future, these models may also integrate endoscopic or medical imaging features as well as the phenotyping of immune cells and mucosal molecular signatures. One of the key issues for the development of these predictive models is still to have a relevant definition of a bad disease outcome.
Standardised recording of parameters related to the natural history – From Montreal to Paris

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Similar to adults there is heterogeneous phenotypic expression of inflammatory bowel disease (IBD) in children. Thus, a classification system for disease characteristics is obligatory if one seeks to understand and eventually change the natural history of IBD. Features that often differentiate IBD in children from adults include more extensive and severe disease at presentation, frequent corticosteroid dependency, change in location and behavior over time, and the implications of disease for growth and sexual maturation. In the Montreal classification where all patients < 17 years were grouped together, the Paris classification recognizes the different expression of pediatric IBD between those patients age < 10 years and those 10 to 17 years of age. The recent identification of monogenic disorders in very young children (< 2 years) with severe IBD-like disease has further clouded the issue of where appropriate pediatric age guidelines should be drawn though it is clear these infantile onset cases should not be grouped with older children. In contrast to the Montreal classification the Paris classification recognizes the importance of upper tract disease on natural history and divides it into L4a and L4b, proximal to and distal to the Ligament of Treitz, respectively. Complicated disease behavior in the Montreal system mandated a single category preventing the concomitant designation as stricturing and penetrating whereas the Paris classification recognizes that both stricturing and penetrating behavior may occur at the same or different times. Growth delay is recognized in the Paris classification as a serious manifestation of IBD in children affecting therapeutic decisions. Any IBD classification system will likely change over time with improved understanding of the basic molecular mechanisms involved in disease pathogenesis. A single classification system that reflects both pediatric and adult disease is needed.
Session II

Can we change the natural history of Crohn’s disease?
Can we change the natural history of Crohn’s disease with early immunomodulation?

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In both children and adults, the natural history of Crohn’s disease is characterized by relapsing and remitting bouts of intestinal inflammation, often associated with a progressive shift from inflammatory (B1) to complicated stricturing (B2) or penetrating (B3) disease behavior. The past two decades have seen a dramatic shift in therapeutic approach with the increasingly common use of early thiopurine immunomodulation. These maintenance medications were initially introduced primarily as corticosteroid sparing agents capable of minimizing recurrent flares of inflammatory disease, and have proven to be quite efficacious. Increasing evidence suggests, however, that thiopurines may only delay rather than prevent the development of complicated disease behavior. Data from both adult and pediatric Crohn’s disease populations from around the world will be reviewed in terms of the effect of early immunomodulation on progression to complicated disease behavior, need for surgery, and prevention of recurrent disease post-resection. Whether early immunomodulation may be more beneficial to subgroups of patients based on particular genetic factors underlying the inflammatory disease state or drug metabolism will also be considered.
Are we changing the natural history of Crohn’s disease with biologics?

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Crohn’s disease (CD) is a progressive condition, with most patients developing a penetrating or stricturing phenotype over time. The introduction of anti-tumour necrosis factor (anti-TNF) therapies over the past 10–15 years, along with accumulating evidence from landmark trials and clinical practice, has led to a significant change in patient management, monitoring and treatment algorithms. The anti-TNFs were demonstrated to be effective for the treatment of both luminal and fistulising disease. Scheduled therapy with both infliximab and later adalimumab was shown to be associated with an increased likelihood of clinical remission, mucosal healing in a proportion of patients, reduced need for hospitalisations and lower corticosteroid requirements, especially in patients with pediatric onset, shorter disease duration and in combination with immunosuppressives. Long-term clinical benefit was also demonstrated for both agents. The treatment goals are also evolving, clinicians apply early aggressive therapy in a selected group of patients with bad prognostic factors. In addition, since mucosal healing was demonstrated to be associated with better long term clinical outcomes, it has been questioned if there is need for treating beyond symptomatic remission to achieve not only symptomatic relief but also sustained steroid-free remission. Exploratory clinical trials are underway, to prove if optimization of therapies to achieve mucosal healing is leading to superior disease outcomes. In contrast, higher rates of infections and possibly lymphomas are associated with earlier and combined immunosuppression, and it is questionable if patients are willing to accept these risks. In addition, evidence from long-term population-based studies suggests that there is already a change in the natural history of the disease as early administration of immunosuppressives was associated with decreasing surgical rates in the last decades. A restructuring of the costs is also evident, in a short term study from The Netherlands anti-TNFs already accounted for as high as 2/3rd of the direct costs in CD and 1/3rd in UC.

In conclusion, there are promising data on the short and medium term clinical efficacy of anti-TNFs in CD from clinical trials and everyday practice also suggesting a significant capability to induce mucosal healing and affect surgery rates and need for hospitalizations. However, more long-term clinical data are needed to assess whether the early aggressive therapeutic strategy in pediatric patients and young adults with anti-TNFs or combination therapy and tight monitoring can further improve long term disease outcomes.
Have we changed the natural history of pediatric Crohn’s with biologics?

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Considerable debate exists as to whether the risk of complications and need for surgery has truly decreased in Crohn’s disease over time. A recent systematic review and meta-analysis reported by the University of Calgary group recently reported that after the year 2000 (since the approval of biologics targeting TNFα), the surgical rates at 1, 5 and 10 years have significantly decreased. There are many hypotheses as to why these rates have decreased. It is unclear whether this decrease can be solely attributable to the introduction of biologics, the more effective use of thiopurine dosing with monitoring or perhaps earlier disease recognition and early use of effective interventions. Emerging discussions emphasizing the need for more data surrounding the role of mucosal healing and proof that tight control over patients with dose optimization alters the natural history. In the short term, surgical and hospitalization rates do appear to be reduced one year after the introduction of biologics based on clinical trial data as compared to placebo. Uncontrolled observational studies confirmed that scheduled maintenance of anti-TNF as compared to episodic or discontinued use of anti-TNF resulted in less surgeries. Recent population based studies have shown similar improved disease outcomes with early immunomodulator use. The limitations of meta-analyses as well as the lack of controlled prospective longitudinal data render this question ripe for debate. There is a dearth of pediatric specific natural history studies for both short and long term. Multiple pediatric observational cohort studies have reported that up to one-third of pediatric onset CD patient’s progress to surgery within 5 years. This is slightly higher that adult patients followed in the same time frame. This discrepancy may be explained by less early biologic use in pediatric patients. In a prospective pediatric cohort of over 1000 newly diagnosed CD patients, less than 20% of pediatric patients received anti-TNF within 90 days of presentation. Using System Dynamic Analysis, we have shown that in children predicted to be at high risk of progressing to complication quickly, anti-TNF therapy initiated in the first 90 days after diagnosis had the largest reduction in complication risk. Interestingly children with higher risk factors for disease complications who received early prednisone actually progressed faster to the complication. More data is needed to follow all CD patients for longer follow up periods and an emphasis on pediatric onset to better gauge whether our proposed treatment strategies are actually altering the natural history of disease and what role biologics play in this regard.
Are we under-treating or mistreating patients at the time of presentation?

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Treatment goals in Crohn’s disease are evolving beyond the control of symptoms towards deep remission, which encompasses clinical remission and mucosal healing. The ultimate goals are to prevent bowel damage, reduce long-term disability and maintain normal quality of life. Until recently, goals of Crohn’s disease management focused on induction and maintenance of a symptomatic response and little attention was paid to the delay or even prevention of disease progression. A very different approach is taken with other chronic diseases such as hypertension, diabetes and rheumatoid arthritis. This more comprehensive approach is often referred to as “treat-to-target.” The treat-to-target strategy defines a new treatment objective that aims to achieve and sustain both clinical remission and control of inflammation.

With our new understanding of the etiopathophysiology of inflammatory bowel disease, are we mistreating our patients? The most convincing concept at this time is that of a defective mucosal barrier due to inappropriate recognition of the luminal flora or a defective defense against those bacteria. These recent theories indicate that the paradigm of immune suppression may not be the optimal concept. Therefore, a variety of approaches to improve the barrier function or to modulate luminal components have to be considered. We still have much to learn about these concepts in order to achieve the treatment goals of avoiding structural damage and complications.
Session III

Newer concepts
Crohn's disease: Loss of tolerance or a disorder of autophagy?

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Inflammatory bowel disease (IBD) with its two major entities, Crohn’s disease (CD) and ulcerative colitis (UC) is marked by a dysregulated immune response to intestinal microbiota coupled with an intestinal epithelial barrier defect. These events are most likely genetically driven and recent studies identified almost 150 IBD susceptibility genes.

Polymorphisms within genes being part of innate immunity, such as NOD2 or ATG16L1 as well as adaptive immunity, such as within the IL-23-Th17 pathway, are mainly associated with CD suggesting a stronger involvement of the host innate immune system and intestinal microbiota in the pathogenesis of CD than of UC. Though the intestinal immune system is crucial for sensing of and host defense against invading pathogens, it must maintain tolerance to commensal intestinal microbiota. Since dysregulation of this balance results in intestinal inflammation, maintenance of intestinal tolerance includes unique mechanisms. For example, activation of pattern recognition receptors (PRR) on intestinal macrophages and dendritic cells (DC) does not result in secretion of pro-inflammatory cytokines and DC present antigens to T-cells in intestinal lymph organs leading to the generation of regulatory T-cells.

A key role for the innate as well as the activation of the adaptive immune system plays NOD2. It is involved in microbial recognition, induction of autophagy and antigen presentation. The CD-associated variants of either NOD2 or the autophagy gene, ATG16L1, are associated with defective autophagy, antigen presentation and bacterial handling. All of those events result in prolonged survival of invading pathogens, impaired immune defence mechanisms against invading pathogens and uncontrolled inflammatory responses.

Taken together, it is obvious that a loss of tolerance as well as dysfunctional autophagy play key roles for bacterial handling and the control of inflammatory responses to invading pathogens. Genetically caused dysfunction of such genes, as observed in CD, clearly promotes the onset of chronic intestinal inflammation.
Is rifaximin effective in maintaining remission in Crohn’s disease?

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Introduction: Recent studies indicate that the persistent intestinal inflammation in patients with Crohn’s disease (CD) might be caused by abnormal intestinal microbiota. This hypothesis could suggest the use of antibiotics in therapy. So far guidelines do not recommend antibiotics except for the treatment of complications in CD and few studies have been made on the effects of rifaximin in such patients.

Methods: Between December 2011 and December 2012 we performed a double-blind randomized trial on 168 patients with moderately active CD concerning the efficacy of rifaximin. All the patients previously achieved remission with standard therapy (prednisone/budesonide). Data from patients receiving 800 mg of rifaximin (83 patients) twice a day for 12 weeks were compared with those from patients who received placebo (83 patients). The primary end-point was maintaining remission during the follow-up.

Results: 100% (83 of 83) from the patients who received 800 mg of rifaximin were in remission after 12 weeks of treatment in comparison with 84% (70 of 83) from the placebo group. This significant difference was persistent also at 24th week follow-up (78% [65 of 83] vs. 41% [34 of 83]). The last evaluation performed at 48 weeks revealed disease activity in 45% (38 of 83) of the patients from the rifaximin group, less than in the placebo group (75% [63 of 83]).

Discussion/Conclusion: Remission previously obtained with standard treatment can be sustained in patients with moderately active CD after the administration of 800 mg of rifaximin.
Session IV

Strategy for difficult Crohn’s disease
Loss of response to biologics: What is the next step?

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The robust effect of anti-TNF agents in many patients with inflammatory bowel disease (IBD) also raises disheartening difficulty when facing patients who fail to respond or who lose response to these otherwise very effective drugs. The dilemmas are further enhanced by the non-negligible costs incurred by these biologics. The first step in tackling this challenging situation is to measure inflammatory indices such as CRP or calprotectin to verify IBD inflammation is responsible for symptoms. Ideally, this should be accompanied by drug/anti-drug antibodies (ADA) levels. If CRP is normal and drug level is adequate, expectant management with symptomatic treatment (e.g. anti-spasmotics) may be appropriate for patients with mild symptoms as these may spontaneously abate in many of them. If symptoms are more severe or persistent, but drug levels are adequate and CRP was normal, in-depth assessment of IBD by endoscopy and/or imaging along with infectious work-up is mandatory to verify the etiology of symptoms and treat accordingly. Conversely, if the testing revealed elevated inflammatory indices in blood, treatment is then best tailored by drug/ADA measurements. Practically in these cases, no/low drug coupled with high-titer ADA should prompt a switch to another anti-TNF, or if all anti-TNFs have been exhausted, the addition of an immunomodulator. If no/low drug is coupled with no/low ADA then patient adherence should be verified and re-enforced as skipped or missed injections and infusions are not uncommon. If compliance is verified, dose-intensification is the next course of action.

Thus, in most patients with loss of response, a step-wise approach starting with blood tests of inflammatory and drug level indices and culminating – when necessary – in thorough assessment of IBD activity, can result in rationally-tailored and often successful management decisions.
Exclusive enteral nutrition in Crohn’s disease; Clues to pathogenesis

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Crohn’s disease is a complex inherited disorder of unknown pathogenesis with environmental, genetic, and microbial factors involved in the development of the disease. The microbiome of patients with CD is now known to differ from that of healthy subject (manifested as reduction in diversity, a reduction in *Ffirmicutes*, with increased *Enterobacteriaceae*). Disease specific inflammatory bacteria isolated from ileal tissue from patients with CD, such as adherent-invasive *Escherichia coli* (AIEC), are shown to replicate in macrophages and epithelial cells under certain circumstances and are abundant in patient with CD.

Multiple studies to date have shown an effect of diet on pathogenesis or management. Epidemiologic studies have shown an association between Crohn’s and consumption of a diet rich in animal protein and sugars. Animal studies have demonstrated that consumption of a western diet chow rich in fat and carbohydrates is associated with dysbiosis, increased intestinal permeability and colitis. Emulsifiers allow translocation of bacteria such as adherent Invasive *E. coli* across ileal follicular epithelium, as well as adherence and spread of bacteria into the villous space. However, the most remarkable feature of this disease, especially, but not limited to childhood, is the effective response to exclusive enteral nutrition therapy, and the observed benefit from exclusion of normal diet (principle of exclusivity). About 70% of children fed an exclusive polymeric formula for 6 weeks will enter clinical remission with a decrease in inflammatory markers. This response is associated with mucosal healing. This striking response to dietary intervention poses many questions, primarily regarding the mechanism of response, and the role of diet in pathogenesis of the disease. We have proposed a hypothetical model for the pathogenesis of Crohn’s disease (termed as the ‘bacterial penetration cycle’) that integrates dietary components, bacteria, susceptibility genes, and the innate immune response in the pathogenesis of Crohn’s disease. Identifying mechanisms whereby dietary components in isolation or together, allow the development of Crohn’s disease, would open up new therapeutic targets, the possibility of more widespread dietary interventions as a therapeutic modality, identification of diets that are more user friendly, as well as possibilities in disease prevention.
Rehabilitation after resection

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In general the patient receiving surgery for Crohn's disease makes an uncomplicated recovery with a speed consistent with the degree of surgical “insult” – which in these days of laparoscopic approach and minimalist resection often means very rapidly indeed. However, the patient who has had repeated surgery and in those where there was profound intra-abdominal sepsis this may not be the case. A prolonged period of ileus is to be expected and patients may well require parenteral nutrition to support them through this time. A curious and incompletely understood form of functional short bowel syndrome is also seen in these and other patients after Crohn's resection. Despite apparently limited resection and known adequate residual bowel length, with more than 1.5 metres of healthy small intestine remaining in continuity, some patients develop a high output state with many litres of diarrhoea or stomal effluent each day. Fortunately, in most cases this resolves spontaneously, but the process may take months: again these individuals may need parenteral nutrition support (including home parenteral nutrition in some). Nutritional support is needed in a broader range of postoperative patients however, and it is increasingly recognised that simply providing supplements and encouraging eating will not be enough to restore lean body mass and function unless it is combined with an exercise programme. Analogy with sports training helps both physicians and patients understand this better. The patient who has undergone Crohn's surgery has often been ill for some time beforehand, and the psychological aspects of chronic disease and the changes brought about by surgery – especially the creation of a stoma – may themselves become the most prominent features of the rehabilitative phase. A multidisciplinary approach is clearly justified and should be made available to all post-operative patients as needed.
Session V

Are we doing something wrong?
Are maintenance strategies underused in Crohn’s disease?

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A key aim in the management of Crohn’s disease is to maintain disease remission, whether this has been achieved by medical or surgical treatment. The reasons for doing this are to maintain quality of life, to avoid steroid-dependence and to maintain mucosal healing with a view to preventing relapse, hospital admission and surgery, and improving disease natural history. Options for remission maintenance include smoking cessation, thiopurines, methotrexate, anti-TNFα drugs and surgery. Evidence suggests that in some places now, and in most places in the past, too few patients are/were appropriately treated when in remission, and that, in many instances, treatment regimens are/were insufficiently tailored to the individual’s phenotype, prognosis, and/or genotype.
Should we be treating the bugs instead of cytokines and T cells?

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It is now clear that intestinal microbes are involved in many aspect of the pathogenesis of inflammatory bowel diseases (IBD) and that understanding how microbes lead to disease could present novel opportunities for diagnosis and treatment. While traditionally, IBD are thought to develop as a result of environmental exposures in genetically susceptible hosts, leading to chronic immune activation, microbes are likely involved in all these aspects as they are critical mediators of environmental effects (through food, hygiene, and infection), since most IBD susceptibility genes are linked to microbial handling, and as microbes stimulate, shape, and control gut immunity.

Human and animal-based research further supports the central role of microbes in IBD pathogenesis at multiple levels. Diversion of fecal flow (with its microbial content) can lead to remission, and antibiotics, diet, probiotics, and potentially fecal transplantation are all possible treatments for IBD. Animal models of IBD only develop in the presence of microbes and co-housing mice genetically susceptible to gut inflammation with normal mice can lead, through transfer of microbes, to development of bowel injury in previous healthy mice.

Some of the most exciting advances in gut-related research over the last 5-years relate to our understanding of gut microbiota and how they contribute to health and disease. Key papers in this expanding field have used 16S rRNA sequencing and metagenomics to study the role of microbes in IBD and we are now at the cusp of expanding into clinically-relevant fields, such as diagnosis and therapeutics. However, many challenges still remain, including standardization of protocols, defining what a normal microbiome is, moving beyond composition to more functional characterization of microbiota, and understanding how these can be manipulated to prevent or treat disease. Further focus on early life events, such as changes in nutrition, exposure to antibiotics, and childhood illnesses, as well as establishing how the environment (especially food exposures, metabolic status, geographical location, and aging) and genes alter microbes will likely lead to breakthroughs and new and safe treatments for IBD. In the future, we may be able to predict risk of disease, define biological subtypes, establish tools for primary and secondary prevention, and even cure IBD using microbes or their products. Using a broad spectrum of therapeutic tool, spanning from fecal transplantation, probiotics, prebiotics, microbial products, to microbe-tailored diets may replace current IBD treatments.
Are we using and monitoring thiopurines and biologicals optimally?

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Thiopurines have been used in the management of inflammatory bowel disease for several decades and they remain an important class of drugs despite the evolution of the biological therapies. Our understanding of how best to use thiopurines has evolved over this time; earlier use in Crohn’s disease has improved outcomes although debate continues as to how early they should be started. In addition, measurement of thiopurine methyltransferase has enabled safer and more effective use of thiopurines. Monitoring thioguanine nucleotides and methylated metabolites has become more popular in view of the fact that it enhances our ability to identify poor adherence as well as identifying patients in whom efficacy, tolerance and safety can be improved by manipulating drug doses or metabolism based on metabolite results.

In tandem with advances in thiopurine use, the introduction of anti-TNF therapy has revolutionised how Crohn’s disease and ulcerative colitis are treated. Initial treatment with intermittent therapy was rapidly succeeded by maintenance treatment due improved outcomes. Likewise, our understanding of the risks and benefits of combination therapy with immunomodulators, of earlier use and of withdrawal of anti-TNF therapy continues to evolve. However, the field of drug level monitoring and anti-drug antibody testing is probably the most rapidly advancing area in anti-TNF use and is likely to impact greatly on how we use anti-TNF therapy over the next decade.
Session VI

Problems in ulcerative colitis that won’t go away
Relapsing and refractory ulcerative colitis in children

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Approximately half of children with ulcerative colitis (UC) have refractory, relapsing or steroid dependent disease. UC in children is more extensive than in adults, presents more often with severe attacks and carries a more aggressive disease course. Therefore, although a step-up approach is usually recommended in UC, aggressive therapy will often be indicated in children; steroid dependency should never be tolerated. It is vital to ensure that in every resistant case, the symptoms are truly related to the inflammatory disease activity and not to other conditions, such as poor adherence to treatment, infections, adverse reactions to drugs, irritable bowel syndrome, lactose intolerance, celiac and bacterial overgrowth. The clinician should be ready to escalate therapy in a timely manner but only after ensuring optimization of current treatments. Optimization may include, among others, appropriate dosage, utilization of assays that determine thiopurine, calcineurin inhibitors and anti-TNF levels, introduction of combination therapy when indicated (enemas and immunomodulators) and allowing enough time for treatment to become effective. Colectomy is always a valid option and should be discussed before major treatment escalations. Experimental therapies can be considered when all else fails and the family prefers to avoid colectomy. The management of refractory and relapsing disease is particularly challenging in children and this review summarizes the available evidence to guide treatment decision-making in this setup.
Managing intractable proctitis and the problematic pouch

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Proctitis accounts for a significant proportion of cases of ulcerative colitis, and some patients subsequently develop more extensive disease. However, most patients continue to have limited inflammation, although the changes in the distal colon and rectum can occasionally be severe, and symptoms of increased frequency, rectal bleeding, and urgency can be as disabling as they are for patients with more extensive colitis. Furthermore, although symptoms are typically well-controlled with standard medications, medically refractory proctitis poses particular problems. Patients generally are not systemically unwell, and there is no added fear of cancer. Therefore the prospect of colectomy for such limited disease is resisted by patients, physicians, and surgeons alike. Unusual therapies, often delivered locally by enema or suppository have been tested in small case series, without definitive outcomes. The pathogenesis of such limited, yet intractable inflammation remains unclear, and the differential diagnosis should be carefully reviewed to ensure that local disease, whether it is infectious, vascular, or a result of injury or degeneration, is not overlooked.

Ileo-anal pouch formation is the surgery of choice for the 20% or so of patients with ulcerative colitis who undergo colectomy. In the majority of cases this surgery results in an acceptable quality of life, and freedom from a stoma. However, in a sizeable minority of cases, pouch dysfunction can cause intractable problems. The causes of pouch dysfunction are varied and must all be considered carefully, particularly in refractory cases. Pouchitis is a common issue, and is usually transient and easily treated. However, refractory and chronic pouchitis can be challenging. Ischaemia, injury, infection, and Crohn’s disease can all cause refractory pouch dysfunction. In a minority of cases there appears to be no apparent organic pathology, and the presumptive diagnosis is that of a functional pouch disorder. Although it is much rarer, neoplastic change in the pouch must also be considered, and the risk managed appropriately.

The management of both intractable proctitis and of the problematic pouch is made more challenging by the wide differential diagnosis that must be considered and by the paucity of high quality clinical trials to support any one therapy. Key strategies to overcoming these limitations include methodical and systematic investigation and review, and a willingness to tailor therapy to the individual patient. Clinical trials of new treatments should be supported, and data from experience with small cohorts of patients should be meticulously collected, critically analysed, and widely disseminated.
Extraintestinal manifestations unrelated to disease activity

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Inflammatory bowel disease is associated with a number of extraintestinal manifestations. For those that are associated with gut disease activity, the connection with intestinal inflammation is obvious. However, there are a number of EIMs that appear to be largely unrelated to the activity of the underlying bowel disease. This may be for a number of reasons – the gut inflammation may be subclinical, the EIM may be triggered by an association with more general gut abnormalities, such as increased intestinal permeability, or the association may reflect a common genetic susceptibility between IBD and the extraintestinal inflammation. The most well known of these EIMs include ankylosing spondylitis, some forms of peripheral arthritis, nephrolithiasis and some skin conditions, but there are less clinically obvious EIMs including those that affect the lung, nervous system and heart. There may be little treatment required for the EIMs, but in some cases the EIM can be more of a problem than the gut disease, and it may require specific treatment. For those that are clearly inflammatory in nature this can include steroids, immunosuppressants and biologics. In this case it is important to choose the therapy with the underlying gut disease in mind, so that the drugs chosen can be effective for both the intestinal and extraintestinal symptoms. This lecture will review the range of EIMs unrelated to gut activity, discuss their aetiology and examine the clinical features and treatment options for the commonest of these EIMs.
Primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease caused by diffuse inflammation and fibrosis that can involve the entire biliary tree. The progressive pathological process obliterates intrahepatic and extrahepatic bile ducts, ultimately leading to biliary cirrhosis, portal hypertension and hepatic failure.

PSC is a male predominant, complex genetic disorder: environmental predisposing factors include non smoking. It is closely associated with inflammatory bowel disease (IBD), particularly ulcerative colitis which occurs in about two-thirds of PSC cases. Approximately 5–12% of patients with total ulcerative colitis will have coexisting PSC; 13% of PSC/IBD patients have Crohn’s colitis. Recent studies have suggested that PSC/IBD is a separate disease entity from IBD alone with distinctive genetic and phenotypic characteristics.

Most PSC/IBD patients are asymptomatic at presentation. Clinical symptoms include fatigue, intermittent jaundice, weight loss, right upper quadrant abdominal pain and pruritus. The clinical course of PSC is variable. Serum biochemical tests usually indicate cholestasis; the diagnosis is established by cholangiography. Liver histology is not required unless small duct PSC or overlap with autoimmune hepatitis is suspected.

In symptomatic patients, median survival from presentation to death or liver transplantation is about 12 years. The overall median survival of PSC patients is 22 years. PSC is a premalignant condition, and the majority of patients die from hepatobiliary malignancy particularly cholangiocarcinoma or colonic cancer. UC/PSC patients are at higher risk of colonic dysplasia than UC patients without PSC, requiring yearly colonoscopic surveillance. A minority of patients die in hepatic failure following deepening cholestatic jaundice. The remainder die from complications of colitis.

PSC has no curative treatment. Medical treatment with the bile acid ursodeoxycholic acid (UDCA) may slow progression of the disease. Liver transplantation is the only option in young patients with PSC and advanced liver disease; 5-year survival is 80–90% in most centres. The disease will recur in the donor liver in 30% of patients after 5 years. Paradoxically, the symptoms of colitis may worsen in half of patients after liver transplantation.

Keywords: cholangiocarcinoma; cholestasis; primary sclerosing cholangitis
Session VII

Management of challenging cases
Inflammatory bowel disease and pregnancy

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Patients with quiescent IBD are as fertile as the general population. Patients with IBD have fewer children than the general population, but this may partly be because of voluntary childlessness. It is suggested that active Crohn’s disease (CD) reduces fertility by several mechanisms, including inflammation involving the fallopian tubes and ovaries and perianal disease causing dyspareunia. Several studies have demonstrated that most pregnancies in women with IBD will be uncomplicated, if the patient is in remission or has only minor disease activity at the time of conception. A meta-analysis by Miller with more than 1300 female patients with UC and over 700 patients with CD clearly demonstrated that normal pregnancies are observed in 83% of women with CD (71–93% in individual studies) and in 85% of women with UC (76–97% in individual studies). Malformations were observed in about 1% of all pregnancies and also the frequency of spontaneous abortions and still births were in the same range as observed in the healthy normal population. In contrast, several studies demonstrate that the frequency of normal pregnancies is reduced and the frequency of adverse outcomes of pregnancy is increased, when pregnancies take place in phases with active inflammatory bowel disease. Moreover, compared to pregnant IBD patients with inactive disease, women with a relapse during pregnancy have infants with significantly shorter gestation time and lower birth weight. Therefore, the flares of active disease in pregnant patients have to be treated aggressively, and it is best if conception occurs during remission.

The decision to continue the medication that is maintaining these chronically ill patients in remission during the periconceptional period and pregnancy is difficult as the data for some drugs used in IBD in this setting are limited and evidence-based counselling is hardly possible. It should be underlined that a quiescent disease is a key to the favourable pregnancy outcome and therefore a careful appreciation of the safety of the medication necessary to maintain the remission is crucial in the management of IBD patients with reproductive wish.

The challenges of treating IBD pregnant females will be illustrated by demonstrating clinical cases.
Inflammatory bowel disease unclassified (IBDU)

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Introduction: In 2005, the Montreal Classification of IBD proposed a new terminology IBDU which was defined as “clinical features in keeping with chronic features of IBD within the colon and without small bowel involvement, where the endoscopy is inconclusive and histology reveals chronic inflammation in the absence of diagnostic features of ulcerative colitis (UC) or Crohn’s disease (CD).” [1] Since then the term IBDU has been used (and abused) by the IBD community advice on when the term should and should not be used will be presented. The previous term “indeterminate colitis” was to be reserved only for colectomy specimens.

Methods: A group of interested IBD clinicians were convened from within the ESPGHAN “Porto” group. Review of evidence included both paediatric and adult data, given the paucity of specific studies in many areas. Electronic searches were performed in January 2013.

Results: The incidence of IBDU is variable dependent on definition used and population studied. IBDU is more common in paediatric IBD and comprises approximately 10% of all cases at diagnosis in children. The diagnosis of the condition remains difficult but the recent development of the updated “Porto” criteria have helped both by providing a definition for “atypical” forms of UC helping to remove a label of IBDU in some patients plus suggesting a working framework for developing clinical criteria (as yet unvalidated) for reaching a diagnosis of IBDU. Overtime a diagnosis of UC or CD may become clearer but the exact time line and frequency of these changes in diagnosis is difficult to identify from the current literature. Treatment of IBDU in general should mirror that of UC but with a lower threshold for disease reassessment should treatment need to be escalated. In patients who come to colectomy the published rate of pouch failure matches that of UC but it is the presenters practice to leave a longer period of time (at least 2 years) before reconnection and pouch formation in patients with IBDU.

Conclusions: IBDU is the least common phenotype of IBD and as such represents an area where a minority of good quality clinical studies has been performed. A clear definition for diagnosis will help future studies describe the natural history and treatment outcomes for the condition.

Reference List:

Treatment resistant forms of IBD in young infants

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Inflammatory bowel disorders can affect children at any age, although it occurs most frequently prior or during puberty. Early onset (EO-)IBD before the age of five years and particularly in very young children, under two years of age, is often characterized by an extremely severe evolution and poor response to classical immunomodulator or biological therapy. The clinical presentation in this subgroup of patients with EO-IBD is predominantly in form of severe colitis and less frequently small bowel involvement. On histological examination, epitheloid granuloma can be found in about one third of patients, therefore, these patients are often labeled as early onset Crohn’s disease, however, disease course is atypical and patients do not come into complete remission on therapy. Recent molecular analyses allowed gaining insight into the pathophysiology of EO-IBD forms. In patients with additional perianal inflammation and fistula, a deficient IL10 axis due to mutations in the IL10R1, R2 or IL10 genes were identified in about 2/3 of very EO-IBD patients. Another form of VEO-IBD is seen in boys with mutations in XIAP gene, causing enhanced apoptosis on functional tests. Defects of the respiratory burst and NADPH complex were recently suggested as new variants of VEO-IBD. A systematic and molecular work-up for patients with EO-IBD and non-response to classical IBD-treatment is necessary allowing identifying the monogenetic origin of many of these IBD-like diseases. If the genetic defect affects primarily the function of hematopoietic cells, a new treatment option could be in form of hematopoietic stem cell transplantation, as recently successfully performed for patients with defects in the IL10 axis or mutations in XIAP.
Perianal disease in IBD

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The initial report of Crohn’s disease in 1932 did not mention perianal disease but the link was soon established and fistulae alone can be a disabling part of the disease in 25–80% of patients and may occur as a presenting feature in some patients. This is also true but to a lesser extent in ulcerative colitis. Perianal disease is more often associated with a more aggressive phenotype of disease in Crohn’s, with patients more likely to be steroid resistant and more likely to have extraintestinal manifestations.

Perianal disease in IBD encompasses a wide group of signs and symptoms, ranging from mild to severe and sometimes potentially life threatening. With the advent of more aggressive medical therapies a combined surgical/medical approach should be employed; with accurate diagnosis using a combination of MRI, endoanal ultrasound and an examination under anaesthesia by a specialist prior to planning treatment.

Skin tags, haemorrhoids and fissures are common in IBD but should rarely be treated with surgery. They are often asymptomatic and usually benign. Surgical treatment for skin tags and haemorrhoids may result in significant complications; unhealed wounds, sepsis and stenosis occur relatively frequently, therefore treatment should be conservative if possible. Haemorrhoid surgery in UC is associated with less complications but should be undertaken with care.

Although fissures in IBD are generally described as painless they are often uncomfortable and may be associated with discharge, pruritus and bleeding. They occur in up to 59% of patients with Crohn’s and may present in multiple and unusual locations (not just posteriorly). Once again conservative treatment is advocated although unhealed fissures may progress to a fistula or abscess in 26%.

Perianal fistulae occur in 10–26% of patients with Crohn’s disease. The risk increases with more distal disease. Fistulae may be simple or complex and should be fully evaluated and sepsis drained before a treatment plan is made. 82% will require surgery with approximately 20% eventually needing a proctectomy (but up to 50% presenting with complex fistulae vs. 6% if simple). Images and treatment of these complex cases will be discussed.

A subset of perianal fistulae is recto-vaginal fistulae. The majority are low and transsphincteric. Active rectal disease denotes a poor prognosis. Recurrence rates are reported as high as 72% but anti-TNF therapies has reduced the need for surgical interventions.

Natural history of perianal disease in IBD is influenced by disease location, fistula type and location, age at onset and presence of associated abscesses and strictures. Good imaging and a combined medical, surgical approach may reduce the long term morbidity of treatment.
Session VIII

IBD Research 2013: What is new?
Morphologic individualised medicine: A break through approach for early determination of anti-TNFα responders and non-responders among patients with ulcerative colitis in a prospective study

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Introduction: The immunopathologic processes of ulcerative colitis (UC) and Crohn’s disease (CD) have not been fully elucidated. Anti-TNFα antibodies have proven efficacy yet about 30–40% of patients are non-responders. Up to date there are no reliable predictors for therapeutic success in this regard. As it has been shown so far, “-omics” alone cannot help. Physiological intermolecular modification spectroscopy (PIMS), a cutting edge technology is able to reconcile these data with the clinic. PIMS is a label free technology through which dynamic molecular resonance of entire proteins and macromolecules of an individual is recorded, on real time, as the temperature within the sample rises from -37 to 37°C. It discriminates the responders from non-responders to a given treatment.

Methods: Protein extracts of peripheral blood mononuclear (PBMC) of 47 outpatients (female = 16, mean age = 40.8 ± 16.4 years & men = 31, mean age = 41.5 ± 18.6) diagnosed with UC or CD (UC = 20, CD = 27) and treated with anti-TNFα therapy, were subjected to PIMS analysis. Patient’s data were blinded. 1 µg of total protein from each patient’s PBMC was challenged with 10 ng of infliximab. After determination of base line the samples were frozen at -37°C. Dynamic changes in macromolecular interaction were registered while the temperature rose from -37 to 37°C. Individual macromolecular volume (IMV) and molecular elasticity (ME) were determined for each patient. A change in ratio of ME from -10 to -5°C less or equal to zero was considered as non-responder.

Results: After deblind, 65% (n = 13) UC and 59% (n = 16) CD patients were responders to infliximab. These correlated with PIMS predictions (correlation 0.95) which had stratified patients to responder and non-responders groups.

Discussion/Conclusion: PIMS in a blinded transversal study were able to stratify patients into two distinct groups of responders and non-responders to infliximab. It seems to be a powerful method for adapted IBD treatment and morphogenetic individualised medicine.
Herbert Falk Prize Lecture

Inflammatory bowel disease today: Are we taking the right steps to understand and cure it?

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Since the identification of what we currently believe to be the major components of inflammatory bowel disease (IBD) pathogenesis, i.e., the environment (exposome), the genetic make up (genome), the gut microbes (microbiome) and the immune system (immunome), there has been a sense of tangible progress in the understanding of what IBD is all about, and a positive feeling that a cure can be actually achieved. While these hopes are justified, they have been tempered by the realization that both forms of IBD, Crohn's disease and ulcerative colitis, are far more complex that previously anticipated. In fact, as advances of primarily technical nature have given and are still giving us an indispensable hand in making progress, the information that they are generating continuously adds novel and often unexpected clues that do not immediately fit in previously accepted paradigms of disease pathogenesis. Moreover, the amount of data that is so rapidly accumulating far exceeds the capacity of the IBD research community to absorb it, process it and taking advantage of it in a timely and efficient manner. As a result, this overwhelming accrual of new information is converted into better understanding at a slow pace, and at even slower pace when it comes to translating it into novel and untested forms of therapy. In addition, when this new information is obtained and validated (or not) the implementation of sound clinical trial slows down progress even further. Resources, of both human and practical nature, to expand investigation in IBD are and will continue to be scarce and below the level necessary to substantially speed up progress. Therefore, a solution to our current limitations is perhaps to “get smarter” or, as it is repeatedly stated, “think outside of the box”. Unfortunately, this is easier said than done, as most investigators, in IBD or any other field of biomedicine, tend to be focused on a particular field of research, no matter how important or advanced, and it is extremely difficult to branch off in totally new directions or even start meaningful collaborations to complement each other efforts. Let’s consider some examples below.

The emergence of IBD is unequivocally linked to complex evolutionary changes of the exposome. The exposome is infitinitively complex and not entirely identifiable as humans continuously modify it, and we will have to restrict ourselves to study only a few, but hopefully carefully selected components. Of these, the diet and the intestinal microbiota offer the most promising possibilities for evaluation and eventually therapeutical intervention. At the same time, given increasing evidence that the diet strongly influences the composition of the microbiota, and subjects with different genomes have different (if not individualized) gut microbial ecosystems, diet and microbiota should be assessed in light of each other, as well as in the context of individual genomes.
Genetic heterogeneity in IBD appears to be overwhelming, at least at the moment. After the discovery of the association of \textit{NOD2} with ileal Crohn’s disease over 10 years ago no less than 162 additional associations have been discovered, but we have yet to figure out how variants of the \textit{NOD2} gene mediate disease. How long will it take to work out the 162 (or more) associations that explain only 20–25\% of all IBD cases? Novel approaches, like to study of gene-gene and gene-environment interactions, become mandatory to learn how each genetic variation, alone or in combination, contributes to IBD pathogenesis.

The immune/inflammatory process that mediates IBD involves more components than previously anticipated, and it is likely that the relative importance of each component varies depending on the stage of the disease. For instance, traditional antigen-mediated responses (both innate and adaptive response induced by pathogen-associated molecular patterns – PAMPs) are probably more relevant early in the disease process, while damage-associated molecular patterns (DAMPs) may come into play later on. Both immune and non-immune cells are clearly involved in IBD pathogenesis, and the study of particular cell types, like specific subsets of immune cells, makes less and less sense in the intricate network of immune responses mediated by multiple cells and a myriad of molecules.

Taking the above into account, IBD can no longer be seen as a condition with a fixed set of pathogenic events and clinical manifestations. On the contrary, IBD is a dynamic condition with a time-dependent evolution of disease mechanisms and clinical expression. The in depth study of each mechanism at the exclusion of all others will never deliver a comprehensive picture of IBD etiopathogenesis. Therefore, the only hope is to implement methods that allow to generate what can be called an “IBD integrome” view of the disease. To generate this integrome we need to concomitantly study (without necessarily fully comprehend) all IBD-implicated “omes” and create interactomes to understand reciprocal influences that underlie disease cause and mechanisms. This is the hope that \textit{systems biology} can offer and, unless we accept the inadequacy of our current approaches and are willing to invest in brand new systems, the goal of understanding and curing IBD will remain out of reach.
Session IX

Recognizing complications
Infective colitis exacerbating or mimicking IBD

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The histopathologist plays a central role in both the initial diagnosis and subsequent clinical management of colitis. In the correct clinicopathological context, the pathological diagnosis of inflammatory bowel disease is based primarily on the demonstration of a colitis with histological features suggestive of chronicity (> 6 weeks duration). The colonic crypt architecture is perhaps one of the most useful features in this situation, the presence of crypt architectural distortion suggesting colitis of at least six weeks duration. Most infective colitides are self-limiting and of relatively short duration but a number of infective agents can produce a chronic colitis with histological features that overlap with those of inflammatory bowel disease. These include amoebiasis, salmonellosis/shigellosis and some sexually transmitted diseases.

It should also be borne in mind that patients with IBD have a similar, if not increased, risk of acquiring an infective colitis as the general population. The fact that many IBD patients are taking immunosuppressive drugs almost certainly increases their risk of contracting a superimposed infection. This is particularly the case with CMV infection which is well documented to complicate and exacerbate ulcerative colitis. Other pathogens which have also been associated with exacerbating IBD include salmonella and clostridium difficile. In acute exacerbations of longstanding IBD which appear refractory to increasing immunosuppressive therapy careful examination of biopsies for viral inclusions and/or evidence of pseudomembranous colitis should be considered.
Unusual manifestations of IBD in the elderly

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Inflammatory bowel diseases (IBD) have a bimodal peak of incidence. Approximately 15% of IBD manifest after the age of 65 years and account for broadly 25% of all IBD-related hospitalizations. Older patients with IBD have a greater comorbidity than younger patients. The most common comorbidities in the elderly population include diabetes, cardiac complications, chronic pulmonary diseases and cerebrovascular disease, with polypharmacy and drug interaction. Malnutrition, sarcopenia and osteoporosis are also frequently associated with IBD in the elderly and need specific care. Depression occurs in about 25% elderly IBD patients and is associated with reduced medication adherence. In Crohn’s disease colonic location and stenosis disease are more frequent than in younger patients. A change in disease behaviour is uncommon in the elderly. In ulcerative colitis, extensive disease is less frequent than in younger patients. The risk of colorectal cancer or high-grade dysplasia is higher in elderly than in younger patients. There are no specific therapeutic guidelines for elderly IBD patients. However, increased age is associated with a higher risk for postoperative complications and an increase in immunosuppressive therapy and corticosteroids-related adverse events. In the Cesame study, the yearly incidence rate (per 1000 patient-years) of lymphoma in patients on thiopurine was 0.37 in patients < 50 years; 2.58 in patients 50–65 years, and 5.41 in patients > 65 years [1]. Several publications suggest that anti-TNF agents may increase the risk for severe infection and mortality in elderly people. In a recent paper, severe infections were reported in 11% of patients > 65 years treated with biologics, 0.5% of elderly people receiving other drugs, and 2.6% of individuals <65 years treated with anti-TNF agents. The corresponding figures were 10%, 2%, and 1% for overall mortality (2). Similar results have been observed in rheumatoid arthritis. Taken together these results suggest that anti-TNF-agents should be prescribed with caution in this patient population and that the risk/benefit ratio should be carefully measured. With the aging of the population the burden of IBD will increase in this patient population and specific therapeutic guidelines for elderly IBD patients are urgently needed.

References:


Cancer risk and avoiding colectomy

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There is an increased risk of colorectal cancer in both ulcerative colitis and Crohn’s colitis. In a large Swedish population-based study, Ekbom found a standardised incidence ratio (SIR) of 5.7 (95% CI 4.6–7.0) [1]. However, the magnitude of risk in recent population-based studies appears smaller than in earlier studies: The more recent Swedish population-based study found a SIR of 2.3 (95% CI 2.0–2.6) [2]. A recent meta-analysis of population-based cohort studies determined that UC increases the risk of CRC 2.4-fold [3]. Sadly, when cancers do occur, they tend to develop at a younger age – approximately 10 years earlier than in sporadic colorectal cancer.

Established risk factors for cancer in inflammatory bowel disease include disease extent [1], disease duration [4], severity of inflammation [7], family history of colorectal cancer [5] and co-existence of primary sclerosing cholangitis [6]. Whether early age of onset of colitis is an independent risk factor for cancer is controversial: some studies suggest it is [1], others do not [8].

Regarding managing this cancer risk, our primary aim must be to preserve life, with secondary aims of maximising quality of life and preventing unnecessary surgery. Studies have raised the possibility of chemoprevention in colitis-associated cancer, particularly with 5-ASA drugs, which may have direct anti-neoplastic effects beyond their anti-inflammatory properties [9]. Establishing patients on appropriate drugs is important not just for disease control, but for cancer prevention as well.

Most dysplasia is visible at surveillance colonoscopy [10], even with standard resolution endoscopes. Raised dysplastic lesions on a background of colitis (formerly referred to as DALMs) were previously considered an indication for colectomy. It is increasingly recognised that well-circumscribed visible lesions may be amenable to complete endoscopic resection regardless of their location within or outside areas of documented UC and irrespective of the presence of LGD or HGD. A recent meta-analysis confirms this [11]. If the lesion is not resectable, or is associated with dysplasia in the adjacent mucosa, then colectomy is indicated due to the high risk of concomitant CRC [10, 12].

My talk will review the current literature on colitic cancer risk and provide the audience with a practical guide on how to minimise the lifetime cancer risk whilst preventing unnecessary surgery.

References:


IBD-associated neoplasia in children and young adults

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Advances in our understanding of the pathophysiology of ulcerative colitis and Crohn’s disease have led to the widespread use of increasingly potent immunosuppressive therapies. This has greatly benefited the majority of patients with IBD and has resulted in improved overall clinical outcomes and quality of life. However, a growing body of data now indicates that long-term use of these agents may at the same time place patients at risk for a number of adverse effects including colorectal and skin cancer, as well as lymphoma. Children and adolescents may be at particular cumulative risk for the development of these malignancies as a result of their young age at diagnosis, often increased disease extent and severity, and greater lifetime exposure to immunosuppressive agents. More recent epidemiologic studies are now identifying specific genetic and treatment related factors that may place patients at increased risk for the development of IBD-related cancer. Improved understanding of these risk factors should contribute to a more rational approach to the pharmacologic management of children and young adults with IBD. Similarly, clinicians will be better able to counsel their patients about the risks and benefits associated with specific therapies and develop improved monitoring guidelines to reduce the incidence of these rare but often severe oncologic complications.
Session X

Off the wall!
Future methods for diagnosis of IBD

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The diagnosis of IBD remains a challenge for clinicians, and patients. Clinical suspicion of these disorders leads to a diagnostic pathway that may include stool testing, colonoscopy, radiological tests and capsule examinations. This work-up is unpleasant, embarrassing, painful and occasionally dangerous. Alternative means of diagnosing IBD are being explored. Genetic testing and serology have not been found to be sufficiently specific or sensitive to be used for diagnosis. Faecal markers however have demonstrated some potential. Faecal lactoferrin and calprotectin may be used to differential IBD from non inflammatory disorders and these tests are now commonly used, with support from NICE.

Recent research has focused upon volatile organic compounds emitted from bodily fluids, including faeces, urine and breath. Headspace gas from faeces or urine may be analysed by gas chromatography/mass spectrometry. Models have been built based on these compounds to enable Crohn’s disease and ulcerative colitis to be distinguished from IBS and from healthy controls. Similar work has found that headspace gases from urine may be used to diagnose IBS. Faeces is relatively easy to obtain but patients dislike collecting samples, so a urinary test is an attractive alternative. Early data from breath samples also shows potential and will be presented.

Non-invasive diagnosis of IBD is becoming a reality that will save patients from discomfort, embarrassment and risk, and may mean significant savings for healthcare providers.
Cannabis for inflammatory bowel disease

Dr. Timna Naftali
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The marijuana plant cannabis sativa is mainly known for its recreational properties. However, it has been used for centuries as a medicinal treatment for a variety of ailments. The cannabis plant contains over 60 different compounds which are collectively referred to as cannabinoids. Although D9-tetrahydrocannabinol (THC) and cannabidiol (CBD) seem to be the most active, other as yet unknown ingredients may also have beneficial effects. Although the medical use of cannabinoids is expanding, and although cannabis seems to have a wide therapeutic index, one must remember that cannabis use is not free of side effects, including panic or anxiety attacks, exacerbation of psychiatric disorders and a motivational syndrome. Studying the functional roles of the endocannabinoid system in immune modulation reveals that almost all major immune events involve the endocannabinoid system. Cannabinoids may, therefore, be beneficial in inflammatory conditions. In several mouse models of colitis cannabinoids decreased histologic and microscopic inflammation. In human subjects, cannabis has been used to treat anorexia, emesis, abdominal pain, gastroenteritis, diarrhea, intestinal inflammation and diabetic gastroparesis.

Despite many anecdotal reports on the use of medical cannabis in inflammatory bowel disease, there are very few controlled studies. An observational study in 30 patients with Crohn’s disease found that medical cannabis was associated with improvement of disease activity index and reduction in the use of other medications. In a prospective placebo controlled study in 21 Crohn’s disease patients, a decrease in CDAI score of >100 was observed in 10/11 subjects in the cannabis group and 4/10 in the placebo group. Complete remission (a CDAI score < 150) was achieved by 5/11 subjects in the cannabis group and 1/10 in the placebo group.

In summary, evidence is gathering that manipulation of the endocannabinoid system could have beneficiary effects in IBD, but further research is required before cannabinoids can be declared a medicine. We need to establish the appropriate medical conditions, dose and mode of administration for cannabinoids use.
The mucosal barrier consists of (i) the surface epithelial layer, whose integrity is determined to a large extent by tight junctions between adjacent cells; (ii) the glycocalyx – a “fuzzy” coat of heavily glycosylated glycoproteins on the luminal aspect of the surface epithelial cells; (iii) the secreted mucus – which forms a continuous layer in the colon but a discontinuous layer in the small intestine. Other secretions – particularly defensins and secretory immunoglobulin A in the small intestine, contribute to the defence against bacteria.

In health there is probably relatively little direct interaction between the luminal microbiota and the epithelium – the continuous mucus layer in the colon keeps the surface epithelial cells out of contact with bacteria and the ileo-caecal valve ensures that the distal small intestine is relatively microbe-free. Most interaction take place at the Peyer's patches in the distal ileum and their smaller colonic equivalents the lymphoid follicles. Peyer's patches are overlain by a “dome” epithelium 5% of whose cells are specialized M (microfold) epithelial cells which act as the major portal of entry for bacteria – either invading pathogens or commensals being “sampled” by the immune system. There are no goblet cells in the dome epithelium and also a very sparse glycocalyx allowing easy microbial interaction. It is intriguing that the peak ages of CD incidence are also peak ages for possession of Peyer’s patches which are arguably the site of the initial lesions in CD and that the “anti-pancreatic” antibody associated with CD has been shown to have as its epitope the GP2 glycoprotein that serves as the receptor for bacterial fimbrial protein (fimH) on M cells.

There are many reasons to believe that the mucosal barrier is critically important in IBD pathogenesis. These include (i) associations between both CD and UC with genes that are relevant to the mucosal barrier; (ii) increased intestinal permeability in unaffected relatives of CD patients; (iii) increased immune reactivity against bacterial antigens; (iv) animal models in which altered mucosal barrier – e.g. denudation of the mucus layer associated with oral dextran sulphate in rodents – induces colitis.

Whilst some IBD patients may have genetic factors leading to weakening of the mucosal barrier it is likely that environmental factors may be even more important. Some may be subtle and indirect e.g. the effects of stress on the mucosa barrier whilst others may be more obvious e.g. the effect of pathogen-related gastroenteritis, known often to act as trigger for IBD relapse. We have also been very interested in the potentially harmful effects of ingested detergents – either by contamination of cutlery by inadequate rinsing or via ingestion of processed foods containing emulsifiers. In vitro and ex vivo studies show that even very small trace amounts of these can greatly increase bacterial translocation.

Implications for therapy are not yet so obvious. We advise our IBD patient to avoid processed foods containing emulsifiers and to rinse their dishes well – whilst accepting that there is no direct evidence yet to support this. Therapies that aim to enhance the mucosal barrier have yet to come to market with the possible exception of sucralfate enemas but trials of enteric-delivered phosphatidyl choline in UC are
promising. The faecal concentration of mucus-degrading bacterial enzymes (particularly proteases, sulphotases and sialidases) correlates with disease activity and UC and these represent good targets for therapy.

Much of the above is reviewed in:

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POSTER ABSTRACTS

Poster Numbers 1 – 83
(* = Posters of Distinction)

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Efficacy and safety of adalimumab in moderate to severe paediatric Crohn’s disease: Single tertiary centre outcome

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**Introduction:** The role of adalimumab in the treatment of paediatric Crohn’s disease (CD) is increasingly recognised. The aim of our study was to evaluate the efficacy and safety of adalimumab in children with Crohn's disease who failed.

**Methods:** All patients with CD receiving adalimumab between September 2006 and January 2013 were identified retrospectively. All patients had either failed to respond to infliximab, lost response or had allergic reaction before commencing adalimumab. Clinical response and long term outcomes were assessed.

**Results:** Twenty-one patients (10 females) with median age 12.7 years (8.8–16.6 years) at the time of first adalimumab injection were included. Seventeen patients (17/21, 81%) showed sustained clinical response to adalimumab with symptomatic improvement and increased time between relapse (if at all) over a mean period of 2 years 6 months. Ten patients (10/12, 83%) responded to combined therapy of adalimumab and methotrexate, compared to four patients (4/4, 100%) responding to adalimumab and azathioprine. For the remaining four patients where treatment failed to work over a mean of 11 months, medical treatment was escalated with other immunosuppressive agents, but disease progression remained. Links were also found indicating that those with a higher atopic activity (IgE) and lower inflammatory status (ESR) tended to respond better to the drug. Lastly, there was no major difference in age between groups, with 12.4 years for the responders compared to a mean of 11.7 years for the non-responders. Methotrexate and azathioprine were the most successful adjuvants, when combined with adalimumab. No adverse reactions were recorded with the use of adalimumab during the study period.

**Discussion/Conclusion:** Adalimumab was efficacious in 81% of children and adolescents with moderate to severe CD unresponsive to infliximab and should therefore be considered as a treatment option. Adalimumab was additionally found to be safe as no adverse reactions recorded. Results linked to IgE and ESR warrant further studies.
Distribution of diagnostic criteria for collagenous colitis – Pooled analysis of 2 European clinical trials

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Introduction: The diagnosis of collagenous colitis (CC) relies on the histological evaluation of colonic biopsies. There is uncertainty about where and how many colonic biopsies should be obtained to make a reliable diagnosis.

Aims: To determine the topographical distribution of diagnostic histopathological criteria of CC.

Methods: We analyzed patients with active CC from 2 prospective multicenter trials (BUC60/COC, BUC63/COC) in whom biopsies from multiple colonic segments have been obtained during baseline colonoscopy. Collagen band thickness and chronic lamina propria inflammation were assessed for each colonic segment based on H&E and van Gieson staining.

Results: 187 patients were available for analysis including 79 patients with biopsies from all 5 segments. While chronic lymphoplasmocytic (LP) inflammation was evenly distributed throughout the colon, the mean collagenous band thickness in the rectum (15.8 µm) and sigmoid (18.9 µm) was significantly lower compared to descending (21 µm), p < 0.0001, p = 0.018) and ascending colon (20.9 µm, p < 0.0001, p = 0.043). Thus, the diagnostic criteria of a collagenous band > 10 µm was significantly more common in the ascending (89.9%) compared to the sigmoid (75.9%, p = 0.043) and the rectum (55.7%, p < 0.0001). Biopsies taken from the ascending, transverse and descending colon resulted in a diagnostic yield for a collagenous band >10 µm of 96.2%.

Conclusion: To establish the diagnosis CC it is advisable to perform a complete colonoscopy as the thickened collagenous layer is mainly found in the right colon. In this disease a chronic inflammation in the lamina propria seems to be present in the whole colon which should prompt the pathologist to look for the characteristic findings of CC.
Anaemia can add morbidity in inflammatory bowel disease

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Introduction: Tumor necrosis factor-α has a central role in the pathogenesis of mucosal inflammation and other complications in Crohn's disease. The pathogenesis of the anaemic syndrome in inflammatory bowel disease (IBD) are complex and the chronic inflammation by TNF-α and other cytokines induce increased levels of the iron-regulatory hormone hepcidin, which sequesters iron in macrophages, shunting iron away from erythropoiesis.

Material and Methods: We have evaluated a number of 54 patients with IBD during a period of 8 years, out of which 34 were diagnosed with ulcerative colitis (UC) and 20 with the Crohn’s disease (CD).

Results: Out of these ones, 17 of the patients with UC and 9 with CD presented anaemia (Hb under 13.5 g/dl in men and under 11.5 g/dl in women). The medium Hb value in the lot of patients with anaemia was of 8.3 ± 1.6 and Ht value was of 28 ± 3.5. In 11 of 18 anaemic patients ($\chi^2 = 3.51$, $p < 0.055$), the intestinal disease was active. In 5 of 7 patients with anaemia without active disease, the investigations and the epidemiologic study suggests an associated cause of the anaemia (iron deficiency). In one case, the red cell indices suggest macrocytosis and anaemia is remitted after treatment with folic acid and B$_{12}$ vitamin.

Discussion/Conclusion: The anaemia follows frequently IBD in 37.75% percentage. The increased prevalence of the anaemia in IBD may be justified in a way by the local socioeconomic conditions. The anemia is also correlated with the activity degree of the disease.
Age at diagnosis of the disease could be a prognostic factor in ulcerative colitis

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**Introduction:** In ulcerative colitis (UC) extension and severity of the disease, need for steroids, occurrence of steroid-free remission as well as major complications were studied in different age groups.

**Methods:** The data of 126 patients with UC who were admitted and followed in outpatient in Sohar Hospital in Oman during the period from June 2006 till February 2013 were studied and analyzed retrospectively. Patients were classified according to their age at diagnosis of the disease into group I (early onset; below 30 years; No. 72 patients) and group II (late onset; above 50 years; No. 54 patients). All patients were diagnosed to have UC; clinically, laboratory, colonoscopic examination and histopathological confirmation.

**Results:** We found that 58% of group I have mild colitis on diagnosis compared to 72% in group II (p < 0.016). On the other hand severe colitis was considered in 18% in group I compared to 11% in group II. Regarding extension of the disease, proctitis and limited disease was determined in 28% of group I compared to 43% of group II (p < 0.01). On the contrary, pancolitis was considered in 67% of group I compared to 46% of group II. Only 18% of group I had achieved steroid-free remission compared to 48% in group II. Finally, serious complications (toxic megacolon, laparotomy and colectomy) happened in 7 cases (10%) of group I compared to 2 patients (3.7%) of group II (p < 0.01).

**Discussion/Conclusion:** We can conclude that in ulcerative colitis late onset disease tends to be mild in severity, limited in extension and can achieve steroid-free remission more frequently compared to the disease when started in younger age.
Vitamin K deficiency occurred in patients with pouchitis

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Pouchitis is the most frequent complication, which not only influences negatively on quality of life of sick persons, but can also cause metabolic disorders. A vitamin K is a group of chemical compounds of the exogenous origin, at least they are also partially produced by bacteria in the large intestine. Aim of the study was evaluation of the PIVKA level as the indicator of a vitamin K deficiency at patients after restorative proctocolectomy.

They were carrying out research in the group of 49 persons after restorative proctocolectomy performed in 1985–2011 due to the UC or FAP.

Elevated PIVKA level proving about lowered level of the vitamin K was reported at 22 patients (44.9%). Statistically significant differences of the PIVKA level were present in groups with pouch inflammation and without such inflammation. More frequently increase of the PIVKA level above 2 ng/ml was observed at persons with the presence of inflammation assessed in the PDAI scale, Moskowitz scale and with the presence of chronic inflammation. The characteristic increase in the PIVKA level was also found at patients with increased CRP and with presence of parenteral symptoms. A vitamin K deficiency characteristically has more often been stated at persons with, both acute and chronic pouch inflammation. The primary diagnosis didn’t have statistically significant of influence on the elevated PIVKA level, at least in group of patients operated for UC this level was higher.
Safety and adverse events in IBD patients occurring during biologic therapy

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Introduction: Biologic agents (BA) have significantly improved the treatment options of inflammatory bowel diseases (IBD) in the last decade. The aim of this study is to point out the adverse events (AE) and safety profile when BA are administrated.

Methods: 18 IBD patients (pts) (5 with Crohn’s disease-CD, 13 with ulcerative colitis-UC), 8 females, 10 males, aged 17–58, who fulfilled the criteria for biologic therapy, underwent BA treatment: 13 pts on infliximab, 5 pts on adalimumab. All pts were screened for HBV, HCV, HIV viruses and tuberculosis, being negative. The prospective follow-up was two years.

Results: From the infliximab group, 2 UC pts and 1 CD pt experienced anaphylactic shock (AS), needing urgent rescue therapy. In the adalimumab group, 1 CD pt had pruritus and erythema at the injection site, 1 UC pt developed tuberculosis (tbc).

Discussion: AE during BA administration are usually hypersensitivity reactions, which can range from dizziness, headache, edema, erythema to anaphylactic shock. In our study, although the small number of pts, in the infliximab group, 3 pts (23%) developed immediate-type hypersensitivity reaction after the 3rd iv administration, despite proper administration of infliximab. The explanation is infliximab antibodies: transient and persistent, the latter having a twofold increased risk of acute AE during iv administration. An option for reducing AE would be infliximab desensitization. Treatment for AS: epinephrine, oxygen, iv corticotherapy. In the adalimumab group hypersensitivity reactions were only local, at the injection site, the pt. that developed tbc having a history of tbc sequels.

Conclusion:
1. AE are mostly hypersensitivity reactions and occur during infliximab treatment.
2. Hypersensitivity reactions can be overcome by desensitization techniques and protocols and should become standard of care.
3. Premedication and correct administration of BA are very important.
4. Patient’s safety is the most important objective, benefits and risks of BA have to be rigorously evaluated.
Faecal calprotectin: A reliable tool to pick up needles from haystack?

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Introduction: Endoscopic evaluation with histopathological sampling plays a crucial role in diagnosing and managing inflammatory bowel disease (IBD). Recent evidence suggests that faecal calprotectin (FC) plays an important role in the diagnosis and follow-up of IBD. We aimed to ascertain if negative calprotectin results can act as screening tool to exclude the need of colonoscopy in a district general hospital setting by comparing it with histopathological diagnosis.

Methods: We performed a retrospective study of histological records, endoscopic records, clinic letters and blood results of 219 patients referred to gastroenterology clinic of Rotherham General Hospital in between June 2009–May 2011. Consecutive patients referred with chronic diarrhoea from community or other specialties were taken as sample group. Patients who had calprotectin and histological diagnosis within two months of each other were only included in this study. Patients with no biopsy results were excluded to remove any bias. Sensitivity and specificity of FC was calculated together with negative predictive value for IBD.

Results: Total of 119 patients were included in this study. 50 patients had FC results < 8. 44 patients had FC values ≥ 8 and < 150 and 25 patients had FC results ≥ 150. The negative predictive value of FC for values < 8 is 99% which decreases to 91% on increasing the cut-off limit to < 150. 8/94 patients in this group (faecal calprotectin < 150) had some form of biopsy positivity with only two patients histologically proven to have Inflammatory bowel disease. 10 out of 25 patients with FC > 150 had IBD.

Discussion/Conclusion: FC result of less than 8 can exclude organic bowel pathology in 99% of cases. A high calprotectin value of more than 150 warrants endoscopic investigation though high calprotectin level is seen in absence of bowel pathology. Further studies are needed to understand significance and natural history of this group of chronic diarrhoea patients with high calprotectin results and normal colon biopsies.
A multicentric study: Use of Pearls Winter+® as probiotic as adjunctive to a treatment with mesalazine oral plus rectal in patients with mild-to-moderate left-side ulcerative colitis

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Introduction: The use of probiotics in the treatment of UC is not so clear enough. The aim of this study was the assessment of the efficacy of oral and rectal mesalazine with or without probiotic, Pearls Winter+® or placebo, in reducing the activity of mild-to-moderate left-side UC.

Pearls Winter+® is a probiotic that contains 1000 millions ufc of Lactobacillus acidophilus, Lactobacillus plantarum, Bifidobacterium longum, Bifidobacterium lactis, and 15 mg of lactoferrina.

Methods: We studied 50 patients with mild-to-moderate left-side ulcerative colitis. A group of 25 patients were treated with oral mesalazine (Salofalk® 2–3 gr/d), rectal mesalazine (Salofalk® foam enema 1 gr/d) and Pearls Winter+® (1 cp/d) for 8 weeks. Another group of 25 patients were treated with the same treatment, but we used placebo instead of Pearls Winter+®. We evaluated clinical disease activity using UCDAI score, and Response when the decrease in the UCDAI score was 50% or more from baseline to week 8.

Results: The group treated with Pearls Winter+®, 17 of 25 patients had a response at week 8 (68% of response), with a decrease in UCDAI from 5.84 at baseline to 2.74. In the placebo group, the rate of response was 60% (15 of 25 patients) at week 8, with a decrease in UCDAI from 5.78 at baseline to 2.84, in the patients who reached response.

Discussion/Conclusion: In our study, the use of Pearls Winter+® as probiotic in patients with mild-to-moderate left-side ulcerative colitis, as adjunctive treatment, increased the rates of response at week 8 (68% vs. 60%), although these parameters do not reach statistical significance.
Anemia and regulation of iron metabolism in patients with inflammatory bowel diseases

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Introduction: Anemia is a frequent systemic manifestation of inflammatory bowel diseases (IBD) which has significant impact on the quality of life, associates with severity of disease and resistance to therapy. Anemia in IBD is multifactorial and frequently is the result of combination of iron deficiency (first cause) and anemia of chronic disease (second major cause). Recent studies have shown that changes in the distribution of iron in the body are dependent on cytokines and acute-phase proteins. Among them the leading role in the iron homeostasis belongs to hepcidin. Aim of the study was to determine the level of hepcidine-25 in serum of patients with IBD in different types of anemia.

Methods: 69 anemic patients with IBD were observed, 54 with ulcerative colitis and 15 with Crohn’s disease, mean age 38.97 ± 1.47 years, disease duration 6.04 ± 0.9 years, and compared with 15 healthy controls (HC). The examination included total blood count, parameters of iron metabolism (serum iron, unsaturated and total iron binding capacity, transferrin saturation, ferritin, soluble transferrin receptor [sTfR]), as well as serum hepcidin-25 level and IL-6.

Results: The mean level of serum iron in patients with anemia was decreased – (8.63 ± 0.51) µmol/l compared to HC (17.20 ± 1.53) µmol/l, p < 0.01. According to established diagnostic criteria based on sTfR/log ferritin ratio patients were divided into groups: 44% – with iron deficiency anemia (IDA), 34% – anemia of chronic disease (ACD) and 22% – combination of IDA and ACD. The serum level of hepcidin-25 was decreased in patients with IDA – (3.95 ± 0.89) ng/ml compared to HC – (7.2 ± 1.1) ng/ml, p < 0.05, and increased in patients with ACD and ACD+IDA – (31.32 ± 6.07) ng/ml and (18.26 ± 2.99) ng/ml, p < 0.01, respectively. Correlation between serum IL-6 and hepcidin-25 was found: r = 0.627, p = 0.005. Serum IL-6 level was 1.6-fold higher in patients with ACD than in IDA.

Discussion/Conclusion: Increase of hepcidin production as an acute phase protein in patients with IBD leads to functional iron deficiency due to deposition of iron in macrophages, which is one of the main causes of ACD. The data obtained confirmed connection between anemia development and serum hepcidin-25 and IL-6 level in patients with IBD.
Patient’s perception of health and diagnosis in paediatric inflammatory bowel disease

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Abstract: Evaluation of patients and families’ perception of current health status and diagnosis in paediatric inflammatory bowel disease (IBD).

Introduction: Health status reported by children and parents in a chronic and disabling condition such as paediatric IBD can influence clinical judgment and management of IBD.

Methods: The project was part of a service evaluation and audit. Patients (consecutively enrolled between November 2012 and February 2013) were asked to fill in a patient satisfaction questionnaire (adapted from QUOTE-IBD). The questionnaire contained items regarding “health in the last 3 months” and “current health compared to same period last year” (answered on a 5 points scale), “current disease activity” and “current diagnosis”. Patient responses were used if patients were 12 years of age or older at the time of the visit, otherwise parent’s responses were used. Clinical data were collected from medical notes and electronic records (e-MR) and disease activity was scored using w-PCDAI and PUCAI.

Results: Participants were 76 patients and their families consecutively attending the paediatric IBD service (mean age: 12.89 ± 2.5; M/F: 1.1/1). Forty-three patients (63%) had Crohn’s disease (CD), 17% had ulcerative colitis (UC) and 20% had inflammatory bowel disease unclassified (IBDU). Overall 39% (95% CI: 28–50%) were found to be in remission. Only 33.3% reported their well-being as “very good or excellent” in the previous 3 months with 70.7% reporting their health as being “much better or better compared to the previous year”. The reported well-being was found to correlate significantly with disease activity index (r = -0.4133, p = 0.0007). The awareness of own disease status was found to be significantly higher (p = 0.042) in patient in remission (72.4%) compared to those not in remission (36.9%). Overall 77.6% was found to be aware of own diagnosis, 18.4% reported a different diagnosis, 4% was not sure. The awareness of diagnosis was statistically higher (p = 0.0057) in patients with CD (85.4%) and UC (84.6%) compared to IBDU patients (46.6%).

Discussion/Conclusion: Overall the reported well-being was found to correlate significantly with clinical scores of disease activity, indicating a family’s correct perception of health status. However patients not in remission seem to be less aware or underestimating their disease status compared to patients in remission. Moreover, there is a high proportion of patient with IBDU not aware of their diagnosis.
Prevalence of paediatric-onset inflammatory bowel disease: A systematic review

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Introduction: Previous systematic reviews have shown that the incidence of both adult-onset inflammatory bowel disease (IBD) and paediatric-onset IBD (PIBD) is increasing worldwide, particularly in developed countries, but little is known about PIBD prevalence. Although trends in incidence are important, the determination of prevalence is crucial to inform effective service provision and delivery.

Aims and Methods: We aimed to determine the trends in the worldwide prevalence of PIBD by systematic review. A literature search was performed using MEDLINE (1950–2012), Medline in progress, Cochrane database and EMBASE (1980–2012) to identify relevant population-based studies. Studies were included that reported paediatric prevalence data on either Crohn’s disease (CD) or ulcerative colitis (UC). Data was extracted for each eligible study and results were collated.

Results: 4190 references were found and reviewed; 26 studies which presented data on the prevalence of PIBD and/or CD and/or UC from 11 countries were included. The prevalence of PIBD ranged from 6.0–30.0 per 100,000 while CD ranged from 0.5–85.3 per 100,000 and UC from 3.0–90.1 per 100,000. Only one study provided trend analysis over time, showing an increasing PIBD prevalence during a 5-year period. There was a preponderance of reports from Western countries: 8 from North America, 8 from Europe, 6 from the Middle East, 2 from Asia, 1 from Africa, and 1 from Australasia. Prevalence rates were highest in North America and lowest in Africa and Asia.

Discussion: Reported prevalence of PIBD was highest in North America and Europe with little data from developing nations. Insufficient data exists to analyse trends in prevalence of PIBD over time. Further work is needed to confirm if the increase seen in the worldwide prevalence of adult IBD is mirrored in PIBD with these data used to enhance clinical services and drive future funding for research.

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Anti-TNF dependency in paediatric IBD – The Scottish experience

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Introduction: Management of paediatric IBD (PIBD) has changed significantly in the last 10 years with the advent of biological agents. Evidence is emerging on biological dependency and our aim is to identify patients who became dependent on infliximab (IFX) and/or adalimumab (ADA) after response to induction therapy.

Methods: A retrospective case note review was carried out in all PIBD treatment centres in Scotland. Children < 18 year were included who were given infliximab (IFX) and/or adalimumab (ADA) in a paediatric centre and dependency was defined as relapse of symptoms requiring repeated infusions to regain complete or partial response. Data was collected from 1.1.00 until 01.03.12 with follow up until 30.9.12.

Results: 65 patients had IFX and/or ADA for ≥ 12 months (42 males), 64 with CD and 1 with UC. 38 of 65 (58%) had anti-TNF dependency. 49 patients were on IFX for a median of 1.67 years receiving 4–25 doses (median 11). 40% required escalation of therapy, either increased dose or frequency. 55% stopped treatment after 12 months (44% loss of response, 33% successful planned IFX withdrawal and 7% allergic reaction); 45% continued to study end. 16 patients (14 prior IFX) were on ADA for a median of 2.18 years, all had CD and 12 were male; 13 were on ADA at study end, 2 stopped for loss of response and 1 had successful planned ADA withdrawal. IFX failure was most commonly primary non-response, in 7 (44%). 9 (56%) required escalation of therapy to weekly dosing. No serious adverse events were noted during or after biological therapy.

Conclusions: 58% on IFX/ADA at 12 months then become dependent on anti-TNFs, with only a minority having successful planned drug withdrawal. Both drugs appear safe and well tolerated; only 7% stopping IFX or ADA due to allergy or side effects after 12 months.

Acknowledgements: Dr. Fiona Cameron is kindly supported by a CICRA research training fellowship.
Calprotectin: A cost effective screening tool in paediatric inflammatory bowel disease

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Introduction: Up to 70% of children referred to a paediatric gastroenterology centre with suspected inflammatory bowel disease (IBD) do not have the disease. Faecal calprotectin (FC) is a white cell protein and a marker of intestinal inflammation. The aim of this study was to evaluate the use of FC in children with possible IBD and to determine if this test resulted in health service cost savings by avoiding unnecessary endoscopies.

Methods: A retrospective analysis of FC measurements carried out between 1st October 2011 and 5th February 2013. FC values were defined as follows: < 50 µg/g (normal); 51–200 µg/g (possible GI inflammation); > 200 µg/g (active GI inflammation). FC results were obtained from the biochemistry department. Following a computerised search of the departmental records the presenting complaint, endoscopy result if applicable, diagnosis of IBD or alternative diagnosis, and follow-up or discharge were recorded for each patient. Using this information, patients were divided into those who were scoped based on their FC value and those who were not scoped. Established IBD patients who had a FC test as part of their disease management were treated as a separate group.

Results: 125 patients had a FC test – just 28 (22%) ultimately underwent endoscopy. Eleven of these patients had a FC > 200 µg/g, while 6 were subsequently diagnosed with IBD. 21 patients with known IBD had a FC test when they became symptomatic: 12 FC values were consistent with GI inflammation. FC costs ~ €75 per test while endoscopy costs at least €1000/test (very conservative estimate). The net cost saving in the year examined was ~ €49,700.

Discussion/Conclusion: Faecal calprotectin is a valuable test for excluding IBD in patients who present with abdominal pain or diarrhoea. FC can confirm relapse in symptomatic patients known to have IBD. Appropriate FC use and interpretation can reduce unnecessary endoscopic procedures in children and yield significant cost savings for the hospital. Continued internal auditing of FC use is needed.
The changing behaviour of new onset IBD in Irish children from 2010–2011

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Introduction: The rise in the incidence of paediatric inflammatory bowel disease (IBD) in Ireland from 2000 to 2010 has been recently documented. The aim of this current study was to examine the phenotypic attributes of IBD among children diagnosed with new onset IBD in 2010 to 2011.

Methods: A retrospective review of paediatric IBD was undertaken using nationally representative data from the National Centre for Paediatric Gastroenterology, Hepatology and Nutrition (NCPGHN) in Ireland. IBD was phenotyped using the Paris classification and compared against previous Irish data from 2000 and 2008 and international figures.

Results: The incidence of IBD from October 2010 to October 2011 was 7.5/100,000/year. Seventy nine children were diagnosed with IBD during the defined review period (49 boys, 32 girls, median age of diagnosis 12.7 years). The phenotype of new onset IBD has changed significantly from historic cohorts (Table 1). There is a distinct increase in complex disease behaviour (27%) such as stricture and penetrating disease. The incidence of UC (n = 29) has increased three-fold in 10 years (16 boys, median age of diagnosis 13.1 years). At one year, 21 (46%) children with CD and 19 (66%) with UC were in remission, with 91% steroid free.

Table 1: Location of Crohn’s disease and ulcerative colitis as defined by the Paris classification

<table>
<thead>
<tr>
<th>Location of Crohn’s disease n (%)</th>
<th>2000 (n = 25)</th>
<th>2008 (n = 31)</th>
<th>2010 (n = 46)</th>
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<tr>
<td>L1</td>
<td>2 (8)</td>
<td>6 (19)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>L2</td>
<td>11 (44)</td>
<td>6 (19)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>L3</td>
<td>9 (36)</td>
<td>10 (32)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>L1+L4</td>
<td>1 (4)</td>
<td>4 (13)</td>
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<td>L2+L4</td>
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<table>
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</tr>
<tr>
<td>E4</td>
<td>11 (84)</td>
<td>9 (64)</td>
<td>7 (24)</td>
</tr>
</tbody>
</table>
Discussion/Conclusion: The incidence of IBD in Ireland remains high. The phenotypic behaviour of CD is changing with more complex disease behaviour evident at presentation. The prevalence of UC has tripled over 10 years. Future prospective longitudinal studies are needed to fully elucidate the factors underlying IBD in Irish children.
Risk factors of thrombotic complications in inflammatory bowel disease

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Introduction: Thromboembolic disease is a significant cause of morbidity and mortality in patients with inflammatory bowel disease (IBD).

Methods: In the present study we evaluated risk factors of thrombotic complications in 65 IBD patients (M/F = 40/25). 35 patients had ulcerative colitis (UC) and 30 had Crohn’s disease (CD) as compared with control group matched for age and gender. We measured hematocrit, basic haemostatic parameters (platelet count, activated partial tromboplastin time, protrombin time, functional antithrombin level, protein C chromogenic activity and protein S antigenic level), resistance to factor V degradation by activated protein C (APC), hyperhomocysteinemia and prothrombin gene mutation (P20210A).

Results: Thromboembolic complications were found in 1.7% of UC patients and 2.3% of CD patients, while chronic coronary heart disease accompanied IBD in 10.7% of patients. Platelet levels were significantly higher (p < 0.001) in IBD as compared with control group, whereas aPTT was moderately prolonged in 24.5% of IBD pts. We observed decrease of functional antithrombin levels in 20% of IBD pts whereas protein C activity in all patients was normal. Moreover, protein S levels were significantly lower (p < 0.02) as compared with control group. Mean homocystein levels were found to be significantly higher (p < 0.01) and APC resistance ratio (mean 2.70) significantly lower in IBD patients compared to controls (p < 0.01). There was no significant difference detected between patients with UC and CD. There was no significant increase in the incidence of P20210A gene mutation in IBD patients.

Discussion/Conclusion: Coagulation abnormalities are potential risk factors of thromboembolic complications in IBD. Higher homocysteine levels may relate to relative folate deficiency in IBD patients. Lower APC ratios are more likely to be genetic. Evaluation of prothrombotic risk factors and associated ischemic diseases is valuable in the management of IBD.
Inosine triphosphate pyrophosphatase and xanthine oxidase gene variability in Croatian inflammatory bowel disease patients

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Introduction: Thiopurines are widely used but not effective in one-third of inflammatory bowel disease (IBD) patients (pts). Up to one-fifth of pts discontinue thiopurines due to adverse reactions. The observed interindividual differences in therapeutic response and toxicity to thiopurines are explained by the variable formation of active metabolites, which is at least partly caused by polymorphisms of the genes encoding crucial enzymes in metabolism. Among them, of recognized importance are thiopurine S-methyltransferase (TPMT), xanthine oxidase (XO) and inosine triphosphate pyrophosphatase (ITPA). While genetic variability in TPMT has been translated into practical guidelines the importance of XO and ITPA is not fully understood. ITPA catalyzes the pyrophosphohydrolysis of inosine triphosphate (6-TITP) to inosine monophosphate, thereby preventing an abnormal accumulation of 6-TITP nucleotides in cells and their incorporation into RNA and DNA. ITPA deficiency has been related with adverse effects such as pancreatitis, nausea, flu-like symptoms and skin rashes in patients treated with AZA/6-MP. XO catalyzes the catabolism of 6-MP to 6-thiouric acid. 6-MP induced adverse effects may increase in poor XO metabolizers. Regarding to the fact that genetic variability shows marked interindividual and interethnic differences, the aim of the study was to examine the allelic variations of ITPA and XO in Croatian IBD patients.

Methods: DNA of 235 IBD patients was genotyped for ITPA 94C>T, ITPA 124+21A>C, XO 837C>T, XO 2211C>T by methods based on RealTime Polymerase Chain Reaction.

Results: Concerning the 94C>A variant of the ITPA gene, 198 (86.1%) individuals were homozygous for the wild-type allele, 30 (13%) were heterozygous, and 2 (0.9%) were homozygous mutants. For ITPA 124+21A>C, 143 (60.8%) individuals were homozygous for the wild-type, 89 (37.9%) were heterozygous and 3(1.3%) were homozygous mutants. Concerning the 837C>T variant of the XO gene, 203 (90.2%) individuals were homozygous for the wild-type allele and 22 (9.8%) were heterozygous. For XO 2211C>T 98 (43.6%) individuals were homozygous for the wild-type, 89 (42.6%) were heterozygous and 31 (13.8%) were homozygous for the mutated allele.

Discussion/Conclusion: ITPA and XO exhibit considerable gene variability in Croatian IBD patients which could be an additional risk factor for thiopurine drug adverse reactions.
Practicalities of varicella screening and vaccination in the paediatric inflammatory bowel disease patient

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Introduction: Varicella zoster virus (VZV) has been suggested to cause significant morbidity and mortality to the immunosuppressed child with IBD. Pre-emptive strategies should be considered for a child with IBD to reduce the impact of the varicella infection in line with published guidelines. We aim to describe the impact of our VZV screening and immunisation programme.

Methods: Universal varicella serology screening was introduced at the time of IBD diagnosis in our tertiary unit from 2009. Children identified as VZV negative, were then considered for vaccination. A two stage varicella vaccination programme was implemented, using either the Varivax® or the Varilrix® vaccine, with an interval time of 4 weeks. For children with negative serology unsuitable for vaccination, varicella specific education was delivered by the IBD Nurse. Median values were compared using a Mann-Whitney test (Minitab v.15).

Results: Between 2009–2011, 136 children were diagnosed with IBD, 91 (67%) Crohn's disease (CD), 30 (22%) ulcerative colitis (UC) and 15 (11%) IBD unclassified. 6/136 (4.4%) were not tested for varicella serology. Of the remaining 130 patients, 117 (90%) were positive and 13 (10%) negative. Of the negative patients 10 CD and 3 UC. Median age of varicella negative patients was significantly younger than positive patients (8.77 years vs. 12.16 years, p = 0.01). 8/13 (62%) varicella negative patients were successfully vaccinated. In the children with negative serology, 4 received exclusive enteral nutrition therapy, of which 75% were successfully vaccinated. There was only one opportunity to vaccinate 1 of these patients post completion of steroid therapy. Patients not vaccinated, 4 (80%) were treated with steroids. 6/8 of patients vaccinated demonstrated sero-conversion post vaccination. Of the remaining 5 (38%) children not immunised, 2 required post exposure prophylaxis, no varicella symptoms were noted. However 7 children with IBD who were immunosuppressed and diagnosed with IBD prior to 2009, required treatment for varicella (5 with IV aciclovir and 2 oral aciclovir) within the 3 year period.

Discussion/Conclusion: At diagnosis 10% of newly diagnosed paediatric patients were found to be VZV negative. Serology negative patients can be successfully vaccinated. The ability to vaccinate is dependent on early treatment choices. The IBD Nurse is identified as having a pivotal role in co-ordinating management strategies that may reduce the need for treatment of varicella infection.
The use of hydrogen breath test for the diagnosis of small intestinal bacterial overgrowth in patients with inflammatory bowel diseases

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Introduction: SIBO is quite often in different gastrointestinal diseases.

Aim: To establish the prevalence of small intestinal bacterial overgrowth (SIBO) in patients with inflammatory bowel diseases (IBD).

Methods: 46 patients with IBD (17 men, 29 women), aged 19 to 60 years including 18 patients with Crohn's disease (CD) and 28 with ulcerative colitis (UC) were examined. IBD duration was from 1 to 40 years. Hydrogen breath test “Gastrolyzer” (England) was used for evaluation of SIBO.

Results: Before the study most of the patients complained of bloating, flatulence, abdominal pain, and diarrhea. SIBO was found in 19 patients (42.9%). In the group of UC SIBO was diagnosed in 12 patients (42.3%), in the group of CD in 7 patients (38.9%). During the hydrogen breath test procedure bloating, rumbling in the stomach, single or double diarrhea were more common in patients with SIBO than in those SIBO was not detected in (66% vs. 36%). The average weight of patients with SIBO was significantly lower (59.6 kg vs. 67.5 kg) than in those without SIBO. 5 patients out of 46 were found to be "non-H₂-producers". Rifaximin 400 mg 2 times a day for 7 days and probiotics were prescribed for all patients with SIBO resulting in reduction of bloating, abdominal pain and diarrhea.

Discussion/Conclusion: Hydrogen breath test can be used for differentiation of SIBO contribution to clinical symptoms of IBD.
Inflammatory bowel disease and colorectal carcinoma – Management and clinicopathological parameters

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Patients with inflammatory bowel disease have increased risk of developing colorectal carcinoma.

Introduction: The objective of our study was to assess the clinicopathological features and survival rates of patients with inflammatory bowel disease (IBD) who developed colorectal carcinoma (CRC).

Methods: A retrospective review was performed on a prospectively maintained institutional databased (2002–2012) to identify patients with inflammatory bowel disease who developed colorectal carcinoma. Clinicopathological parameters, management and outcomes were analysed.

Results: A total of 243 patients with inflammatory bowel disease were identified. 139 had ulcerative colitis (UC) and 104 had Crohn’s disease (CD). Following exclusion criteria, there were 14 patients with biopsy-proven colorectal carcinoma, 9 had ulcerative colitis and 5 had Crohn’s disease. 19 patients had a preoperative diagnosis of malignancy/dysplasia; 8 of these were diagnosed at surveillance endoscopy. Distant metastases were identified at presentation in 43% of the ulcerative colitis and 72% of the Crohn’s disease. Operative morbidity for UC and CD was 36 and 19%, respectively. Despite the less favourable operative outcomes following surgery management of UC-related CRC, overall 5-year survival was significantly better in the UC group compared to the CD group (43% vs. 28%).

Discussion/Conclusion: Patients who undergo surgery for ulcerative colitis related colorectal carcinoma have less favourable short-term outcomes but present at a less advantage and have a more favourable long-term prognosis than similar patients with colorectal carcinoma and Crohn’s disease.
Point-of-contact faecal calprotectin (FC) testing in diarrhoea helps decision making for referral to gastroenterologists: A primary care pilot study in North East England

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Introduction: Faecal calprotectin (FC) is a cytosolic protein belonging to the S-100 family of calcium binding proteins found in neutrophils. It is excreted in the intestinal lumen in inflammatory conditions of the gut and can be used to distinguish irritable bowel syndrome (IBS) from other inflammatory bowel conditions such as colitis, diverticulosis, etc. Point-of-contact qualitative FC tests are now available and can be used in primary care to aid decision making for referrals to gastroenterologists for young patients presenting with chronic diarrhoea.

Aims: To assess the feasibility and cost effectiveness of a primary care pathway using a point-of-contact FC test (Caldetect®) to aid decision making for referrals to gastroenterology in young patients presenting to their primary physicians with chronic diarrhoea.

Methods: Primary care data indicated that approximately 253 referrals are made annually to gastroenterologists from primary care to assess patients < 60 years presenting with diarrhoea, costing approx. £119,000 for investigations and consultations. Using a Caldetect® (Preventis, GmbH) point of contact FC test, it was estimated that a saving of £89,000 could be achieved. A pathway for investigating chronic diarrhoea using Caldetect® was designed and implemented in the community (population 150,000) between September 2011 and March 2012. (this will be presented). FC results were categorised using manufacturer cut-offs of < 15 µg/g, 15–60 µg/g and > 60 µg/g. Patients with FC results of 15–60 and > 60 were deemed to have an inflammatory process and referred to Gastroenterology Clinics. Cost analysis was carried out using the 2010-11 tariffs for the NHS.

Results: 142 Caldetect® tests were carried out in primary care during this pilot phase. Of these, a negative result (< 15 µg/g) was present in 89, with 36 tests being > 60 µg/g. 3 tests were at the intermediate level and 14 tests could not be accurately reported. Negative results were managed in primary care as IBS. A monthly cost savings of £6100 was calculated taking consultation and endoscopy tariffs into account.

Conclusion: This pilot study demonstrates the feasibility and cost effectiveness of a Pathway for decision making and a point-of-care faecal calprotectin test in rationalising referrals to gastroenterologists for chronic diarrhoea.
Maintaining remission in ulcerative colitis: 5-Aminosalicylic acids (5-ASA) therapy

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Introduction: 5-Aminosalicylic acids (5-ASAs) play a key role in both the induction and maintenance of remission in ulcerative colitis (UC). A number of questions remain poorly assessed by clinical trials including the dose, dose interval, preparation and delivery method that is most effective in maintaining remission in this group of patients.

Methods: An inception cohort of 100 (45 males) newly diagnosed UC patients were retrospectively assessed and followed up for 3 years. Data were collected on 5-ASA maintenance therapy along with information relating to disease activity. Length of remission was estimated using median time to relapse and groups were compared using Mantel-Cox (log rank) test and Hazard Ratios.

Results: 77 received an oral 5-ASA, 11 topical therapy and 12 had combined treatment. 76% of patients relapsed by 3 years follow up; with a mean time to relapse of 11 months (range 1–32). No significant difference was found in the length of first remission or risk of relapse between Asacol and Pentasa preparations, once, twice and three times dosing schedule, high dose (4.8 g/day) or low dose (2.4 g/day) and oral or combined delivery methods. Moderate disease at presentation had a significantly shorter length of remission (p = 0.006) and a 2-fold increase in risk of relapse compared with mild disease at presentation. All patients who presented with severe disease relapsed with a median time to relapse of 8 months. Disease extent at time of diagnosis, agents used to induce remission and time to remission did not predict risk of relapse.

Discussion/Conclusion: The results would suggest that differences in 5-ASA preparation or dosing schedules do not influence the maintenance of remission in UC. Low dose and uni-directional approaches to therapy may have a more favourable outcome indicating that concordance with therapy remains a vital aspect of 5-ASA efficacy. Disease severity and not disease extent may have an independent role in determining the risk of relapse.
Morphologic individualised medicine: A break through approach for early determination of anti-TNFα responders and non-responders among patients with ulcerative colitis in a prospective study

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Introduction: The immunopathologic processes of ulcerative colitis (UC) and Crohn’s disease (CD) have not been fully elucidated. Anti-TNFα antibodies have proven efficacy yet about 30–40% of patients are non-responders. Up to date there are no reliable predictors for therapeutic success in this regard. As it has been shown so far, “-omics” alone cannot help. Physiological intermolecular modification spectroscopy (PIMS), a cutting edge technology is able to reconcile these data with the clinic. PIMS is a label free technology through which dynamic molecular resonance of entire proteins and macromolecules of an individual is recorded, on real time, as the temperature within the sample rises from -37 to 37°C. It discriminates the responders from non-responders to a given treatment.

Methods: Protein extracts of peripheral blood mononuclear (PBMC) of 47 outpatients (female = 16, mean age = 40.8 ± 16.4 years & men = 31, mean age = 41.5 ± 18.6) diagnosed with UC or CD (UC = 20, CD = 27) and treated with anti-TNFα therapy, were subjected to PIMS analysis. Patient’s data were blinded. 1 µg of total protein from each patient’s PBMC was challenged with 10 ng of infliximab. After determination of base line the samples were frozen at -37°C. Dynamic changes in macromolecular interaction were registered while the temperature rose from -37 to 37°C. Individual macromolecular volume (IMV) and molecular elasticity (ME) were determined for each patient. A change in ratio of ME from -10 to -5°C less or equal to zero was considered as non-responder.

Results: After deblind, 65% (n = 13) UC and 59% (n = 16) CD patients were responders to infliximab. These correlated with PIMS predictions (correlation 0.95) which had stratified patients to responder and non-responders groups.

Discussion/Conclusion: PIMS in a blinded transversal study were able to stratify patients into two distinct groups of responders and non-responders to infliximab. It seems to be a powerful method for adapted IBD treatment and morphogenetic individualised medicine.
Psychological impact of Crohn’s disease: a case-control study

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Background: Crohn’s disease has a major psychological impact. It is a chronic disorder that is often a factor of long-term disability. In addition to the gastrointestinal manifestations, there is a psychological and psychiatric comorbidity which is essentially anxiety and depression.

The aims of our study were to evaluate the prevalence of depression and anxiety among Tunisian patients with Crohn’s disease, to compare them with a control group and to identify predictive factors of these disorders.

Methods: This cross-sectional study included patients treated for Crohn’s disease in remission for at least six months, and controls matched for age and gender. The anxiety and depression were assessed using the Mini International Neuropsychiatric Interview (MINI), the Beck Depression Inventory (BDI) and the Hamilton Anxiety Rating Scale (HARS).

Results: We included 70 patients and 70 controls. Depression was noted in 45.7% of patients, with a rate of severe depression of 21.4%, while it affected only 22.8% of controls (p = 0.006). In the group of patients, there were significantly more anxious, subjects (57.2%) than in the control group (37.2%) (p = 0.007). Univariate analysis revealed that older age, women sex, disease duration, perianal lesions, extraintestinal manifestations, history of severe acute exacerbation and the surgical treatment were associated with depression (p < 0.05).

Conclusion: Our results emphasize the importance of anxiety and depressive symptoms in Crohn's disease. Therefore, clinicians should systematically screen for those disorders in order to discuss a specific care.
Outcome measures in paediatric IBD: Data from a tertiary level center in UK

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Abstract: Evaluation of a proposed outcome panel including self-reported outcome in a tertiary paediatric IBD setting.

Introduction: Measures to evaluate quality of care in paediatric inflammatory bowel disease (IBD) are not well established. Given the costs, resource utilization, morbidity associated with IBD and the evidence of a gap between recommended and delivered care, efforts to define IBD standards, measure performance are becoming increasingly important.

Methods: The panel of outcome measures was designed based on a detailed literature review of currently available quality measures both within IBD and related immune mediated diseases. Patients, consecutively enrolled between November 2012 and February 2013, were asked to fill in a patient’ satisfaction questionnaire (adapted from QUOTE-IBD-this needs a reference). Data were collected from medical notes and electronic records (e-MR) and the self-reported outcomes were extrapolated from the questionnaire. The project was registered as an audit. Eighty-one questionnaires were handed out, 76 patients returned the questionnaire (96%) and were prospectively included in the study (mean age: 12.89 ± 2.5; M/F: 1.1/1).

Results: Forty-three patients (63%) had Crohn’s disease (CD), 17% had ulcerative colitis (UC) and 20% had inflammatory bowel disease unclassified (IBDU). Overall 39% (95%: CI 28–50) were found to be in remission, with 31.66% being in 6 months steroid free remission (95% CI: 19.9–43.4). No differences were observed between CD, UC and IBDU patients. Patients with a satisfactory growth status (height > 10°percentile) were 83.4% (95% CI: 74–92.8) and those with satisfactory nutritional status (BMI > 10° percentile) were 93.6% (95% CI: 87.4–99.8). A quarter of the IBD patients (23.8%; 95% CI: 11–36.6) had at least one unplanned admission in the previous year, with a median length of stay of 2.5 days (IQR: 2.75). Regarding the school attendance only 38.1% (95% CI: 23.3–52.9) achieved the average national school attendance (95%).

Discussion/Conclusion: This study represents the first effort to test a set of proposed outcome and quality measures in the management of children with IBD. We found the vast majority of the tested measures to be useful for assessing the quality of care delivered to children with IBD in a local setting. Further studies are now required to be performed in other UK centers ultimately allowing to set a national standard and thereby continuing to improve the quality of care.
Identification of disease-associated DNA methylation in blood from patients with inflammatory bowel disease

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Introduction: It is well known that inflammatory bowel disease (IBD) is caused by a complex interplay between genetic predispositions of multiple genes, combined with an abnormal interaction with environmental factors. Germline variation in the IBD implicated by genome-wide association studies (GWAS) only accounts for approximately 25% of estimated heritability. The contribution of epigenetic alterations to disease pathogenesis is emerging as a research priority. In this study, we extended this approach to identify IBD-associated changes in DNA methylation in blood from 12 IBD patients (6 Crohn’s disease, CD and 6 ulcerative colitis, UC).

Methods: The promoter methylation status of 22 genes (ATF2, CCL25, CXCL14, CXCL3, CXCL5, CXCL6, FADD, GATA3, IL10RA, IL12A, IL12B, IL13, IL13RA1, IL15, IL17C, IL17RA, IL4R, IL6R, IL6ST, IL7, INHA, TYK2) whose involvement in inflammation and autoimmunity were profiled using the Human Inflammatory Response and Autoimmunity EpiTect Methyl II Signature PCR Array profiles.

Results: Using this approach with strict statistical analysis, we identified concerning the CD that the CCL25, CXCL14, CXCL3, CXCL6, GATA3, IL15, IL17RA, IL4R, IL6R, IL6ST, IL7, INHA, TYK2 were hypomethylated compared to healthy individuals and for the genes tested was found to be hypermethylated. Regarding the UC cases the CCL25, CXCL3, IL10R, IL12A, IL13, IL15, IL17RA, IL7, INHA and TYK2 were found to be hypomethylated, whereas the CXCL14, CXCL5, GATA3, IL12B, IL17C, IL4R and IL6R were found to be hypermethylated compared to the controls.

Conclusion: IBD- and subtype-specific changes in DNA methylation were identified in blood from IBD patients. Many of these genes have important inflammatory and autoimmunity response functions. These data provide an important insight into the impact of epigenetic mechanisms in the pathogenesis of IBD.
The relationship between bone mineral density, disease activity and remission maintenance therapy in inflammatory bowel disease

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Introduction: Aim of study was to identify possible relationships between the bone mineral density (BMD) and the localization and activity of disease, BMI, the long term therapy with steroids drugs, Vitamin D deficiency or immunosuppressant treatment in remission maintenance of IBD.

Methods: We investigated 32 patients with IBD: 22 patients with ulcerative colitis (UC) and 10 patients with Crohn’s disease (CD). The osteoarticular manifestations were clinical, radiological and biochemical investigated. BMD was measured by dual energy x-ray absorptiometry (DEXA) of the femoral neck and lumber spines.

Results: The incidence of osteoporosis was significant higher in UC patients (36.36%) comparative with CD patients (20%). Osteopenia was presented more frequent in CD (20%). The rheumatic manifestations of UC patients were: pauciarticular peripheral arthropaties (7 cases), polyarticular peripheral arthropaties (3 cases) and only one patient was diagnose with ankylosing spondylitis. CD patients present polyarticular peripheral arthropathies in 2 cases (20%) and ankylosing spondylitis in one case. We have not found a correlation between BMD and ages, gender or severity of IBD activity, but T-score was correlated with BMI values, C-reactive protein and hypocalcemia. Mean values of BMI was lower in patients with osteoporosis (17.88 ± 4.63 kg/m² in patients with T-score < -2.5 vs. 22.13 ± 6.51 kg/m² in IBD). Also, we not identified a relationship between maintenance therapy of IBD (azathioprine vs. infliximab) and BMD. History of long-term treatment with corticosteroids (in the last 3 years) was associated with less than minus-2.5 values of T-score. IBD patients with an abnormal BMD (15 cases) had a significantly higher rate of vitamin D deficiency (mean values of vitamin D 25-hydroxy levels: 17.3 ± 4.28 ng/mL). The localization of IBD and values of clinical disease activity index (CDAI in CD and Powell Tuck Index in UC) were not significantly correlated with T-score, but osteoporosis was present more frequent in patients with CDAI > 150 or large extension of disease.

Discussion/Conclusion: The low BMD, common in both CD and UC patients, uncorrelated with the localization, duration and severity of disease, remains an important problem in IBD management. Though low BMI, vitamin D deficiency and long-term treatment with corticosteroids were independents risk factors for osteoporosis, maintenance therapy for IBD not affected the BMD.
Distinctive response to usual therapies of moderate ulcerative colitis in elderly patients

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Introduction: The aim of this study was examining the differences in UC presentation in the elderly: the clinical features, the response to usual therapies and risk to develop complications. Also, we assess comparatively the efficacy and safety of mesalazine-budesonide combined therapy versus azathioprine in inducing remission in moderate UC.

Methods: This comparative analysis was performed on 37 patients, which were structured in 2 groups: A group composed of 12 older patients (ages > 60 years, mean age 67.3 ± 8.71 years) and B group consist of 25 patients with ages < 59 years (mean age 37.3 ± 9.55 years). In A group 5 patients were treated with oral mesalazine (Salofalk®, 2–3 g/day) and oral budesonide (3 x 3 mg/day), for 6–8 weeks and 7 patients (with contraindicated corticoids therapy) were treated with azathioprine (1–1.5 mg/kg/day). In B group 15 patients were treated with oral mesalazine and budesonide and 10 patients were treated with azathioprine. We evaluated the Powell-Tuck Index and endoscopic classification at baseline, after 1, 3, 6 and 12 months.

Results: Most of the older patients (58.33%) present left-sided UC, 4 patients had proctitis and only one extensive colitis. In B group the localization was: left-sided UC in 11 cases and proctitis in 14 cases. The distinctive features in elderly patients consist in the high incidences of: rectal bleeding (66.66%), diarrhea or paradoxical constipation (83.33%) and extraintestinal manifestations (58.33%). Also, they have a lower incidence of abdominal pain (33.33%) or weight loss (8.33%). Rapid response to associated treatment was observed in most young patients (60.0%) and only in one case (20.0%) in A group. Two older patients discontinued treatment with budesonide due to osteoporosis. At 3 months, the rate of clinical and colonoscopically confirmed remission after mesalazine-budesonide therapy was: 40.0% in older patients and 73.33% in B group. Comparatively, the remission rate after azathioprine monotherapy was: 42.85% in older patients and 60.0% in B group. Two patients discontinued azathioprine treatment due to leuko-thrombocytopenia (A group) and increased aminotransferases levels (B group). The diminution of the mean Powell-Tuck score at 3 and 6 months compared with baseline suggest a more slowly response in elderly patients.

Discussion/Conclusion: The elderly patients with UC present particular manifestations and a distinctive response to usual therapies. Mesalazine associated with budesonide achieved high remission rate in short-term treatment in moderate UC. Low-dose azathioprine therapy is an effective alternative for the induction of remission in the elderly.
Familial occurrence of inflammatory bowel disease in children

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Introduction: Familial occurrence of inflammatory bowel disease (IBD) is one of the most important risk factors for this group of diseases. In first-degree relatives the risk of IBD increases 10- to 15-fold and among more distant relatives 3-fold. The NOD2/CARD15 gene mutation may lead to the development of IBD. But not all patients with this mutation developed intestinal inflammation. This can indicate a complex relationship between genes and environment necessary for the development of IBD.

The aim of this study was to assess the prevalence of familial IBD in children, their clinical course, and the presence of NOD2/CARD15 gene mutations in children with familial and sporadic Crohn's disease.

Patients and Methods: The study comprised 178 children with IBD aged 3–18 years (80 children with Crohn's disease and 98 with ulcerative colitis [UC]). The analysis included: age at diagnosis, sex, disease activity (PCDAI, PUCAI). In children with Crohn's disease, mutations R702W, G908R, L1007fs of the NOD2 CARD15 gene were marked. Family occurrence is defined as occurrence of at least one patient with IBD among first-, second- and third-degree relatives.

Results: Familial IBD occurred in 10% of patients (11.2% in Crohn's disease, 10.2% in UC). Among studied children, the familial form of UC occurred in children at the younger age by 2 years. Children with familial Crohn's disease had twice as likely severe form (p = 0.028), in children with familial UC significantly more common was a moderate form (p = 0.0029). Almost all children with familial Crohn's disease (88.9%) and 35.2% of children with sporadic Crohn's disease (p = 0.001) had at least one mutation of the NOD2/CARD15 gene. Considering the single NOD2/CARD15 gene mutations, in both the family and the sporadic forms the most common was L1007fs mutation.

Conclusions:
1. Familial occurrence of inflammatory bowel disease in children was similar to the adult population and their clinical course was much more severe than in patients with sporadic form.
2. The high frequency of the mutations of the NOD2/CARD15 gene confirms the dominant genetic factor in the pathogenesis of familial Crohn's disease.
Inflammatory response in intestinal epithelium is higher in children with ulcerative colitis

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Introduction: Ulcerative colitis (UC) is a lesion of unknown etiology. The main component (neutrophils, eosinophils, lymphocytes) of inflammatory infiltrate is an exponent of the stage of the disease and involved cells are responsible for the extent of the intestinal epithelium damage. The aim of our study was to evaluate the inflammatory infiltrate in patients with UC in relation to age.

Materials and Method: The study included a group of 52 patients with ulcerative colitis (33 adults and 19 children). Endoscopic materials were taken from archival paraffin-embedded tissue. Sections were stained with H&E and subjected to routine histological evaluation. An analysis of the severity and activity changes was performed according to the Geboes criteria that included chronic inflammatory infiltration and its composition (neutrophils and eosinophils in lamina propria, the presence of neutrophils in crypts).

Results: In biopsy specimens we observed a small (7/52), moderate (13/52) and marked (32/52) increase in the incidence of neutrophils in the lamina propria. However, 65% of cases have confirmed a significant increase in the presence of eosinophilia in the lamina propria. It was also examined the activity of neutrophils in the intestinal crypts. There was the occurrence of neutrophils in the epithelium at < 5% of the occupied crypts in 11 cases, at < 50% in 7, at > 50% of the occupied crypts in 34 cases. Statistical analysis showed a negative correlation between the patients’ age and the presence of neutrophils and eosinophils in the lamina propria and the percentage of neutrophils in the intestinal crypts. The tissue of young patients was characterized by higher parameters mentioned above than adults.

Conclusion: Our results suggest that the local immune response of the intestinal epithelium in the patients with UC is higher in children than adults. It is associated with a more aggressive course of disease causing the greater extent of changes in this age group.
Clostridium difficile in IBD: An under diagnosed cause of disease relapse?

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Introduction: Patients with IBD have an increased incidence of developing Clostridium difficile infection (CDI) over the general population. These can often be difficult to distinguish from a flare. They have worse outcomes than the general population when infected with CDI. Our study aimed to assess testing and detection rates of CDI in a cohort of relapsing IBD patients requiring hospital admission.

Methods: A single centre retrospective review of patients admitted with a relapse of IBD was undertaken. Patients were identified using Hospital Inpatient Enquiry (HIPE) data between December 2011 and December 2012. Only patients with definitive IBD were included. A review of investigations during admission was performed to check whether a CDI sample had been sent. In positive cases, notes were reviewed and medication history noted.

Results: In total, 50 patients were admitted with relapsing IBD. Of these, 26 (53%) were male and the mean age was 39 years (range 18–81). Within the cohort, 26 (51%) had Crohn’s disease (CD), 14 (28%) had Ulcerative colitis (UC) and 10 (20%) had IBD unclassified. Testing rates overall were high at 73% (n = 36). Two patients (4%) were diagnosed with CDI within the entire cohort and both had CD. In total, 6 (12%) patients required a colectomy during admission. One CDI patients required a colectomy. Our colectomy rates were 50% and 10% for CDI positive and CDI negative groups (p < 0.04), respectively. There was no difference in length of stay between groups.

Discussion/Conclusion: High clinical suspicion should be maintained for CDI in IBD patients. The prevalence of CDI in our cohort is in keeping with other reported data. However, the majority of relapsing IBD patients are treated as outpatients and it would be interesting to see if our testing rates remained high in this cohort.
The impact of wireless capsule endoscopy in suspected Crohn’s disease – A longitudinal study

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Introduction: A definitive diagnosis of Crohn’s disease (CD) can be difficult to make often resulting in a treatment delay. Wireless Capsule Endoscopy (WCE) is a modality which has an enhanced diagnostic yield for CD in comparison studies with other imaging modalities. The ability of WCE to differentiate CD from other causes of small bowel inflammation has been questioned. Studies are required to assess long term impact of WCE findings in suspected CD.

Methods: A retrospective review was carried out on WCE procedures performed for suspected CD since 2010. Only patients with at least 6 months documented follow up were included. A chart review was undertaken to assess the impact of WCE findings and to correlate with subsequent clinical diagnosis and outcome. All statistics were performed using SPSS 19.

Results: In total, 130 patients were identified. In 35 (27%) follow up data was unavailable. Of the remaining 95 patients, 56 (58%) were female. The mean age was 44 (range 17–69). In all, 72 (76%) WCEs were negative. The mean follow up was 13 months (range 8–24). Of the 72 negative tests, three patients (4%) were later diagnosed with CD, following histological confirmation one year after WCE. Of the 23 positive WCE investigations, 20 (87%) have a confirmed diagnosis of CD. The negative and positive predictive values are 96% and 87%, respectively. A univariate analysis using Pearson’s coefficient showed a strongly positive correlation between results of WCE and subsequent clinical diagnosis (0.828 p < 0.01). Of interest, the Harvey Bradshaw Index (HBI) and CRP were both poorly correlated with WCE findings and final diagnosis.

Discussion/Conclusion: Our data suggests that WCE is a reliable tool in effectively out-ruling the diagnosis of CD where baseline investigations have been inconclusive. The poor correlation between the HBI and CRP with WCE findings suggests the possibility of a reservoir of small bowel disease not previously recognised and poorly correlated with current established tests.
Differences in full blood count parameters at paediatric inflammatory bowel disease diagnosis: A pilot case-control study

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Introduction: Whole blood analysis during functional and epigenetic profiling in inflammatory bowel disease (IBD) may be influenced by differing cell proportions and other cell properties. We aimed to determine differences in full blood count (FBC) indices in a cohort of children undergoing endoscopy for suspected IBD.

Methods: Children (< 18 years) undergoing their initial diagnostic endoscopy for suspected IBD were identified from our prospective IBD database and local endoscopy lists. Case-note review and laboratory records were used to ascertain FBC results obtained closest to diagnostic endoscopy. Regional paediatric haematology laboratory normal values for age were used. The R statistical package was used for analyses.

Results: 50 IBD cases (28 Crohn’s disease, 14 ulcerative colitis and 8 IBD-unclassified) and 50 controls (all with endoscopy determining a non-IBD diagnosis or normal findings) were included. For all patients the median time from diagnostic scope to blood sampling was 2 days (IQR 0–34). There were significant differences between cases and controls in the proportion of neutrophils (69.4% vs. 47.7%, p < 0.0001), lymphocytes (19.6% vs. 41.5%, p < 0.0001) and eosinophils (1.0% vs. 2.2%, p = 0.013); there were no differences in monocyte or basophil fractions. The neutrophil:lymphocyte ratio for cases (3.35) and controls (1.18) were significantly different (p < 0.0001). There were also differences with regard to low haemoglobin (64% vs. 12%, p < 0.0001), low haematocrit (52% vs. 16%, p < 0.001), low mean cell volume (54% vs. 10%, p < 0.0001), high total white cell count (24% vs. 2%, p = 0.002) and high platelet count (44% vs. 12%, p < 0.001).

Discussion/Conclusion: Delineation of FBC indices and peripheral blood composition of both suspected and confirmed paediatric IBD patients are important and relevant, with a high neutrophil:lymphocyte ratio prompting further assessment if indicated. Future functional and epigenetic research will most likely require analysis of specific white blood cell subtypes to determine aetiopathogenetic pathways.
The effect of commonly used IBD drugs on autophagy induction using an in vitro cell culture system

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Introduction: Genome wide association studies and functional experiments in inflammatory bowel disease (IBD) have delineated the importance of the autophagy pathway in IBD pathogenesis. We aimed to determine the effect of commonly utilised IBD drugs on autophagy induction and the pathways involved using an in vitro cell culture system.

Methods: HEK293 and HCT116 cells stably expressing green fluorescent protein-labelled light chain 3 (LC3) were treated with varying concentrations of 6-thioguanine, azathioprine, methotrexate or infliximab at different time points; rapamycin, serum-starvation and bafilomycin served as positive controls. Cells were also co-cultured with ERK (U0126) and autophagy (3-methyladenine) inhibitors were appropriate. For immunofluorescent microscopy images were captured using an Axioskop 2 fluorescent microscope and ImageJ software used to identify cells with > 5 punctate foci indicating autophagy induction. For western blot analysis cell lysates were immunoblotted with antibodies to LC3, p62, phospho-rpS6 or total S6. All statistical analyses were performed using GraphPad Prism.

Results: All four drugs induced significant autophagy induction in HCT116 cells, with only azathioprine inducing autophagy robustly in both cell lines. Azathioprine induced autophagy in a dose-dependent manner in HEK293 cells with significant autophagy induction at all concentrations (30–90 μM) in HCT116 cells. HCT116 cells treated with 6-thioguanine, azathioprine and methotrexate showed strong LC3-I to LC3-II conversion and a reduction in p62, with 6-thioguanine and azathioprine showing loss of phospho-S6K suggesting autophagy induction through the mTOR pathway. Use of U0126 and 3-MA in HCT116 cells treated with azathioprine demonstrated that azathioprine may exert its autophagic effect via mTOR through the class I PI3K/Akt pathway.

Conclusions: Commonly used IBD drugs effect autophagy induction in an in vitro cell culture system suggesting that manipulation of the autophagy pathway may be partly involved in the mechanism of action of many of these drugs. Further work is now required to replicate these findings and further delineate the pathways in vivo.
The diagnostic accuracy of combining faecal calprotectin with common blood tests in the investigation of suspected paediatric inflammatory bowel disease

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Introduction: FC has better diagnostic accuracy than individual blood parameters in suspected paediatric inflammatory bowel disease (PIBD). We aimed to determine the diagnostic accuracy of a panel of PIBD biomarkers using a case-control design.

Methods: Cases of PIBD have been recorded prospectively since 1997, with FC available since 01.01.05. A retrospective search of the PIBD database and endoscopy records (01.01.05–31.12.11) identified PIBD and non-PIBD (control) cases (> 1 yr and < 18 yr) with FC and haemoglobin, WCC, platelets, albumin, ESR and CRP taken in the 6 months prior to upper and lower endoscopy for suspected PIBD. Children with known gastrointestinal disease or who had undergone previous endoscopy were excluded. Statistics were performed using R and GraphPad Prism.

Results: 221 children were included, with 108 cases of PIBD (69 Crohn's disease, 28 ulcerative colitis, 11 IBD-unclassified). The PIBD groups were older at endoscopy (12.7 yr vs 9.9 yr) but TI intubation rates were comparable. Indications for endoscopy in the control group included abdominal pain, rectal bleeding and diarrhoea; minimum follow up was 16 months. Median FC level in the PIBD group was 1235 µg/g (IQR 684–1667) compared to 60 µg/g (20–155) in controls (p < 0.0001). Sensitivity and specificity for FC alone (> 50 µg/g) were 0.97 (95% CI 0.92–0.99) and 0.48 (95% CI 0.38–0.57) compared to the best blood parameter (ESR) at 0.71 (95% CI 0.61–0.79) and 0.86 (95% CI 0.78–0.92). Combining an abnormal ESR or abnormal FC provided a sensitivity of 0.99 (95% CI 0.93–1.00) with specificities of 0.38 (95% CI 0.28–0.47) and 0.69 (95% CI 0.59–0.77) using > 50 µg/g and > 200 µg/g FC cut-off values.

Discussion/Conclusion: FC provides excellent sensitivity and moderate specificity for PIBD but diagnostic accuracy is improved when combining an abnormal ESR (> 20 mm/hr) and a FC cut-off of > 200 µg/g; the addition of certain symptoms such as rectal bleeding would likely improve this diagnostic utility.
Influence of early therapy and other risk factors at diagnosis on relapse and surgery rate in children with Crohn’s disease

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Introduction: The aim of this study was to evaluate risk factors associated with the relapse rate in the first year and the need for surgery in children with Crohn’s disease (CD).

Methods: Data of all children (n = 74) diagnosed with CD from January 2004 to June 2011 was retrospectively analyzed. Cox proportional hazard regression model was used to assess independent risk factors at diagnosis (age, gender, disease location, presence of perianal disease, Pediatric Crohn’s Disease Activity Index [PCDA] score, CRP, ESR, fibrinogen, height for age standard deviation score [SDS] and weight for height SDS, induction and maintenance therapy) associated with the relapse in the first year as well as risk for surgery.

Results: The relapse occurred in 36 (48.6%) patients in the first year from diagnosis. Only significant parameter associated with negative risk of relapse in the first year was exclusive enteral nutrition (EEN) used as induction therapy (HR 0.462, 95% CI 0.230–0.928). EEN led to remission in 84.2% of patients. The only risk associated with treatment failure was the involvement of the upper gastrointestinal tract. During the follow-up, 25 (33.7%) children underwent surgery. Identified risk factors associated with surgery were high CRP levels and low weight for height SDS score at diagnosis (HR 1.011, 95% CI 1.001–1.021 and HR 0.678, 95% CI 0.521–0.883).

Discussion/Conclusion: This study underlines the importance of early EEN in the treatment of CD; it is not only efficacious in the remission induction but also prevents relapses in the first year of the disease.
Is rifaximin effective in maintaining remission in Crohn’s disease?

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Introduction: Recent studies indicate that the persistent intestinal inflammation in patients with Crohn’s disease (CD) might be caused by abnormal intestinal microbiota. This hypothesis could suggest the use of antibiotics in therapy. So far guidelines do not recommend antibiotics except for the treatment of complications in CD and few studies have been made on the effects of rifaximin in such patients.

Methods: Between December 2011 and December 2012 we performed a double-blind randomized trial on 168 patients with moderately active CD concerning the efficacy of rifaximin. All the patients previously achieved remission with standard therapy (prednisone/budesonide). Data from patients receiving 800 mg of rifaximin (83 patients) twice a day for 12 weeks were compared with those from patients who received placebo (83 patients). The primary end-point was maintaining remission during the follow-up.

Results: 100% (83 of 83) from the patients who received 800 mg of rifaximin were in remission after 12 weeks of treatment in comparison with 84% (70 of 83) from the placebo group. This significant difference was persistent also at 24th week follow-up (78% [65 of 83] vs. 41% [34 of 83]). The last evaluation performed at 48 weeks revealed disease activity in 45% (38 of 83) of the patients from the rifaximin group, less than in the placebo group (75% [63 of 83]).

Discussion/Conclusion: Remission previously obtained with standard treatment can be sustained in patients with moderately active CD after the administration of 800 mg of rifaximin.
The routine measurement of thiopurine metabolite levels results in dose optimisation in one third of IBD patients: Results from a district general hospital

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Introduction: Measuring azathioprine or mercaptopurine (AZA) metabolite levels 6-TGN and 6-MMPN allows identification of patients who are: 1. Non-compliant with their medication, 2. On a sub-optimal dose, 3. On a supra-therapeutic dose, 4. Are preferentially metabolising azathioprine to methylated metabolites (6-MMPN:6-TGN ratio > 11). Our own and others published data demonstrate that measuring metabolite levels in patients failing azathioprine therapy followed by appropriate changes in dosing and/or the addition of allopurinol (with 75% dose reduction in AZA) can result in clinical remission in the majority of patients 1. We report the outcome of the routine measurement of metabolite levels in patients treated with AZA who were in a clinical remission without side effects or abnormal liver function tests (LFTs).

Methods: All patients underwent TPMT testing, azathioprine and mercaptopurine were initiated at doses of 2 mg/kg and 1 mg/kg respectively in those with wild-type TPMT with a 50% reduction in dose in TPMT heterozygotes. We searched the prospective database maintained by our biochemistry department for all patients who underwent metabolite level testing from September 2011 to November 2012; hospital case notes for these patients were reviewed. The indications, results of testing, changes in clinical management and patient outcomes were recorded.

Results: 108 patients underwent metabolite testing, median length of follow-up since testing was 287.6 days (range 21–441), all were stable on AZA for > 4 weeks with normal LFTs and in a clinical remission. 38 (35.2%) had UC, 66 (61.1%) CD, 52 (48.1%) were male. 17 (15.7%) patients had a sub-therapeutic 6-TGN, 10 (9.3%) supra-therapeutic 6-TGN level (> 800) all of whom had dose optimisation. 6 (5.6%) patients were hypermethylators, these were switched to allopurinol co-therapy with an appropriate reduction in AZA dose.

Discussion/Conclusion: In the present study the routine measurement of AZA metabolites resulted in a change in clinical management in 30.6% of patients. Whilst unproven in prospective longitudinal studies logic suggests that the routine measurement of AZA metabolites in all patients commenced on thiopurines followed by appropriate dose optimisation (with or without allopurinol co-prescription) should reduce or prevent the development of drug side effects, abnormal LFTs and bone marrow suppression and reduce the risk of disease relapse. We recommend that AZA metabolite testing is performed in all patients 4–6 weeks after commencing AZA.

Disclosure of Interest: None Declared
Low-dose thiopurine and allopurinol co-therapy results in significant cost savings at a district general hospital

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Introduction: Thiopurines are used for maintenance of remission in IBD. In England and Wales biologics are approved by NICE (National institute for health and clinical excellence) for Crohn’s disease (CD) but not ulcerative colitis. Adalimumab is recommended in preference to infliximab in patients over 65 kg due to cost. Published data report > 50% of patients stop thiopurines due to therapeutic failure, hepatitis or side effects. In this situation most UK clinicians start biologics in CD patients. This has significant cost implications. An alternative treatment strategy is low dose thiopurine and allopurinol (LDTA) co-therapy which is effective in most patients who fail standard dose thiopurines. Some patients require liquid thiopurine to achieve the correct (low) dose – this formulation is significantly more costly than tablets. We report the annual cost savings from adopting this strategy at our centre.

Methods: We maintain a prospective IBD database. Patients with CD treated with LDTA in preference to biologic therapy were identified. The annual drug costs of their treatment with LDTA compared with biologic therapy (adalimumab for patients over 65 kg, infliximab for patients < 65 kg) were calculated including the cost for the formulation of thiopurine used (liquid/capsule/tablets) and the dose prescribed. Costs of attending the day unit for an infusion were not included.

Results: 17 CD patients who failed standard thiopurine and were eligible for biologics were identified over a 1 year period (September 2011–September 2012). Of these 4 (24%) failed LDTA and progressed to biologics, 13 (76%) entered a sustained clinical remission. Mean weight of patients = 77.3 kg (range: 53.5–105 kg), 6 (46%) patients required a liquid thiopurine. Mean calculated costs were: thiopurine £451.95 (range: £48.48–£1345.44). Biologic: £11,331 (range: £10,560–£16,081). Mean cost saving per patient: £10,879 (range: £9,215–£15,146). Total cost saving: £141,427.

Discussion/Conclusion: We have previously reported that low dose thiopurine and allopurinol co-therapy is safe and effective. In the present study we have identified significant annual cost savings can be made when this treatment strategy is used to prevent escalation to biologics. These cost savings are likely to be even more significant in the long term since a significant proportion of patients treated with biologic therapy require dose escalation. We believe adopting this strategy more widely could lead to significant health-care savings.

Disclosure of Interest: None Declared
Long term outcome of azathioprine therapy in 353 consecutive IBD patients

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Introduction: Thiopurines are the mainstay of therapy in Inflammatory Bowel Disease (IBD). Azathioprine (AZA) and Mercaptopurine are very effective at maintaining remission but have a wide range of side effects which can limit their use as long term maintenance therapy. To assess how effective AZA was in IBD, and what its limitations were, the outcome of 353 consecutive IBD patients started on AZA with at least one year follow up was assessed.

Methods: Since 2005 all patients started on AZA for IBD have been recorded and monitored. These data were then used to assess the outcomes of patients where there had been at least one year of follow up. Outcomes recorded were whether AZA was still being taken or not. If still being taken information about the disease activity was recorded. If AZA therapy had been discontinued then the reason for this was recorded and subsequent therapeutic interventions noted.

Results: 353 patients had started AZA and had at least one year of follow up. TPMT status was checked in all patients. Dosing was as follows: low TPMT; 50 mg and increased as tolerated. Normal TPMT; 2–2.5 mg/kg. Of the 353 patients, 204 had Crohn’s disease (CD), 141 had Ulcerative Colitis and 8 had IBD-unclassified. The male:female ratio was 184:169 (52.1% male). Age range was 16–86 years (mean; 46). 322/353 (91%) remain under follow up. 127 (36%) of patients stopped taking AZA at one year. After six years 152 (43.1%) remained on AZA, 182 (51.6%) had stopped and in 19 (5%) the outcome was unknown. Nausea and myalgia were the main reasons for stopping AZA. 40 (11.3%) patients developed hepatitis (ALT rise > 2 x ULN), 6 (1.7%) developed myelosuppression and 7 (2%) developed pancreatitis (consistent clinical presentation and raised amylase). Of the 182 patients who stopped AZA, 67 (37.8%) had an escalation of therapy – 20 started methotrexate, 18 started biologics and 29 underwent surgery. Of the 152 who continued AZA, 138 (90.8%) were in a clinical remission based on clinical assessment supported by normal C-reactive protein in 126 (91.3%), Harvey Bradshaw Index in those with CD 55 (40%) patients and endoscopic findings in 22 (15.9%). 112 (73.6%) patients had blood monitoring (FBC and LFTs) at least quarterly and 147 (96.7%) at bi-annually.

Discussion/Conclusion: For such an important drug in IBD management a significant number of patients stop AZA due to side effects. This study highlights these so that patients can be accurately informed. It also highlights that AZA when tolerated is a very effective maintenance medication. Published data from our own and other units suggest that low-dose AZA in combination with allopurinol reduces side effects and increases tolerability and may make AZA a more effective long-term maintenance agent.

Disclosure of Interest: None Declared
Features and long term outcomes of our patients with ulcerative colitis

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Introduction and Aim: Ulcerative colitis (UC) is a chronic relapsing and remitting inflammatory disease of the colorectal mucosa. Although incidence of that disease varies between countries, with developing of diagnostic tools, it is getting increased. For that reason early diagnosis, treatment and follow up of the UC is very important. We aimed to present, long term results of a large number of UC patients who were followed up in our clinic, according to the condition of disease and treatment.

Methods: Two hundred forty-seven patients with UC, who have adequate data and regular follow up, were evaluated retrospectively. Demographical features of the patients were recorded, and disease duration after diagnosis, colonic involvement site, extraintestinal involvement, the drugs for treatment, complications and surgery requirement were evaluated. The colon involvement was defined as isolated proctitis, distally colitis, left side colitis and pancolitis.

Results: One hundred forty-one of the patients were male (60%). The mean age of the patients were 44.28 ± 13.63 years old for males and 43.01 ± 14.35 years old for women. The mean disease duration after diagnosis was 4.7 (1–28 years). The mean follow up period was 36 months. According to the involvement sites, 39 (16%) were distally colitis, 155 (63%) were left sided colitis and 53 (21%) patients were pancolitis. Extraintestinal symptoms were: sclerosing cholangitis in three patients (1.2%), pyoderma gangraenosum in 2 patients (0.8%), arthritis in 5 patients (2%) and spondylitis in one (0.4%) patient. Treatment options were: topically and/or oral mesalazine in all patients, mesalazine plus azathioprine in 33 patients, anti-TNF in 3 patients who did not respond to mesalazine plus azathioprine (at least 1 year with exacerbations). 50 patients were taken steroids for 160 exacerbation attacks in following period. 195 patients (78.9%) were steroid-free and at remission since 12 months in following period, only with oral mesalazine treatment (mean dosage was 2.5 grams per day). Major acute complications were: toxic megacolon in two patients which required surgery (0.8%) and venous thrombosis in one (0.38%) patient. Although, pseudopolyps and some flat lesions were seen in 25 and 6 patients respectively, there was no confirmed malignancy at biopsies.

Conclusion: The early diagnosis and beginning the treatment of UC is a crucial condition. Those patients must follow up for exacerbations, complications and malignancy. Effective treatment and regular follow up of the disease will protect undesired conditions. Also, striking situation was that 80% of the patients were at remission under only mesalazine treatment with regular controls since 12 months.
The rs1568885 and rs1813443 polymorphisms are associated with anti-TNF drug response in patients with Crohn’s disease

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Treatment with tumour necrosis factor (anti-TNF) has proven very efficient in patients with Crohn’s disease, however, some patients do not respond for unknown reasons. Identification of these patients before treatment using genetic markers predicting anti-TNF treatment outcome could be an attractive approach. Recently, rs1568885 and rs1813443 polymorphisms have been identified to be associated with response to anti-TNF treatment in patients with rheumatoid arthritis.

Aim: To determine whether these reported loci reflect an association with anti-TNF therapy in Crohn’s disease patients.

Methods: A case-control study in a cohort of 126 Greek patients with Crohn’s disease receiving anti-TNF therapy was performed. Clinical and serological responses were assessed using the Harvey-Bradshaw Index (H-BI) and the serum levels of C-reactive protein (CRP), respectively, at baseline (before the 1st infusion of IFX), the day before each subsequent IFX infusion and after 12 weeks of treatment. The rs1568885 polymorphism was determined using allele-specific PCR.

Results: Eighty patients (63.49%) were classified as complete and 32 (25.39%) as partial responders to IFX, while 14 (11.11%) patients were primary non-responders. The TT genotype of the rs1568885 polymorphism was significantly associated with partial and non-response to anti-TNF status (p = 0.03 and p = 0.016, respectively). Concerning the rs1813443, the CC genotype was significantly associated with non-response to IFX (p = 0.04).

Conclusion: If association with anti-TNF response can be confirmed in additional replication studies, future functional studies are needed to prove the biological link of rs1568885 and rs1813443 polymorphisms with anti-TNF response.
An exploration of the health and social needs of people living with inflammatory bowel disease: A metasynthesis

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Introduction: The Inflammatory Bowel Disease Questionnaire and the Rating Form for IBD Patient's Concerns are widely used measures in IBD but fail to capture the essence of living with IBD from the patient's perspective. To deliver patient centered care it is imperative that we have an understanding of the experience of living with IBD. This study aimed to synthesize the findings of qualitative papers that explored the health and social needs of patients living with IBD.

Methods: CINAHL, British Nursing Index via the OVID platform. 1395 papers were generated by the preliminary search. Qualitative studies which explored the phenomena of living with IBD, English language and sample population adults > 16 years were included. Study eligibility judgments and data extraction were independently completed by the authors. The papers were quality appraised using the Critical Appraisal Skills Programme. Synthesis was achieved by comparing the themes and findings of each study with one another to identify 1st order constructs. Repeated comparison between the papers revealed the similarities and differences, which led to 2nd order constructs and the new interpretation of the synthesised studies.

Results: Six papers and one unpublished thesis were included, all from Western countries, one study included patients from an immigrant background. Combined sample of the studies was only 86 patients to describe the phenomena of living with IBD. First iteration of synthesis identified 16 themes, 2nd iteration synthesised these into three main constructs: 'detained by the disease'; 'living in a world of disease'; 'wrestling with life'. 'Detained by the disease' is the fear of incontinence, and the behaviour the patients displays as a result of this. Social isolation and missing out on life events all serve to 'pull' the patient back from normal living. 'Living in a world of disease' is living with the fear of a long term condition.' Wrestling with life' is the 'push' to continue normal living.
<table>
<thead>
<tr>
<th>1st order constructs</th>
<th>2nd Order constructs</th>
<th>Line of argument synthesis</th>
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<tr>
<td>Limitations/missing out on life events. Humiliation of incontinence Social isolation Unpredictability Powerlessness Feeling damaged Impact on relationships Negative emotions Stress</td>
<td>Detained by disease (&quot;Pull&quot;) <em>Fear of incontinence</em> – unpredictability, humiliation <em>Behaviour due to fear of incontinence</em> – avoidance <em>Impact of behaviour</em> –socially isolated, missing out on life events, limited life, relationship burden, feeling damaged</td>
<td>“Pushed and Pulled: a compromised life”</td>
</tr>
<tr>
<td>A disease for life. Fear of long term effects</td>
<td>Living in a world of disease</td>
<td>Constant conflict between IBD and normal life results in a compromised life. <em>Pushes</em> to be normal but <em>IBD pulls</em> individual back.</td>
</tr>
<tr>
<td>Acceptance yet fight Knowing my body Control Maintaining normality Invisible disease</td>
<td>Wrestling with life (&quot;Push&quot;) Striving to thrive</td>
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**Discussion/Conclusion:** People with IBD endure many daily challenges, stress, pain, fighting for control. The combined impact of living with IBD is the tension they live with. The value of metasynthesis is the interpretation of all of the synthesised studies to provide a global representation of living with IBD: ‘Pushed and pulled: a compromised life’, people living with IBD experience a constant conflict throughout their lives, they push to be normal but IBD pulls them back.
The development of a stratified model of follow up care for adult patients with inflammatory bowel disease

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Introduction: There is concern in the UK that services for pts with long term conditions are not organised to promote independence, with silo working in primary and secondary care with reactive services. These may be brought together formally through the development of models of care. In addition, utilization of current out-pt spaces to regularly review stable pts is inappropriate and is now challenged by commissioners. The question remains as to what models of follow up (FU) are we able to offer pts which are acceptable and feasible. The aim of this study was to develop an integrated, acceptable, modern model of FU care for pts with IBD.

Methods: Using the MRC Framework for complex interventions, development/theoretical phase, qualitative interviews with 24 IBDs (18 pts had CD, and 6 UC, age range 27–72 years, disease duration range 2–40 yr), 20 interviews with purposively selected GPs from across NW England, and 3 IBD Nurses (specialist, advanced practitioner, consultant nurse). Participants were asked about the role of FU in IBD, experience of FU patterns, service delivery, other models of FU. Thematic analysis was undertaken using NVivo 9.0. Analysis of 3 groups of interviews were synthesised by a Cons Gastroenterologist, pt, GP, IBD Nurse, to develop the model of FU care.

Results: There were similarities and commonalities between 3 groups of interviews. Pts did not want to be seen when well, GPs wanted more involvement in care and there is scope for an IBD outreach nurse at interface of primary/secondary care. Discharging quiescent pts into enhanced GP care was acceptable to all, as was the concept of ‘virtual’ clinics. Patients would initiate self referral within the virtual arm whilst pts under GP care would be referred by GP. Pts would be referred as a rapid FU < 7 days and not as a new pt tariff. Complex IBD patients would remain under secondary care. Patients will move across the 3 arms depending on disease.
Discussion/Conclusion: This study provides an acceptable integrated model of FU for pts with IBD. It takes into account UK policy drivers to reduce inappropriate FU, with emphasis on self management and integrating primary and secondary care, placing the pt closer to home, with secondary care emphasis on complex pt management.
IBD patients' partner – How important is their support?

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Introduction: Chronic inflammatory disease of the bowel causes significant distress to the patient and his family. Data assessing the need of these patients for support and sharing with their partners is scares. Our aim was assess patients' view regarding information sharing with their partners.

Methods: All IBD patients treated at the Sheba Medical center between 1.2011 and 1.2013 were asked to fill an anonymous questionnaire. Only patients that had a stable partner and that completed more than 95% of the questionnaire were included.

Results: One hundred thirty four patients filled the questionnaire, of them 101 were included; 53 were men. Mean age: 45 ± 15. 50% had academic education. Only 42% of patients reported that their partner accompanies them to the doctor. 93% of patients share health problems with their partner. 64% would like their partner to receive more medical information, and 70% would like their partner to be more involved. 88% of patients believe that more partners' involvement can help them deal better with the disease. 70% think that support group for partners should be established. No association was found between patients' demographic data to their answers. Patients that felt that their partner's involvement can help them dealing with the disease tended to share with them medical information and wanted them to be more involved in health decisions (p < 0.001)

Discussion/Conclusion: Most IBD patients want their partner to be more involved with their health problems, and believe that greater involvement can help them deal better with their disease. Therefore, more attention should be attributed towards better cooperation with patients' families.
Blockade of the β7 integrin prevents adherence of T lymphocytes to MAdCAM-1 in an in vitro model of vascular microcirculation post-capillary shear flow

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Introduction: The intestinal vascular microcirculation plays a pivotal role in the immune cell dysregulation that drives inflammatory conditions of the gut, including Crohn’s disease and ulcerative colitis. T lymphocyte recruitment, adherence and migration are dependent on the integrin heterodimer α4β7, which binds with high affinity to vascular endothelium expressing MAdCAM-1 prior to lymphocyte diapedesis into the lamina propria. This integrin therefore provides a potential therapeutic target.

Methods: Using Cellix® technology, a dynamic in vitro model was created, testing the potential of β7 integrin blockade to impair lymphocyte adhesion to MAdCAM-1 under shear flow. The Cellix® system comprises a microfluidic platform and nano pump, with specifically designed biochip channels that can replicate the shear flow and stress that cells are exposed to in post-capillary venules. Peripheral blood mononuclear cells (PBMC) were utilised, along with HuT78 T lymphocytes that constitutively express the α4β7 integrin and the chemokine receptor CXCR4, known to be upregulated on T cells in inflammatory bowel disease. Channels were coated for 12 hours at 4°C with 10 μg/ml MAdCAM-1 Fc, then blocked with 0.1% BSA for 30 minutes to prevent non-specific adherence to plastic. Adherence of T cells was quantitatively assessed by microscopy at a physiological flow rate of 1 dyne/cm³. The effect of an anti-human β7 integrin monoclonal antibody (clone Fib504, BD Pharmingen) on lymphocyte adherence was measured. 3nM of the chemokine CXCL12 (ligand for CXCR4) was added to the system to model the pro-inflammatory environment present in inflammatory bowel disease. All experiments were undertaken at 37°C.

Results: HuT78 lymphocytes and PBMC (5 x 10⁶/ml) provided consistent adherence to MAAdCAM-1 under flow, mean ± SE adherent cells/hpf of 32.8 ± 4.5 and 46.2 ± 3, respectively. Adherence was significantly improved with the addition of 3nM CXCL12 to 45.7 ± 2.8 (p < 0.05) and 78.5 ± 1.5 (p < 0.001). Incubating the cells with the Fib504 anti-β7 integrin antibody, led to a significant reduction in adherence of unstimulated cells to 17.8 ± 2 (p < 0.001) and 18 ± 3.2 (p < 0.0001). This reduction was maintained even on stimulation with CXCL12, at 17.3 ± 0.9 (p < 0.001), and 5.3 ± 0.9 (p < 0.0001) respectively.
**Discussion/Conclusion:** This novel *in vitro* model, demonstrated significant modulation of α4β7 lymphocyte adhesion to the ligand MAdCAM-1 with an anti-β7 antibody, maintained on CXCL12 activation. Although this highly controlled model system does not precisely reflect the *in vivo* situation in inflammatory bowel disease, it is a more physiological representation of chemokine driven responsiveness than previously published chemotaxis or adhesion assays, and thus the Cellix® platform may serve as a useful tool for the development and validation of future anti-lymphocyte adhesion therapeutics. This research supports the clinical investigation of therapeutics targeting the β7 subunit or α4β7 heterodimer in this disease setting.
Prevalence and clinical significance of small intestinal bacterial overgrowth in patients with inflammatory bowel disease

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Background/Aim: Clinicians are frequently challenged to interpret diverse gastrointestinal symptoms in patients with inflammatory bowel disease (IBD). Small intestinal bacterial overgrowth (SIBO) is a condition characterized by excessive proliferation of colonic bacterial species in the small bowel, and results in symptoms including bloating, flatus, abdominal pain, diarrhea and/or constipation. The aim of this study was to estimate the prevalence of SIBO and investigate the clinical role of SIBO in IBD patients.

Methods: This study involved 61 patients reporting variable intestinal symptoms with IBD, 36 with ulcerative colitis (UC) and 25 with Crohn’s disease (CD). The glucose breath test (GBT) was performed to diagnose SIBO. All patients completed symptom questionnaires comprised of 13 symptoms. Fecal calprotectin was measured in a single stool sample in all patients. 30 historical healthy controls who were enrolled for determining normal values of GBT at Seoul St. Mary’s hospital in 2007 were used.

Results: Sixteen patients (26.2%) were diagnosed with SIBO based on positive findings at GBT (32% in CD and 22.2% in UC). SIBO was significantly more frequent in patients with IBD than healthy controls (26.2% vs. 6.7%, p = 0.028). SIBO patients reported a higher rate of bloating and flatus (p = 0.013, 0.025, respectively) compared to negative GBT patients. The positivity of GBT was not correlated with fecal calprotectin.

Conclusion: The prevalence of SIBO was higher in patients with IBD than healthy controls, and gastrointestinal symptoms of patients with IBD were correlated with the positivity of GBT. SIBO could be a new therapeutic target for managing intestinal symptoms in IBD patients.

Key words: Inflammatory bowel disease; Small intestinal bacterial overgrowth; glucose breath test
Usefulness of fecal calprotectin in assessing inflammatory bowel disease activity

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Background: Mucosal healing is reported to be associated with sustained remission and reduced risk of surgery in inflammatory bowel disease (IBD). Fecal calprotectin (FC) is known to correlate with disease activity and can be used as a predictor for relapse or treatment response in IBD. We aimed to assess the usefulness of the FC as a marker of disease activity and mucosal healing (MH) in patients with IBD. In addition, we compared a quantitative rapid test (Quantum Blue®) with established ELISA method.

Methods: Seventy nine patients with IBD were enrolled, of which 49 were ulcerative colitis (UC) and 30 were Crohn’s disease (CD). FC levels were analyzed by both ELISA and quantitative rapid test. Patients’ medical records were reviewed for clinical, laboratory and endoscopic data. In UC, MH was defined as a Mayo endoscopic subscore of 0.

Results: The mean FC level was 998.1 ± 1610.1 µg/g in UC and was 1167.3 ± 1317.3 µg/g in CD, respectively. There was a strong correlation between FC level and clinical activity indices (Mayo score and CDAI) (p < 0.001). FC levels showed good correlations with WBC count and C-reactive protein levels. There were no differences in FC levels according to disease location and extension both in UC and CD. FC level was significantly lower in patients with MH compared to those without MH in UC (81.0 ± 59.5 vs. 1039.7 ± 1598.1 µg/g, p = 0.021). The results from a quantitative rapid test corresponded well to those from ELISA.

Conclusions: FC test is a simple and useful method for investigating IBD activity. In particular, FC is a good surrogate marker for MH. The quantitative rapid test, which is more rapid and easier to use, can be used as a reliable alternative to the time consuming ELISA. Thus, FC has the potential to replace colonoscopy for assessment of mucosal inflammation in clinical practice.
Clinical parameters of inflammatory bowel disease in children do not correlate with four polymorphisms of the transforming growth factor beta 1 gene

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Introduction: Transforming growth factor beta 1 (TGF-beta 1) is a cytokine affecting cell proliferation and development, which also has an immunomodulatory activity. Correlations between polymorphisms of the TGF-beta 1 gene and clinical parameters of inflammatory bowel disease (IBD) were reported previously in adults. Here, we tested whether such correlations occur in pediatric patients suffering from IBD.

Methods: One hundred and four pediatric IBD patients were involved in this study. Among them, 36 were diagnosed with Crohn’s disease (CD) and 68 were diagnosed with ulcerative colitis (UC). The control group consisted of 103 children, in which IBD was excluded. TGF-beta 1 levels were determined in plasma and intestinal mucosa samples. The presence of the TGF beta 1 protein and the amount of TGF beta 1 mRNA were estimated in intestinal mucosa by immunohistochemistry (IHC) and reverse transcription real-time PCR, respectively. Four polymorphisms of the TGF-beta 1 gene were investigated: -800G/A, -509C/T, 869T/C and 915G/C.

Results: No significant correlation between TGF-beta 1 genotypes and (i) TGF-beta 1 levels in plasma and tissue samples, (ii) TGF-beta 1 gene expression efficiency in intestinal mucosa, (iii) IBD clinical parameters and (iv) inflammatory activity could be detected in children suffering from IBD. The only statistically significant differences detected were: (i) lower number of -509CT heterozygotes in IBD patients relative to the control group (p = 0.04), (ii) increased platelet count in -509TT homozygotes (p = 0.04), and (iii) increased CRP level in -509CC homozygotes (p = 0.01).

Discussion/Conclusion: The studied four polymorphisms of the TGF-beta 1 gene do not influence the susceptibility or clinical parameters of IBD in the tested population of children.
Cross sectional imaging techniques data compared to per-operative data in patients with Crohn’s disease

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Introduction: Surgical indications in Crohn's disease (CD) should be carefully weighted and intestinal resection should be as short as possible. The operative indications rely, in large part, on the radiological assessment of disease. The aim of this study was to compare cross sectional imaging techniques data to per-operative data in patients with CD and for whom surgery was indicated.

Methods: A retrospective analysis included among all CD patients for whom surgery was indicated between 2007 and 2012, only patients who have had their disease assessed by the mean of cross sectional imaging techniques: computed tomography (CT), computed tomography enterography (CTE), magnetic-resonance imaging (MRI) or magnetic resonance enterography (MRE). Imaging data were compared to those found per-operatively concerning location and length of disease, strictures, fistula, and abscesses.

Results: Forty five patients were included. They were 26 women (58%) and 19 men (42%) with an average age of 33.4 years (14–64). The average time between disease diagnosis and surgery was 1.6 years. Disease location was colic in two cases, ileal in 26 cases and ileocolic in 17 cases. Eleven patients had stricturing disease, 5 patients had penetrating and 29 had both. Surgery was indicated for symptomatic or complicated ileal stenosis in 41 cases, symptomatic colonic stenosis in 2 cases and for a diagnostic purpose in 2 cases. Pre-operatively, 15 patients had CTE, 24 had MRE, 5 had CT and one patient had MRI. The average time to surgery was 28.9 days. Cross sectional imaging data were consistent with per-operative data for the extent of disease in 35 patients (77%) and in 37 patients (82%) for stenosis. Regarding any fistula presence and their tracks, imaging data and per-operative observations gave similar results for 62% of cases. Cross sectional imaging had overestimated fistula in 12 patients, had not found per-operatively described fistula in 3 patients and had incorrectly described the fistula tracks in 3 patients.

Discussion/Conclusion: In this study, cross sectional imaging data were not consistent with per-operative data in 53.33% of the cases. This discrepancy concerned mainly the fistula tracks description and the exact extent of disease.
Could we predict surgery in acute severe colitis?

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Introduction: Acute severe colitis should be considered as a medical emergency and can be life-threatening. While many patients with acute severe colitis will respond to a short course of intravenous corticosteroids, up to a third will fail to improve and may require urgent colectomy. The purpose of this work was to identify predictive factors of surgery after first and second-line medical treatment failure.

Methods: We conducted a retrospective study recruiting patients admitted in our department between 2002 and 2007 for in-patient management of acute severe colitis. The diagnosis of acute severe colitis was attested according to the Truelove and Witts criteria. Response to intensive medical treatment was assessed by analysis of clinical and biochemical data on days 3 and 7. Data were entered and analyzed using statistical package software (SPSS version 19.0).

Results: Sixty-two patients were included. They were 23 men and 39 women with a mean age of 36 years (14–78 years) at acute severe colitis diagnosis. They were 28 patients with Crohn’s disease, 31 with ulcerative colitis and 3 with indeterminate colitis. Medical treatment failure was observed in 12% of the patients. We looked for clinical, biological and endoscopic parameters predictive of surgery after first and second line medical therapy failure. In univariate analysis, no predictive factor of surgery was found.

Discussion/Conclusion: This study shows that in an early stage clinical, biological and endoscopic parameters couldn’t predict colectomy in acute severe colitis although severe endoscopic lesions were classically regarded as predictive factors of surgery. This result must prompt us to a close monitoring of all patients in order to determine the optimum timing for colectomy.
Are outcomes for adults and children undergoing resection for inflammatory bowel disease comparable?

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Introduction: The prevalence of inflammatory bowel disease (IBD) in Europe is 505 per 100,000 for ulcerative colitis and 322 per 100,000 for Crohn's disease. Up to 40% of patients will require surgery for their disease, the majority within the first year of diagnosis. Since 2007, a single surgeon whose main practice is in adults has performed resection surgery for IBD in adults and children within separate dedicated adult and paediatric IBD multidisciplinary teams in a tertiary referral centre. Our aim was to assess short-term outcomes for adults and children following resection surgery for IBD.

Methods: Analysis of a prospectively collected database was carried out to include all patients who had undergone resection surgery for IBD (excluding stoma formation alone) by a single surgeon between December 2007 and July 2012.

Results: Seventy-eight patients underwent surgery over the period (30 children and 48 adults). Median age for children was 14 years (range 8–16 years) and adults 33.5 years (range 17–64 years). The median BMI in adults was 23 (range 18–38) and 19 (range 13–29.5) in children (p < 0.0001). Laparoscopic resection was performed in 27 (90%) children and 36 (75%) adults (p = 0.14). Six (7.7%) operations were converted to open, all in the adult group (p = 0.08). Operative time was longer in adult cases (210 vs. 175 minutes [p = 0.03]). Postoperative complication rates were comparable: 11 (23%) in the adult population versus 6 (20%) in children (p = 1.00). There were 2 Anastomotic leaks, both occurring in the adult group. Median length of stay was 5 days in adults versus 6.5 days in children (p = 0.31).

Discussion/Conclusion: Resectional IBD surgery in children is safe when performed by an experienced surgeon whose normal practice is in adults, with good outcomes when compared to the adult population. The longer operating time for adults likely reflects the higher BMI in this group.
Risk factors for symptom relapse in collagenous colitis after withdrawal of short-term budesonide therapy

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**Background and Aim:** Oral budesonide has been proven effective in short- and long-term treatment of collagenous colitis; however, symptom relapse frequently occurs after drug withdrawal. The aim of this study was to identify risk factors for symptom relapse in collagenous colitis after withdrawal of short-term budesonide therapy.

**Methods:** 123 patients from 4 randomized controlled who achieved clinical remission after short-term treatment with budesonide (9 mg/day) were analyzed, including 40 patients receiving subsequent budesonide maintenance therapy (6 mg/day) for 6 months and 83 patients without active maintenance treatment. Variables available for analysis were age, gender, baseline stool frequency, duration of diarrhea, collagenous band thickness, and lamina propria inflammation. Hazard ratios (HR) were calculated by logistic regression analysis with 95% confidence intervals.

**Results:** The overall symptom relapse rate was 61%. By multivariate analysis, a baseline stool frequency > 5/day (HR 3.95; 1.08–14.39), a history of diarrhea > 12 months (HR 1.77; 1.04–3.03), and the absence of budesonide maintenance therapy (HR 2.71; 1.37–5.38) were associated with symptom relapse. The time to relapse was shorter in patients with a baseline stool frequency > 5/day (56 vs. 199 days, \( p = 0.024 \)), as in those with a history of diarrhea > 12 months (56 vs. 220 days, \( p = 0.009 \)). Budesonide maintenance therapy delayed the time to relapse (56 vs. 207 days, \( p = 0.005 \)).

**Conclusion:** Our data demonstrate that a high stool frequency at baseline and a long duration of diarrhea are risk factors for symptom relapse in collagenous colitis, while budesonide maintenance therapy is a protective factor against symptom relapse.
Randomized, placebo-controlled multicenter study of budesonide and mesalamine for short-term treatment of collagenous colitis

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Background: Budesonide is effective for the treatment of collagenous colitis: However, the studies that provided evidence thereof were small and differed in efficacy measures. Mesalamine has been proposed as a treatment option for collagenous colitis although its efficacy has never been investigated in placebo-controlled trials.

Objective: To evaluate budesonide and mesalamine for short-term treatment of collagenous colitis in a placebo-controlled multicenter study.

Methods: Patients with active collagenous colitis randomly received either pH-modified release oral budesonide capsules (9 mg budesonide once daily; Budenofalk⁵) or mesalamine granules (3 g mesalamine once daily; Salofalk⁶) or placebo for 8 weeks in a double-blind double-dummy fashion. The primary endpoint was clinical remission (CR) at 8 weeks defined as ≤ 3 stools/d. Secondary endpoints included CR according to the Hjortswang-Criteria of disease activity, which also take stool consistency into account.

Results: Ninety-two patients were randomized. The proportion of patients in CR at week 8 was higher with budesonide than with placebo (intention-to-treat 80.0% vs. 59.5%, \( p = 0.072 \), per protocol 84.8% vs. 60.6% \( p = 0.046 \)). According to the Hjortswang-Criteria, CR was achieved in 80.0% with budesonide and 37.8% with placebo (\( p = 0.0006 \)). Mesalamine was not better than the placebo (CR 44.0%), but budesonide was superior to mesalamine (\( p = 0.0035 \)). Budesonide significantly improved stool consistency and histology, and alleviated abdominal pain. The rate of adverse events did not differ among the three treatment groups.
Conclusion: Oral budesonide (9 mg OD) is effective and safe for short-term treatment of collagenous colitis, while short-term treatment with oral mesalamine (3 g OD) appears to be ineffective.
Do we need a “Montreal” classification in ulcerative colitis?

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Introduction: Ulcerative colitis (UC) is a chronic disease with extremely varied clinical manifestations. The aim of the study was to assess the impact of age on the phenotype, activity and treatment of UC.

Methods: A prospective study included 105 patients newly diagnosed with UC, hospitalized between January 2010 and December 2012. We have noted: age, sex, area of origin, status smoker/non-smoker, presenting symptoms, presence of inflammatory syndrome, the extension of lesions, severity, treatment, complications. All the patients were examined by colonoscopy and diagnosis of UC was confirmed histologically. The activity of the disease was quantified using Truelove and Witts clinical score of: mild, moderate and severe.

Results: Patients were divided into 3 groups according to the age: group 1: 51 patients under 40 years, group 2: 36 patients, aged between 41 and 64 years and group 3: 18 patients over 65 years. Characteristics of extreme groups were followed by age (young under 40 years and elderly over 65 years), to clarify whether there are significant differences between them on UC behavior. In both groups were predominantly men from urban area. The smoking status was more common in younger patients than elderly, but no statistically significant differences (18/51 vs. 6/18, p = 1). Regarding the symptoms of debut, in the young prevailed abdominal pain (younger vs. older 58.8% vs. 41.8%, p = 0.09), and in the elderly bloody diarrhea (66.67% vs. 41.1%, p = 0.089). Proctitis was met in 2.94% of the cases (only in the elderly) and left-sided colitis and pancolitis were more prevalent in young patients (52.17% vs. 18.8% for left sided colitis respective 29.4% vs. 16.66% pancolitis). As severity, there is a significantly large number of moderate to severe forms of the young versus elderly (60.8% vs. 13.04%, p = 0.028). There were no differences between inflammatory syndrome (CRP and fecal calprotectin) and complications between younger and elderly patients. 14.49% patients received only aminosalicylates, all elderly patients. The necessary of introducing corticosteroids and biological therapy was increased in young people with moderately severe forms of disease (corticosteroids: 47.05% vs. 16.67%, p = 0.0270; biological agents: 23.52% vs. 5.55%, p = 0.0279).

Discussion/Conclusion: A more aggressive phenotype with extensive localization of lesions, more severe activity and increased need for steroids and biological therapy was seen in younger patients. Elderly patients experienced mild forms, with limited extension of the lesions, and the majority were able to remain in remission only with aminosalicylates. UC seems to have different behavior in young and elderly patients.
Prevalence of extraintestinal manifestations in patients with inflammatory bowel diseases

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Introduction: Inflammatory bowel diseases (IBD) (ulcerative colitis and Crohn’s disease) may be associated with extraintestinal manifestations.

Aims of study: The aim of this study was to investigate the prevalence, type and time of onset of extraintestinal manifestations in patients with ulcerative colitis and Crohn’s disease.

Patients and Methods: 136 patients with IBD entered this study between January 2008 and March 2012. Statistics analysis pointed out the prevalence of male (84 patients); mean age was 41.3 ± 7 years. The research protocol contained clinical, biological, complete imagistic evaluation, neurological and endoscopic exams.

Results and Discussions: 136 consecutive IBD outpatients were retrospectively studied. Of this 107 patients (79%) were affected by ulcerative colitis and 29 patients (20.4%) by Crohn’s disease. Extraintestinal manifestations were observed in 59 patients with ulcerative colitis and 21 with Crohn’s disease, with a prevalence of 55.1% and 72.4% respectively. The extraintestinal manifestations found were: 46 arthritis (ulcerative colitis 28.9% and Crohn’s disease 51.7%), 17 uveitis (ulcerative colitis 7.4% and Crohn’s disease 24.1%), 14 erythema nodosum (ulcerative colitis 5.6% and Crohn’s disease 27.4%), 5 ankylosing spondylitis (ulcerative colitis 1.8% and Crohn’s disease 3.7%), 2 Hashimoto thyreoiditis (ulcerative colitis 0.9% and Crohn’s disease 3.4%), 2 pyoderma gangraenosum (ulcerative colitis 0.9% and Crohn’s disease 3.4%). Other extraintestinal manifestations found were 5 sclerosing cholangitis (ulcerative colitis 2.8% and Crohn’s disease 6.8%) and 3 pyoderma gangraenosum (ulcerative colitis 1.8% and Crohn’s disease 3.7%).

Conclusions: Extraintestinal manifestations in IBD were frequently. These manifestations were significantly more frequent in Crohn’s disease than in ulcerative colitis, in particular arthritis, uveitis, erythema nodosum, sclerosing cholangitis and ankylosing spondylitis.
Sirolimus use in children with refractory inflammatory bowel disease

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Introduction: Refractory inflammatory bowel disease (IBD) in children is challenging to treat with limited therapeutic options.

Methods: A retrospective review of medical records of all patients with IBD on sirolimus (23 patients) between 2006 and 2012. Clinical response was assessed by PUCAI or PCDAI scored at baseline and 3 months after induction of sirolimus. Endoscopic and histological findings before starting sirolimus were compared to the next available endoscopy at least 3 months later. A total of 8 cases were excluded, 6 due to incomplete data and 2 due to short treatment time.

Results: Four patients were Crohn’s disease (CD), 11 were ulcerative colitis (UC). Nine were males, 6 were females. The mean average age of onset of disease was 8.7 years. The mean number of years after diagnosis until induction with sirolimus was 3.1 years. Before commencement of sirolimus all patients had failed standard medical therapy and all stayed on conventional treatment. 8/11 patients with UC had a response shown by improvement in their PUCAI score at 3 months, 3/11 had no response. Of the responder, 2 achieved remission with concomitant administration of basiliximab, 1 was started on mycophenalate while the fourth child required parenteral nutrition. 3/8 responders and 2/3 non-responders went on to have colectomys. One patient was weaned off adalimumab. Of the patients with CD 3 had a clinical response on PCDAI scores. One CD patient was weaned off prednisolone and one was weaned off methotrexate. Endoscopy results did not appear to correlate well with PCDAI/PUCAI scores, however, these were not performed at standard intervals; many were performed during flare ups and well after the 3 month period when the scores were calculated. 5/11 patients with UC and one CD patient achieved histological mucosal healing.

Discussion/Conclusion: We demonstrated clinical and histological response to sirolimus in children with refractory IBD.
Correlation of the pediatric indexes of IBD activity with common indices of the intestinal inflammation

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Introduction: Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn’s disease (CD), is a group of chronic autoimmune disorders. Pediatric Ulcerative Colitis Activity Index (PUCAI) and Pediatric Crohn’s Disease Activity Index (PCDAI) are validated instruments used to estimate current disease status. The aim of study was to evaluate correlation of PCDAI and PUCAI with C-reactive protein (CRP), hematocrit (Hct), white blood cells (WBC), hemoglobin (Hb), platelets (PLT), erythrocyte sedimentation rate (ESR) and total IgE (tIgE).

Methods: IBD was diagnosed on the basis of Porto criteria. Pediatric disease activity indexes (PUCAI and PCDAI) were assessed in all study children. Blood samples were collected from the children with UC (n = 17) and CD (n = 19) for the purpose of diagnostic examinations. Biochemical and hematological parameters were determined with standard laboratory techniques. Correlation between the independent parameters was evaluated using non-parametric Spearman’s correlation test. Data are median and range.

Results: In children with UC disease activity index ranged from 5 to 65, median 30.6. PUCAI correlated with Hb, Hct and PLT (r = -0.73, p = 0.001; r = -0.77, p = 0.001; r = 0.53, p = 0.036, respectively). In children with CD disease activity index ranged from 2.5 to 52.5, median 31.7. PCDAI correlated only with CRP (r = 0.59, p = 0.008). There was no significant correlation of tIgE, ESR and WBC with both PCDAI and PUCAI.

Discussion/Conclusion: Current pediatric disease activity indexes, in contrast to adults CDAI and UCAI, use mostly subjective data, with except of Hct, ESR and albumin level in PCDAI. Our data suggest statistically significant correlation between PUCAI and Hb, Hct and PLT, and between PCDAI and CRP. Determination of these parameters may be helpful in the evaluation of disease activity in children with UC and CD.
Fecal lactoferrin as a differentiation marker between ulcerative colitis and irritable bowel syndrome

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Introduction: This study was designed to estimate fecal lactoferrin (LF) concentration and to evaluate its clinical applicability as non-invasive modality for differentiation between cases with ulcerative colitis (UC) and irritable bowel syndrome (IBS) and its relation to disease activity.

Methods: The study included 30 patients with UC and 30 patients with IBS and 15 healthy volunteers as controls. All patients were evaluated clinically for disease activity and underwent colonoscopy for diagnosis assurance. The study participants supplied fresh fecal samples for qualitative and quantitative assay for LF.

Results: There was a significant (p < 0.05) increase of fecal LF in patients with UC (1118.2 ± 277.8 μg/gm feces) compared to controls (1.35 ± 0.48 μg/gm feces) and IBS patients (1.33 ± 0.36 μg/gm feces). Moreover, there was a significant (p < 0.05) increase of fecal LF in patients with active UC compared to those with inactive UC, whereas non-significantly (p > 0.05) different in patients with active IBS compared to those inactive IBS. Furthermore, there was a significant correlation between fecal LF level and score of severity of inflammation in patients with UC (r = 0.623, p = 0.013), whereas the correlation was non-significant in patients with IBS, (r = 0.225, p > 0.05). Determination of LF could identify patients with UC with sensitivity of 93.3%.

Discussion/Conclusion: Fecal LF could differentiate between patients with UC and IBS with specificity 100% and accuracy 97.8% and quantitative estimation of its level could define cases with active UC.
Outcomes after ileal pouch anal anastomosis in patients with primary sclerosing cholangitis

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Introduction: The function and quality of life outcomes in patients with primary sclerosing cholangitis (PSC) and ulcerative colitis (UC) who undergo ileal pouch-anal anastomosis (IPAA) are not well established. Reports conflict about the incidence of pouchitis in patients with PSC and IPAA, with few data on quality of life. This study investigated function and quality of life outcomes in patients with PSC and IPAA.

Methods: Patients with PSC-associated UC who underwent IPAA (PSC-IPAA) between 1983 and 2012 were compared to patients with UC without PSC who underwent IPAA in the same period, for pouch dysfunction, acute pouchitis, surgical complications, incidence of pouch dysplasia or cancer and biologic therapies or immunomodulators for treating pouch dysfunction. Baseline demographic and surgical characteristics were recorded. The Öresland score and Cleveland Global Quality of Life Questionnaire (CGQOL) were used to establish self-reported pouch function and the impact of IPAA on quality of life. Quality of life was also assessed by SF-36 (V1.0) questionnaire, including patients with PSC-associated UC without IPAA (PSC-UC) as a reference group.

Results: Thirteen patients with PSC-associated UC and 79 patients with UC underwent IPAA (UC-IPAA) in the period. More patients with PSC had pancolitis (62% vs. 30%) and more underwent colectomy for dysplasia or cancer (23% vs. 3%). Trends for more patients with PSC-IPAA to suffer pouch dysfunction (69% vs. 47%; p = 0.231), acute pouchitis (46% vs. 20%; p = 0.073) or receive biologic or immunomodulator therapy (23% vs. 5%; p = 0.06) were not significant. Normal Q-Q plots to check the assumption of normality for the Öresland score gave a plausible linear relationship so a two sample t-test was used to compare the means of the two groups. The mean Öresland score for PSC-IPAA was 7.00 compared to 5.62 in patients with UC-IPAA (p = 0.07). The two groups had similar mean CGQOL scores (PSC-IPAA 0.73; UC-IPAA 0.75; p = 0.63). Mean Physical Health Summary (PCS) and Mental Health Summary (MCS) scores from SF-36 for PSC-IPAA versus UC-IPAA were 41.9 versus 48.0 (p = 0.04) and 41.4 versus 47.6 (p = 0.03), respectively. The mean PCS and MCS scores for patients with PSC-UC were 44.4 (p = 0.65 vs. PSC-IPAA and p = 0.11 vs. UC-IPAA) and 43.5 (p = 0.33 vs. PSC-IPAA and p = 0.07 vs. UC-IPAA).

Discussion/Conclusion: Patients with PSC-IPAA have a trend to worse pouch function compared to patients without PSC, although this did not reach statistical significance, probably due to small numbers. Overall quality of life in patients with PSC-IPAA assessed by SF-36 (V1.0) and pouch function assessed by the Öresland score are significantly worse compared to patients with UC-IPAA.
Screening for current, latent and opportunistic infection prior to initiating anti-TNFα treatment in the IBD population

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Introduction: There is a lack of clarity on which screening tests for opportunistic infection should be performed prior to commencing immunosuppressants in the inflammatory bowel disease (IBD) population. The European Crohn’s and Colitis Organisation (ECCO) have published an evidence-based consensus on screening and recommend testing for hepatitis B and tuberculosis (TB) in all patients and considering testing for HIV. Emerging evidence of the benefit for screening patients for Epstein-Barr virus (EBV) has so far only partially changed practice. Checking stool cultures or HIV serology has not been part of our protocol to date.

Methods: At Queen Elizabeth Hospital we introduced a safety questionnaire in October 2010 and started routine screening for latent and opportunistic infections (hep B, hep C, TB and varicella zoster virus [VZV]) prior to commencing anti-TNFα drugs. We audited compliance with our recommended screening tests and looked at HIV testing, stool cultures and EBV serology.

Results: 46 cases were analysed; 34 were Crohn’s disease, 11 were ulcerative colitis, 1 was indeterminate colitis. 19 (40%) patients were also taking an immunomodulator. 31 (68%) were screened for hepatitis B, 27 (59%) for hepatitis C, 27 (59%) for VZV, 44 (96%) for TB. 2 (4%) were tested for HIV; both done as part of pre-natal screening, 23 (52%) for EBV, 11 patients (24%) had stool samples analysed in the 6 months prior to treatment, all were negative.

Discussion/Conclusion: Despite the presence of a checklist for screening tests there were a significant number of patients who were not screened appropriately. We now have a specialist nurse whose role includes screening patients prior to anti-TNFα medications. We are now routinely screening for hepatitis B and C, VZV and TB as well as EBV, HIV and faecal infection and plan to re-audit compliance with screening tests in 12 months.
Use of normal CRP remission as an outcome parameter in pediatric Crohn's disease: Evaluation of the Porto IBD Group "Growth Relapse and Outcomes With Therapy" (GROWTH CD) Cohort Study


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**Introduction:** Induction of remission in clinical trials as well as clinical practice is usually evaluated by symptom reduction or clinical disease activity indices. However, complications and relapse stem from ongoing inflammation, thus a composite outcome evaluating both clinical symptoms and a measure of inflammation might be a more rigorous measure for long term outcomes. We attempted to evaluate clinical, inflammatory and composite outcomes of induction of remission therapies in a large pediatric prospective multicenter study.

**Methods:** Children with new onset Crohn's disease were enrolled at diagnosis into the GROWTH CD study, and evaluated for disease activity, CRP, and fecal calprotectin at diagnosis and at 8, 12 and 52 weeks after starting treatment. The primary end point was week 12 steroid-free remission defined by PCDAI and CRP < 0.5 mg/dL. The protocol required standardized therapies with 5-ASA, steroids or exclusive enteral nutrition. Tapering off corticosteroids (CS) was required by week 11.

**Results:** We analyzed 222 patients, mean age 12.9 ± 3.2 years. Clinical remission at week 12 was achieved in 155 (73%) of patients, however, Normal CRP Remission steroid-free remission (NCR) was achieved in only 33% of patients. Among those in steroid-free remission at week 12, normal CRP predicted one-year sustained remission (86% for normal CRP vs. 61% for elevated CRP; p = 0.02). Baseline severity and early immunomodulation did not differ between groups.
Discussion/Conclusion: Normal CRP steroid-free remission at week 12 was associated with more CS-free remission at week 52 and a trend for less relapses.

Table 1: Comparison of outcomes between NCR clinical remission and elevated CRP remission week 12 and between clinical remission with elevated CRP and no remission week 12

<table>
<thead>
<tr>
<th></th>
<th>Normal CRP remission (n = 89)</th>
<th>Clinical remission + Elevated CRP (n = 53)</th>
<th>No remission (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline PCDAI</td>
<td>33.4 ± 14.4 (NS)</td>
<td>32.6 ± 12.9 (NS)</td>
<td>33.4 ± 11.9</td>
</tr>
<tr>
<td>Baseline CRP (mg/dl)</td>
<td>3.2 ± 3.6**</td>
<td>6.8 ± 9.8</td>
<td>4.9 ± 5.8</td>
</tr>
<tr>
<td>Baseline IMM week 8 (%)</td>
<td>60% (54/89) (NS)</td>
<td>62.2% (33/53) (NS)</td>
<td>46.5% (27/58)</td>
</tr>
<tr>
<td>CS-free remission week 52 *</td>
<td>86% (63/73)**</td>
<td>61.3% (27/44)</td>
<td>13.8% (8/58)</td>
</tr>
<tr>
<td>Relapse by week 52</td>
<td>28% (21/73) (P = 0.067)</td>
<td>45.4% (20/44) (NS)</td>
<td>44.8% (26/58)</td>
</tr>
</tbody>
</table>

** p < 0.01 between normal CRP CS-free remission at week 12 and CS-free clinical remission with elevated CRP

^^p < 0.01 between clinical remission at week 12 with elevated CRP and no remission at week 12
Changing patients with ulcerative colitis to once daily mesalazine improves outcome and reduces cost in primary and secondary care

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Background: Oral mesalazine formulations offer similar efficacy and tolerability for acute and maintenance therapy of UC patients. Therefore choice of mesalazine is based on other factors such as adherence to therapy and cost. Once daily dosing and reduced pill burden are the best determinants of improved adherence to therapy. Newer mesalazine formulations such as Salofalk® Granules have unique release characteristics allowing them to be administered once daily for both acute and maintenance therapy of UC and have, therefore, been recommended [1].

Aims: Two pilot studies were carried in UC patients in primary care. The aims were to assess in patients inadequately maintained on mesalazine therapy, the effect of changing to a “Once Daily” oral mesalazine on disease outcome (pilot study 1), and on outpatient and hospital visits and cost saving (pilot study 2).

Methods: UC patients from 7 general practices covering a population of 103,000 were reviewed by independent clinical pharmacists “Medicines Management Solutions Ltd”. Disease activity was assessed (Walmsley Index) and following patient and GP consent; eligible patients were switched to a once daily mesalazine (Salofalk® Granules 1.5 g/day). A second review after 6 months assessed disease activity, number of visits to hospital and general practice, steroid use and cost of treatment.

Results: In total, 363 UC patients were identified and reviewed, change was recommended in 130 patients (36%). The main reasons for changing to once daily mesalazine were adherence issues (52%), patient preference (36%) and symptoms (12%). The change was actioned in 87 patients (24%). In the first pilot study the second review 6 months later demonstrated that 70% of the patients improved their UC severity score (Walmsley Index) and 30 had no change. There was no worsening of the UC score in any patients. In the second pilot study review after 6 months in patients switched to once daily mesalazine maintenance therapy demonstrated: 47% reduction in all hospital visits, 60% reduction in hospital visits due to flare up of UC, 45% reduction in GP visits and 50% reduction in steroid courses used. The majority of patients preferred once daily dosing and 85% of patients admitted no prior knowledge of the availability of alternative dosing regimes. Both pilot studies demonstrated a substantial cost saving.
**Conclusions:** Maintenance therapy of UC in the community is inadequate in more than one third of patients. Optimising maintenance therapy by switching to a once daily mesalazine leads to improved patient and disease outcomes as well as cost saving.

**Reference:**

1. DTB 2011; vol. 49, No. 1
Comorbidity-associated hospitalizations in IBD patients in a tertiary referral center

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Introduction: Inflammatory bowel disease (IBD) patients tend to have higher incidence of certain diseases in comparison to the general population. These comorbidities can be the cause of recurring hospitalizations among IBD patients. The aim of this retrospective study was to analyze admission of IBD patients to hospital due to comorbidities.

Methods: Hospital database records were searched for comorbidity-associated and IBD-associated hospitalizations during the period of two years (January 2011–January 2013). Crohn's disease (CD) patients were divided into groups according to the age at diagnosis, disease location and behaviour using Montreal classification (L1–4, B1–3). Ulcerative colitis (UC) patients were divided using the same classification. Logistic regression, Fisher's exact and Chi-squared tests were used to identify factors influencing comorbidity-related hospitalizations.

Results: Our study included 257 IBD patients with a total of 506 hospitalizations. Diagnosis of CD was established for 188 patients (73.15%, median age at diagnosis 18 years), while 69 patients were diagnosed with UC (26.85%, median age at diagnosis 32 years). Slight predominance of female patients (n = 140, 54.47%) was observed. Hospitalization due to different comorbidities comprised 16.01% (81/506) of total admissions. Statistical logistic regression model showed ileal disease (L1) CD patients are less likely to be hospitalized for comorbidities of any kind. Also, we found higher likelihood of comorbidity-associated hospitalizations in CD patients assigned to the higher age at diagnosis-groups. UC patients showed no statistically significant difference between groups with regards to comorbidity-related hospital admission.

Discussion/Conclusion: CD patient's age at the time of diagnosis is a significant factor reflecting the rate of comorbidity-associated hospitalizations. Ileal form of CD is associated with lower probability of comorbidity-related hospital admissions. It could be hypothesized that this difference is a result of milder disease course and less potent therapy regimens. These findings require a prospective study on a larger cohort of patients in order to confirm and further elucidate the background of our results.
Ethanol oxidation by intestinal microflora can contribute to bowel inflammation during chronic alcohol intoxication

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Introduction: Several reports suggest a role of acetaldehyde produced by ethanol oxidation in gastrointestinal mucosa in alcohol-associated gastric and intestinal mucosa injury. Recently, the finding of considerable production of acetaldehyde from ethanol by gastrointestinal bacteria was reported, and this may be a new pathogenetic factor related to alcohol associated gastrointestinal morbidity. We studied the effect of chronic alcohol consumption on the composition of fecal microflora and on its ability to produce acetaldehyde from ethanol in vitro.

Methods: Male Wistar rats were fed liquid isocaloric alcohol and control diets for 1 month. After that both groups were given a 2 g/kg dose of ethanol i. g. One hour later, under hexenal anaesthesia, samples of the contents of the stomach, small intestine, colon and rectum were collected for ethanol and acetaldehyde determination. The total amount of aerobic bacteria and yeasts was evaluated in fecal samples.

Results: The acute alcohol administration produced significantly higher acetaldehyde concentrations in the contents of the large intestine and rectum of rats given alcohol chronically. Chronic alcohol treatment produced a considerable increase in the number of fecal aerobic microbes (p < 0.001) and in the composition of the fecal flora: the content of E. coli was significantly increased (p < 0.01), whereas that of Staphylococcus and Candida was decreased (p < 0.05 and p < 0.0001). The oxidation of ethanol in vitro by fecal samples from rats receiving ethanol chronically was 54% higher as compared to the controls. The increased number of fecal aerobic microbes and the changed composition of this flora may explain the increased ethanol oxidizing activity of fecal samples from rats receiving alcohol chronically.

Discussion/Conclusion: Our results demonstrated that colonic microflora can contribute to increased local acetaldehyde accumulation in the colon and rectum during ethanol loading in animals subjected to chronic alcohol treatment and it may be of importance for mechanisms of alcohol-related inflammatory changes in these regions.
Advanced architectural changes of the intestinal epithelium are more frequent in children with UC

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Introduction: Ulcerative colitis (UC) is a chronic intestinal multifactorial disorder of large intestine. It is characterized by a widespread inflammation of the mucous membrane located in the rectum and sigmoid colon at the initial stage, then covers the whole colon. It has been observed the development of ulcers and microabscesses in the crypts that later has been replaced by connective tissue leading to stenosis of occupied segments in advanced cases.

Materials and Method: The study consisted of 52 patients with ulcerative colitis (33 adults and 19 children). Endoscopic materials were taken from archival paraffin-embedded tissue. Sections were stained with H&E and subjected to routine histological evaluation. According to Geboes classification, an analysis of the severity changes (architectural changes, the assessment of crypt destruction, erosions and ulcers) was performed depending on the patients’ age.

Results: The disease process was present in the sigmoid colon (30% of cases), in the rectum (21%) and in the whole large intestine (19% of cases). The location of the disease correlated negatively with age of the patients (p < 0.04). In children, the inflammation is most common in the whole intestine (48%), then in the rectum (28%) and sigmoid colon (24%). Conversely, adult patients with UC had the highest percentage of disease situated on the sigmoid colon (53.3%) lower in the rectum (31.1%), and the whole large intestine (15.6%). Histopathological analysis demonstrated a small, moderate and severe diffuse or multifocal architectural disorders in 10, 17, 24 patients, respectively. It was observed that this parameter correlated with the patients’ age (p < 0.008) too. The degree of structural damage of the intestinal epithelium decreased with the age of the patients.

Conclusion: UC occurs in both children and adults but it seems that the disease process involves much more advanced lesions and causes more structural destruction of the intestinal epithelium in the young patients.
Human intestinal T cell transcriptomes are anatomically unique and inform analysis of complex inflammatory disease genetics

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Introduction: The intestinal mucosa harbours the largest accumulation of T lymphocytes in the human body. These T cells play an important role in the triggering and maintenance of intestinal inflammation but are poorly characterised in humans, whilst in the mouse there are only a handful of reports of transcriptomes generated for individual cell types, many of which lack direct human equivalents.

Aims and Methods: CD4\textsuperscript{+} and CD8\textsuperscript{+} effector T cells purified from the intraepithelial (IEL) and lamina propria (LPL) layers of terminal ileal biopsies from 6 healthy female volunteers were used for expression microarrays analysis alongside reference peripheral blood populations. In silico pathway analysis, protein-protein interaction modelling, transcription factor and kinase prediction modelling were used to predict active pathways in the gut and results confirmed by ex vivo flow cytometric analysis. Genetic risk loci for a range of gastrointestinal and extraintestinal inflammatory pathologies were tested for enrichment of key gut expressed genes.

Results: Key pathways upregulated in gut T cells include TNF-receptor signalling, IL-17A and aryl hydrocarbon receptor signalling and 4-1BB costimulatory signalling. Genetic risk loci for inflammatory gastrointestinal pathologies were significantly enriched for genes upregulated in gut T cell populations, including Crohn’s disease (CD4\textsuperscript{+} and CD8\textsuperscript{+} LPL), ulcerative colitis (CD8\textsuperscript{+} LPL) and coeliac disease (CD4\textsuperscript{+} and CD8\textsuperscript{+} IEL and LPL). Risk loci for extraintestinal pathologies with a significant microbial trigger were also enriched for gut expressed genes (type 1 diabetes, MS), whilst other inflammatory pathologies and non-inflammatory pathologies showed no such enrichment (SLE, rheumatoid arthritis, BMI, height). Transcription factor prediction and interrogation of risk loci using published ChIP-Seq data converge on HNF4a as a key point of genetic regulation of gut inflammation.

Conclusion: We report the first complete transcriptional analysis of all 4 major T cell populations in the terminal ileum of healthy human volunteers. We provide evidence for several gut-specific T cell signalling pathways. Risk loci for gastrointestinal inflammatory diseases are enriched for gut expressed T cell genes; this approach informs our understanding of candidate genes and causal cell populations at risk loci. We also show a surprising role of gut T cell genes in a subset of extraintestinal inflammatory pathologies with strong epidemiological links to microbial influences.
Trends in transition of paediatric IBD patients to adult IBD services: A 15 year regional UK experience

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Background and Objective: There is limited data on the transition of teenagers with paediatric IBD (PIBD) to adult services. We evaluated the transition programme of our regional cohort of PIBD patients over its 15 year existence in terms of epidemiology and emerging trends.

Methods: A retrospective and prospective cohort study of patients with PIBD (diagnosed < 18 years of age) and managed in the regional PIBD centre for SE Scotland over a 15 year period (08/97–12/12).

Results: Joint transition clinics were established in early 1998 with the major regional adult IBD centre, and increased both in numbers of collaborating adult IBD teams and clinics per centre per year. 189 (53%) of our cohort of 352 PIBD patients underwent transition, 122 through a defined joint clinic process to 1 major regional IBD centre and 2 District General Hospitals, and 67 via traditional transfer of material by summary letter and copies of pathology and radiology to a group of smaller adult IBD units. For the defined clinic, the minimum and maximum durations of transition were 9 and 33 months respectively. The age range of transitioning patients was 15–19 years, and the maximum number of patients commencing transition in a calendar year was 19. The number of patients completing transition whilst on maintenance biologic therapies has risen from 4 (7% of those leaving paediatric care) in 2007–09 to 14 (23%) in 2010–12.

Conclusions: Appropriate management of the transition process involves time, careful planning and sensitivity to adolescent and parental issues and needs. The ideal is through a joint clinic; the major problem for the paediatric IBD team is the number of adult IBD centres they transition to within their region. The increasing complexity of transitioning PIBD patients is exemplified by the significantly higher numbers currently on maintenance biological therapy at transition.
A comparison of gastroenterology and non-gastroenterology nurses knowledge of inflammatory bowel disease

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Background: The Inflammatory Bowel Disease (IBD) Service Standards within the UK stipulates that in-patients with IBD should, where possible, be managed within a specialist gastroenterology ward area. [1] There is a general consensus that this, and the IBD Standards, will deliver safe, high-quality patient centered care. The aims of this study were to assess the knowledge base of ward nurses on a specialist gastroenterology ward and then compare to nurses on a non-gastroenterology ward.

Methods: 80 ward nurses, 40 on a gastroenterology ward and 40 on a non-gastroenterology ward, completed the Crohn's and Colitis knowledge (CCKNOW) questionnaire. CCKNOW is a validated questionnaire to assess specific IBD knowledge relating to the disease. The nurses were randomly sampled from 7 hospital trusts in the Northwest of England, UK. The findings of the 2 groups were analysed and compared.

Results: The number of correct answers per validated question is shown for the gastroenterology nurses compared with non-gastroenterology nurses. The mean and median CCKNOW score for the gastroenterology nurses is 16.08 and 16 respectively, with the mean for non-gastroenterology being 13.55 and median 14. The gastroenterology nurses demonstrated more knowledge about treatments of IBD, whereas the non-gastroenterology nurses were more knowledgeable with regards to anatomy. The colorectal cancer surveillance question was answered incorrectly by ALL non-gastroenterology nurses. The overall knowledge of all 80 nurses was deemed to be poor.

Conclusions: This study confirms that gastroenterology ward nurses are no more knowledgeable about IBD than non-gastroenterology ward nurses, apart from treatments. Knowledge of aetiology, symptoms, surgery, complications, pregnancy and fertility were of similar value between the two different groups of nurses. Non-gastroenterology nurses had more knowledge of the anatomy of the gastrointestinal tract. IBD teams need to do more to educate gastroenterology ward nurses on IBD and the anatomy of the gastrointestinal tract.
Reference:

The role of thrombospondin-1 (TSP-1), vascular endothelial growth factor (VEGF) and MMP9 in the angiogeneic balance of inflammatory bowel disease (IBD)


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**Introduction:** Inflammation is a defensive process against tissue injury. If the underlying event inducing inflammation is not addressed and homeostasis is not restored, this process can become chronic and lead to angiogenesis. Angiogenesis is under the control of numerous inducers, including the vascular endothelial growth factor (VEGF) family and inhibitors, such as thrombospondin-1 (TSP-1). Because the molecular mechanisms explaining the role of TSP-1 and VEGF in inflammatory processes are not well understood, we aimed to study the angiogeneic balance in IBD by evaluating of these factors.

**Methods:** We investigated 30 cases affected by inflammatory bowel diseases: 16 with ulcerative colitis (UC; sex ratio 10M/6F), and 14 with Crohn's disease (CD; sex ratio 5M/9F). The reference group was composed of 16 healthy individuals (13M/3F). Age (years) mean of UC was 47 (25–64), for CD 43 (18–78) and 30 (20–61) in controls. The analysis of serum concentrations of total matrix metalloproteinase MMP9, TSP-1 and VEGF was based on a quantitative sandwich ELISA, using Quantikine kits manufactured by R&D Systems, USA. Serum samples were collected before the start of therapy.

**Results:** The levels of MMP9 (490.12 ± 140.72 ng/ml) and VEGF (480 ± 261 pg/ml) in IBD group were higher than in healthy control group (30.18 ± 20.02 ng/ml and 315 ± 120 pg/ml, respectively) presenting statistical significance(p < 0.05). The UC and CD patients had slightly elevated concentrations of TSP-1 than controls (p > 0.05). We suppose that this increase was insufficient to inhibit pathologic angiogenesis and inflammation. It seems that MMPs facilitates the expression of proangiogenic factors such as VEGF in order to overcome the negative signals of angiogenic inhibitors such as trombospondins. The inhibition of MMPs can represents the scientific rationale for the development of chemothrapeutic agents against IBD.

**Conclusions:** IBD are diseases which can be difficult to control with conventional therapies. A better knowledge of IBD physiopathology, will lead to the identification of new therapies aimed at specific targets of the inflammatory cascade.
A distinct clinical phenotype and serological response in newly onset pediatric Crohn’s disease associated with primary sclerosing cholangitis

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Introduction: Primary sclerosing cholangitis (PSC) is strongly associated with inflammatory bowel disease (IBD), predominantly with ulcerative colitis (UC). A distinct clinical phenotype has been reported for UC-PSC but for Crohn’s disease (CD) is poorly defined, especially in children. This study was designed to evaluate clinical and serologic characteristic of pediatric newly-onset CD-PSC.

Patients and Methods: We present findings from a retrospective review of the medical records of IBD children and adolescent from a tertiary pediatric gastro-enterology center. Over the 8 years (December 2004–December 2012) we identified 585 IBD patients (368 CD, 140 UC, 76 IBDU). PSC was diagnosed in 16 children (14 CD, 2 UC) with conventional cholangio-MR criteria (MRCP), results of liver tests and ultrasound imaging. Patients with CD were matched 2:1 with the CD-PSC with age and sex, and served as a control group. Laboratory and serological tests (anti-neutrophil cytoplasmatic antibodies [pANCA], anti-Saccharomyces cerevisiae antibodies [ASCA], anti-pancreas antibodies [PAB] and anti-nuclear antibodies [ANA])) and induction remission regiments were analyzed.

Results: PSC was predominantly diagnosed in CD patients (87%) with male predominance (71% vs. 29%; p < 0.005). MRCP showed mainly extra- and intrahepatic involvement (71%). There were no differences in location and behavior of CD (p > 0.05) except for the more frequent perianal lesion presented in PSC-CD patients (29% vs. 19%; p < 0.005). CD-PSC patients required more frequently steroids to induce remission (p = 0.001), however there was no difference in PCDAI at diagnosis. Altered immunological response with significant higher rate of pANCA (71% vs. 21%, p < 0.0002), ANA (29% vs. 4%; p < 0.04) and PAB (43% vs. 21%; p = 0.0003) was demonstrated in CD-PSC patients and 21% of them expressed an overlap ASCA with pANCA.

Conclusions: CD-PSC patients have a unique clinical presentation with higher rate of perianal disease and male predominance. An altered serological response to microbial and autoantigens with UC-like profile was present.
Further evaluation of the serum neutrophil gelatinase-associated lipocalin (NGAL) in children with inflammatory bowel disease (IBD)

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Introduction: Neutrophil gelatinase-associated lipocalin (NGAL) is expressed in numerous normal tissues, where it serves as anti-inflammatory and bacteriostatic protein. We have recently shown (Falk Symposium No. 183, 2012) that NGAL appears to be a promising biomarker in IBD in children. The aim of the study was to further evaluate clinical significance of NGAL in Crohn’s disease (CD) and ulcerative colitis (UC) in children and to determine normal serum NGAL levels in the cohort of healthy children.

Methods: Blood samples were collected for the diagnostic examinations from children with CD (n = 19), UC (n = 17) and healthy controls (n = 126), aged 1 to 18 years. Diagnosis and IBD activity indexes were established according to the Porto criteria. Serum NGAL was determined with ELISA kit from BioPorto, Denmark. Non-parametric Mann-Whitney U test and Spearman’s correlation rank tests were used. Data are median and range.

Results: Children with IBD, including those with CD and UC, exhibited statistically higher NGAL levels (94.8, range 41.7–240 ng/mL; 112, range: 37.3–245 ng/mL, respectively) as compared to healthy controls (42.0, range 18.1–107 ng/mL) and allergic, non-IBD children (49.3, range 19.3–107 ng/mL, n = 27). Serum NGAL levels in children with PCDAI \( \leq \) 30 and > 30 were not statistically different (75.0, range 50.0–131 ng/mL; 102, range 41.7–240 ng/mL, respectively). The same was found for children with PUCAI \( \leq \) 30 and > 30: 103, range 37.3–245 ng/mL versus 112, range 76.5–184 ng/mL. In healthy children serum NGAL level was positively correlated with age (\( r = 0.51, p < 0.001 \)). There was no statistically significant difference between allergic, non-IBD and healthy children.

Discussion/Conclusion: Children with IBD exhibit minor to several-fold increase of the serum NGAL, although there was no correlation between serum NGAL and degree of the disease activity. NGAL is thought as an unspecific marker and modulator of inflammation of different etiologies. However, our data show that in children with allergy it remained at normal level. Pathways of the NGAL involvement in the inflammatory processes, including IBD, are not fully understood yet, and require further studies.
The risk of relapse after discontinuation of biological therapy in Crohn’s disease patients – Initial experience in a tertiary centre

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Introduction: Biological therapy has revolutionised the treatment of Crohn's disease (CD), but is burdened with high expense and the risk of serious side effects. There are no official guidelines on when to discontinue anti-TNF therapy in patients achieving remission on treatment. We aimed to investigate the risk of relapse after discontinuing biological therapy in CD patients in deep remission.

Methods: We reviewed medical records of CD patients receiving anti-TNF therapy from 01.01. 2007. to 31.12.2012. and identified patients in stable clinical, biochemical and endoscopic remission at the time the therapy was discontinued. Clinical course was retrospectively analysed to assess the risk of relapse after discontinuation of biologic therapy.

Results: A total of 59 patients were treated with anti-TNF treatment. We identified 8 patients (5 female, 3 male) who were in deep remission at the time therapy was discontinued. Reasons for therapy discontinuation were patient preference due to fear of side effects in 7 cases and in one case, pregnancy, where therapy was stopped on the demand of the patient. Colonoscopy was performed prior to treatment discontinuation and complete mucosal healing was confirmed. Six patients were treated with infliximab and two received adalimumab. The median duration of therapy prior to discontinuation was 25.59, interquartile range (IQR) [18.75–30.26] months. After a median of 13.25, IQR [6.70–15.34] months, 6/8 patients developed relapse. Two patients maintained remission (time from discontinuation: 17.62 and 27.35 months).

Discussion/Conclusion: Discontinuation of anti-TNF treatment in patients in deep remission bears a significant risk of relapse in a notable proportion of patients within little over one year after treatment discontinuation. There might be a certain subset of CD patients in whom biological therapy can be safely stopped. However, there are no specific markers which could identify this subset of patients and predict the risk of relapse after discontinuation of anti-TNF treatment.
The use of tacrolimus in refractory ulcerative colitis – A single centre UK district general hospital experience

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Introduction: Rescue therapy is required for patients with moderate to severe ulcerative colitis (UC) not responding to steroids and thiopurines. Anti-TNF agents are widely used before considering a colectomy. Ciclosporin or tacrolimus (calcineurin inhibitors) are alternatives to biologics. Case series assessing the use of tacrolimus in such patients do exist, although UK experience is limited. We reviewed outcomes of patients opting for tacrolimus rather than proceeding to colectomy after failing standard medical therapy.

Methods: This is a retrospective single centre case review series. Barnet District Hospital serves a population of 250,000. All patients refractory to standard therapies were reviewed by a specialist in inflammatory bowel disease. Demographic data, indications, clinical course and outcomes were retrieved from the Electronic Patient records.

Results: Seven patients (F = 2, mean age 61 years) received tacrolimus. 71.4% had pancolitis and 28.6% distal colitis. All patients were steroid dependent prior to starting tacrolimus, and had previously received thiopurines, whilst 6 patients also received infliximab. Only one patient received intravenous ciclosporin before switching to tacrolimus. The remaining 6 patients were initiated as outpatients, with a starting dose of 0.1 mg/kg/day in divided doses. Three patients (42.9%) achieved steroid free remission within 6 months; one patient required a single course of steroids within this timeframe. Three patients failed to respond: 1 had a colectomy, 1 had leukaphaeresis and 1 switched to infliximab. Two patients developed renal impairment, both were non-responders who had treatment withdrawn anyway. Four patients remain in steroid free clinical remission with a good quality of life and no adverse effects.

Discussion/Conclusion: Tacrolimus is an alternative treatment for patients with refractory UC, particularly if the patient is unwilling to undergo a colectomy. With close monitoring and adherence to protocols, it is safe and effective in a district hospital setting in more than 50% of patients not responsive to conventional immuno-modulators and biologics.
The prevalence and predictive factors of anaemia in IBD patients from a tertiary care centre in Romania: A retrospective survey

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Introduction: Anaemia is the most common complication of inflammatory bowel diseases (IBD), its prevalence in this population ranging from 6–75% in different published studies. The aim of our study was to evaluate the prevalence of anaemia in a tertiary care centre from Romania and to assess its predictive factors.

Methods: We included the last 117 consecutive patients with IBD visiting our clinic, regardless of disease activity. Patients were stratified using the Montreal classification for disease localisation in both Crohn’s disease (CD) and ulcerative colitis (UC). Anaemia was defined as Hb < 12 g/dl according to our laboratory parameters. We defined severe anaemia as Hb < 8 g/dl, moderate with Hb between 10–12 g/dl, and mild anaemia with Hb between 10–12 g/dl.

Results: Anaemia was present in 47% of patients, with severe anaemia in 2.5%, moderate in 7.5% and mild anaemia in 37%. There was a trend of significance for the occurrence of anaemia in ileal involvement of CD. Also, anaemia correlated significantly with the severity of both CD and UC, especially with severe flares of activity, and with CRP values, especially in CD. We also observed a higher prevalence in the subgroup of patients receiving azathioprine (AZA), probably due to the drug’s direct antifolinic toxicity.

Discussion/Conclusion: The prevalence of anaemia in IBD patients from our centre is comparable with literature data. We found that CRP value and ileal involvement, in CD patients, and degree of severity along with AZA treatment in both CD and UC represent predictive factors for the presence of anaemia in IBD patients.
Hyperbaric oxygen therapy as a part of treatment of ulcerative colitis

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Hyperbaric oxygen therapy is up-to-date for the treatment in IBD. The curative effect of hyperbaric oxygen therapy is a very important of tissue's hypoxia and compensates organ's reaction.

There were examined 74 patients with active form of ulcerative colitis. All patients were treated by Salofalk® 4 x 500 mg, curative enemas by Salofalk® susp. and hyperbaric oxygen therapy.

The other group of patients with ulcerative colitis (20) we treated with hyperbaric oxygen therapy only.

For hyperbaric oxygen therapy we have used Dragger chambers 1000–1200 for 60–75 min (10–12 sittings). We've found good effect after 5th–6th of treatment. We have made approval after endoscopical examination.

We have made clinical retrace for number of defecation, blood in faeces etc. There were found endoscopical and clinical remission after treatment with Salofalk®, curative enemas and addition hyperbaric oxygen therapy in 82% of patients.

Hyperbaric oxygen therapy is useful as a part of treatment of ulcerative colitis in 82% of patients with ulcerative colitis, but hyperbaric oxygen therapy as single therapy is useful in 60% of patients.
Proteomic analysis of Crohn's disease serum treated with infliximab

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Introduction: The infliximab (IFX), is the first anti-TNF-alpha agent accepted for Crohn's disease (CD) treatment. However, up to 15% of patients do not respond to IFX. In the current study, we tried to identify protein expression alterations in patients following IFX administration, using proteomics technologies, aiming at finding a panel of candidate protein biomarkers of CD, symptomatic of response to treatment.

Methods: We enrolled three groups of patients (n = 18), who either had achieved clinical and serological remission (Rm, n = 6), or response (Rs, n = 6) and/or were PNRs (n = 6), to IFX. Serum samples were analyzed by two dimensional Gel Electrophoresis, and protein spots showing differential expression were further characterized by MALDITOF-MS. Evaluation of identified proteins by immunoblot analysis was followed while functional network association was carried out to assess significance.

Results: Seven proteins were found to be up-regulated in the PNR and Rs groups (apolipoprotein A-I [APOA1], apolipoprotein E [APOE], complement C4-B [CO4B], plasminogen [PLMN], serotransferrin [TRFE], beta-2-glycoprotein 1 [APOH], and clusterin [CLUS]) whereas their levels displayed no changes in the Rm group when compared to baseline samples. Additionally, leucine-rich alpha-2-glycoprotein (A2GL), vitamin D-binding protein (VTDB), alpha-1B-glycoprotein (A1BG) and complement C1r subcomponent (C1R) were significantly increased in the serum of the Rm group.

Discussion/Conclusion: Using proteomics technologies, novel protein serum markers demonstrating high sensitivity and specificity are introduced, as a result, offering an innovative approach regarding the evaluation of CD patients' response to IFX therapy.
Hypothesis-free analysis of ATG16L1 demonstrates gene-wide extent of association with Crohn’s disease susceptibility

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Introduction: The ATG16L1 locus has been implicated in Crohn’s disease (CD) susceptibility. In order to assess the association signal without any bias towards function (coding, splicing, expression or autophagy), we performed a hypothesis-free analysis of the ATG16L1 association signal in two independent case-control cohorts.

Methods: In Cohort-1, 38 SNPs spanning the ATG16L1 gene were imputed for 1735 subjects (800 CD/935 Healthy Controls [HC]: NIDDK cohort). In Cohort-2, 27 SNPs of the ATG16L1 locus were genotyped in 838 CD and 381 European Ancestry HC (1000-genomes.org). Single marker, haplotype, permutation association analyses and logistic regression were performed. Monte Carlo-simulation analysis was used to assess haplotype-structure.

Results: In the first cohort, permutation analysis yielded association of 19 markers (p < 0.05), from intron 1 (rs6752107) to the 3’UTR (rs1045100): 12 markers were in complete LD with rs2241880. rs6758317 and rs6737398 (intron 2), rs3792106 (intron 11), rs4663396 and rs13005285 (intron 12), rs6754677 (intron 14) and rs1045100 demonstrated strong association, independent of rs2241880. Genotype-based regression analysis retained rs3792106, rs6754677 (intron 14) and rs1045100.
In the second cohort, permutation analysis demonstrated association with 8 markers of which rs3792106, rs1045100 and rs7580869 had r²-values < 0.9. Regression analysis retained rs7580869, which is located 37kb upstream of the first exon. In both cohorts, Monte Carlo-simulation showed no significant difference in the total number of observed haplotype blocks. Haplotype permutation-analysis showed association of CD with the block containing the rs2241880, and the block containing rs1045100, (both blocks permutation-p < 10⁻⁵ and permutation-p < 0.05 in cohort-1 and cohort-2, respectively).
Discussion/Conclusion: We have studied the extent of the association of ATG16L1 in two independent cohorts and demonstrated that the rs2241880 alone is not sufficient to explain the strong association signal. Additional variants, independent of rs2241880, could implicate any of the 5' region, coiled-coil domain, the WD domain and/or the 3' UTR, in CD susceptibility.
Natural history confirms the validity of separating paediatric IBD at 10 years of age in the Paris classification

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Introduction: Compared with adult IBD, paediatric IBD (PIBD) is more dynamic and extensive using the Montreal classification. A modified paediatric IBD-classification (Paris; Levine A et al IBD 2011) has been published; a key feature is an age division at 10 years. Our aims were to characterise the phenotype of PIBD in different age groups (A1a < 10 years; A1b ≥ 10 < 17 years), at diagnosis and after 2 & 4 years of follow-up, using the Paris classification.

Methods: 713 patients (< 17 y at diagnosis, male/female 407/306, median age (Q1–Q3) 11.5 y (8.7–13.3): 473 CD/173 UC/67 IBDU) were analysed at diagnosis, 2 (295 CD/100 UC) and 4-year (103CD/56UC) follow-up and Chi-squared analyses were performed.

Results: The A1a-location of CD differs from A1b (p = 0.0002). A1aCD is characterised by less ileal disease (L1+/L4: 6/154 [38.9%] vs. 32/313 [10.2%]; p = 0.01 OR 0.36 [0.15–0.87]) and more limited oral +/- perianal CD at presentation (14/154 [9.1%] vs. 3/313 [0.9%]; p < 0.0001 OR 10.33 [2.92–36.53]). These differences persist during follow-up (p = 0.0007 and p = 0.02 at 2 y and 4 y, respectively). By 4 y, A1aCD is characterised by less panenteric CD (L3+L4ab: 4/67 [5.9%] vs. 18/103 [17.5%]; p = 0.03 OR 0.30 [0.10–0.93]). By 2 y, Paris location (of patients not L3+L4ab at diagnosis), changed in 20.8% (59/283). Extension was more ileal (24/59 [40.7%]) than colonic (13/59 [22%], p = 0.02 OR 2.43 [1.08–5.43]). 28/59 (47.4%) had extension into the upper gastrointestinal tract.

Whereas A1aCD remains largely inflammatory during follow-up, A1bCD behaviour progresses to intestinal penetrating complications (p < 0.0001).

UC presented as pancolitis (E4) in 36/60 (60%) of A1a vs. 77/103 (74.8%) of A1b, p = 0.04 OR 0.51 (0.26-1.00). 4 years after diagnosis, E4 UC was less common in A1a compared with A1b (15/30 [50%] vs. 20/26 [76.9%], p = 0.03 OR 0.30 [0.09–0.96]).

Discussion/Conclusion: We have demonstrated that A1aCD is characterised by less ileal disease with more oral +/- perianal disease and inflammatory disease than A1bCD. Childhood UC is extensive at diagnosis but pancolitis is rarer in A1a than A1bUC; these differences persist during follow-up.
Prevention is better than cure – Are we doing enough for our IBD patients?

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Introduction: Immunomodulators (IM) and biological agents are now widely used in inflammatory bowel disease (IBD) leading to an increase in opportunistic infections (OI) [1]. European Crohn’s and Colitis Organisation (ECCO) recommends screening and vaccinations for Varicella Zoster Virus (VZV), Human Papilloma Virus (HPV) in women, Annual Influenza (inactivated vaccine), Pneumococcus (3–5 yearly) and Hepatitis B (if HBV seronegative) in immune-compromised IBD patients.

Methods: We collected retrospective data on the serology status for Hep B&C, VZV and Chest X-ray (CXR) results of our patients receiving biologics from pathology results and from PACS. Information on BCG vaccination status, previous chicken pox exposure was obtained from the clinic letters and MDT proformas. Information on the vaccination status was obtained by contacting the general practitioners and from patients directly.

Results: Of the 37 patients who are currently receiving biologics (18 males; 19 females; mean age: 37.3 ± 2.3 years), 31 had Crohn’s disease, 5 ulcerative colitis and 1 indeterminate colitis. All patients received anti-TNF therapy with 33 (91.7%) exposed to combination therapy with azathioprine (27) (81.8%) or (6) (18.2%) with methotrexate. Serology status on Hep B, C and Varicella was available in 26 (77%), 5 (13%), and 21 (56%) patients respectively. A CXR was done in 65% of patients with 5 patients having their BCG status documented. IGRA was done on 2 patients with ambiguous mantoux results. Influenza, pneumococcal, HPV vaccines were administered in 6 (16.2%), 4 (10.8%) and 1 patients (2.7%) respectively.

Discussion/Conclusion: Relevant serology status and vaccination history was available/recorded in a minority of patients only. Non-/poor-adherence to guidelines, poor documentation or limits of data collection may explain this. Information leaflets on the ECCO-recommended vaccines are being sent to GPs and patients. Patient education through our IBD nurses and empowering patients with personalized information at diagnosis and during the course of their treatment may increase the uptake of vaccinations in high risk patients. The development of a dedicated IBD database ideally with GP links to allow vaccinations records to be accessed will allow us to audit our practice accurately and determine the efficacy of the current recommendations.

Reference:

Awareness amongst patients with inflammatory bowel disease for the need for vaccinations whilst on immunosuppressive therapy

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Introduction: The ECCO guidelines currently recommend that patients with inflammatory bowel disease (IBD) who receive immunosuppressive medications should be vaccinated with the influenza vaccine yearly and a pneumococcal vaccination 3–5 yearly.

Methods: The aim of the study was to assess patient knowledge and uptake of influenza and pneumococcal vaccines. Patients with IBD were identified from an established database and those receiving immunosuppressive therapy were invited to complete a questionnaire between October and November 2012.

Results: A cohort of 88 patients on immunosuppressive therapy was analysed. 61% were female. 59 (67%) had Crohn’s disease, 26 (30%) ulcerative colitis and 3 (3%) indeterminate colitis. 48 (54%) received immunomodulators including azathioprine or mycophenolate mofetil. 13 (15%) were treated with biologics alone (infliximab or adalimumab), 21 (24%) with combination of biologics and immunomodulators and 6 (7%) received immunomodulators with a reducing dose of steroids. 77% of patients were aware of recommended vaccinations. 42% were aware of the importance of receiving both vaccinations, 35% were only aware of the need for one of the vaccines, and 23% were unaware of the need for either. In this cohort 54 (61%) patients had already had or were planning to have the influenza vaccine this year. Patients aged 31–50 years had the highest awareness of the recommended vaccines (86%), with the majority of uptake of vaccines seen in this age group (63%). 39% of patients were not receiving recommended vaccinations with more than half (56%) being unaware of the need to avoid live vaccinations.

Discussion/Conclusion: Our data suggest that a significant proportion of patients are not receiving vaccinations that were recommended to them. Wider education of our IBD patients as well as their primary care doctors should be implemented to increase awareness and uptake of vaccines to provide adequate protection to this vulnerable group.
Soluble transferrin receptor ferritin index to assess iron status of children with Crohn’s disease treated with exclusive enteral nutrition

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Introduction: Anaemia is common in children with inflammatory bowel disease. Clinical markers of iron deficiency are confounded by the effects of inflammation. The soluble transferrin receptor ferritin index (sTfR-Index) identifies patients with depleted stainable iron in bone marrow (true iron deficiency) and a threshold of $\leq 1.4$ separates patients with anaemia of chronic disease from those with iron deficiency.

Methods: Prospective study of treatment naïve children with Crohn’s disease treated with exclusive enteral nutrition (Modulen® IBD) occurred in a UK regional paediatric gastroenterology centre. Haemoglobin, sTfR-Index, clinical markers of iron status (ferritin, transferrin, transferrin saturation) and systemic inflammation (CRP, ESR, TNF, IL-6) were evaluated at six study time points from diagnosis over the first six months of treatment.

Results: Thirteen children (4 girls), aged 10 to 18 (median 13.6) years at diagnosis, completed 77 study visits. Haemoglobin at last visit was significantly different to haemoglobin at diagnosis (Wilcoxon signed-rank test $p = 0.005$). All clinical markers of iron status were significantly correlated with markers of systemic inflammation ($p < 0.05$); sTfR-Index was not. At diagnosis only one child was iron deficient (sTfR-Index $> 1.4$); she remained iron deficient and anaemic throughout the course of the study although her haemoglobin improved. Four children that were not iron deficient at diagnosis became iron deficient over the course of the study; all four increased or maintained haemoglobin.

Discussion/Conclusion: Few children in this study were iron deficient according to sTfR-Index and all had increasing haemoglobin. Current research and clinical use of iron therapy relies on clinical markers of iron status but anaemia resistant to, or recurring after, iron therapy is common. Further evaluation of responses to iron supplements using appropriate markers of iron status are required.
The clinical outcomes of accelerated step-up therapy for Crohn’s disease

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Introduction: In patients with active Crohn’s disease (CD) who have risk factors for progression, start of thiopurines together with first course of corticosteroids (accelerated step-up, ASU) is recently recommended. We aimed to analyze the clinical outcomes of CD patients who received ASU therapy and risk factors for progression despite ASU approach.

Methods: Thirty-four patients who were given ASU therapy from July 2007 to March 2012 and were followed for more than 12 months were enrolled. As outcomes, development of events (disease flare, CD-related new complications, CD-related hospitalization, major abdominal surgery, or step-up to anti-TNF agents) was investigated.

Results: Median age and median disease duration at starting ASU therapy was 21.0 years (range, 13–42) and 1.7 months (range, 0–22), respectively. Twenty-four patients (70.6%) were male. Ileocolonic involvement was diagnosed in 27 patients (79.4%), isolated ileal involvement in 5 (14.7%), and isolated colonic disease in 2 (5.9%). As for behaviors, 27 patients (79.4%) had inflammatory diseases, 5 (14.7%) had strictureing diseases, and 2 (5.9%) had penetrating diseases. Median follow-up duration was 28.2 months (range, 12–66). Out of 27 patients who could keep thiopurines, 9 patients (33.3%) experienced events. The cumulative risk of developing events was 11.1%, 32.7%, 32.7%, and 55.8% after 1, 2, 3, and 4 years, respectively. Out of 27 patients, all 4 patients with strictures experienced events including penetrating complications in 3 (75%). Strictureing behavior at starting ASU therapy tended to show an association with events (p = 0.059). Among 27 patients, any adverse events related with thiopurine were observed in 14 patients (51.9%), gastrointestinal adverse events in 8 patients (29.6%) and leukopenia in 5 (18.5%).

Discussion/Conclusion: Even with ASU approach, cumulative risk of disease progression was over 50% after 4 years. Patients with strictureing diseases do not appear to be appropriate candidates for ASU therapy.
Anti-glycan antibodies associated with disease activity in inflammatory bowel diseases

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Introduction: Crohn’s disease (CD) and ulcerative colitis (UC) in the gastrointestinal tract, chronic, recurrent, and cause tissue damage and inflammatory bowel disease (IBD), two different subtypes. This study investigated the relationship between disease activity in IBD anti-glycan antibody panel.

Methods: The study of 137 patients with CD and 122 with UC, and 90 healthy control subjects. The anti-chitobioside IgA (ACCA), anti-laminaribioside IgG (ALCA), anti-mannobioside IgG (AMCA), and anti-Saccaromyces cervisiae IgG (ASCA) has been tested in the serum samples. Disease activity will be assessed according to the Crohn’s Disease Activity Index (CDAI) and the Truelove-Witts index for CD and UC, respectively.

Results: The study, 136 patients with CD (F/M 65/71, median age 36.34 ± 11.92), 122 UC patients (F/M 55/67, median age 44.45 ± 14.08) and 90 healthy controls (F/M 43/47, median age 44.49 ± 10.66) were included. In patients with active Crohn’s ASCA, ALCA, and ACCA positivity was significantly higher than those without (p < 0.05). At the same time increasing the level of antibody titers with the severity of CD activity in patients with ASCA, ACCA (p < 0.01), ALCA (p < 0.05) were significant correlations. In patients with active UC anti-glycan antibodies not determined significant correlation (p > 0.05).

Discussion/Conclusion: CD serological markers associated with disease activity, prognosis, and treatment follow-up will be important. Antibodies and disease activity in CD of large-scale studies are needed to determine the diagnostic value.
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