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THE KEYS TO IBD 2010: TREATMENT, DIAGNOSIS AND PATHOPHYSIOLOGY

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Scientific Organization:
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Session I

Impact of new keys in pathophysiology on IBD treatment
New insights into IBD genetics – What have we learned and where do we go from here?

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Clustering of inflammatory bowel disease in large families and the observation of an increased concordance between monozygotic twins suggests heritable components in these disorders. The high concordance in monozygotic twins (> 55%), which is not seen in dizygotic twins (< 5%) points to strong contribution of genetic susceptibility to the overall risk for disease. IBD represents a “complex disease” and may involve a large number of interacting disease genes.

Crohn’s disease has become a paradigm example for the successful molecular exploration of a polygenic etiology. Crohn’s disease was not known before 1920. Incidence has increased since now leading to a lifetime prevalence of up to 0.5% in Western industrialized countries. The current hypotheses propose unknown trigger factors in the life style of Western industrialized nations that interact with a polygenic susceptibility.

It appears that increased expression and production of TNF and an enhanced state of activation of the NFκB system are main drivers of the mucosal inflammatory reaction. The exploration of inflammatory pathophysiology of Crohn’s disease using full genome, cDNA and oligonucleotide based arrays, respectively, has generated large sets of genes that are differentially expressed between inflamed mucosa and normal controls. While this may lead to new targets for a pathophysiology oriented therapy, it appears, however, that the dissection of the inflammatory pathophysiology does not allow to identify the multifactorial etiology of the disease.

In 2001 three coding variations in the NOD2 gene were identified that are highly associated with development of the disease. All variants affect a part of the gene that codes for the leucin rich part of the protein that appears to be involved in bacteria induced activation of NFκB in macrophages and epithelial cells. A particular subphenotype with localization of the disease in the ileocecal region is highly associated with the variants in the NOD2 gene.

Variants in the NOD2 gene by far not explain the genetic risk for Crohn’s disease. With the advent of high-density, genome wide association studies enormous progress has been made to discover the remaining disease genes. More than 40 disease genes have been identified unto today, which however still explain less than 30% of the total genetic risk. In addition to innate immune barrier genes, cytokine response genes (e.g. IL-23R, IL12B, STAT3) and autophagy related genes (e.g. ATG16L1, IRGM) have been identified.

In ulcerative colitis GWAS studies are just at the beginning. The first three published studies pointed among several cytokine and macrophage function related genes point to a locus in the 3’ end of the IL10 gene. In this regard the IL-10 knockout mouse becomes interesting again that in its phenotype is closer to ulcerative colitis than Crohn’s disease.
The genetic further exploration of Crohn’s disease and ulcerative colitis will result in molecular risk maps that are presently completed with amazing speed. The creation of medical systems biology of disease will lead to new models and eventually new therapies. However, before a comprehensive view of the genetic risk map is reached etiologic discoveries remain interesting but are not yet helpful new tools for the clinician. In selected individuals, however, genetic exploration including full genome sequencing can be used to aid the choice of alternative, probatory therapies after the standard repertoire has been exhausted.
T-cell populations in inflammatory bowel disease: What do they tell us?

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The identification of the T cells and the cytokines they produce that are associated with the major forms of inflammatory bowel disease has been among the major advances in our knowledge of the pathogenesis of these diseases and has been one of the chief pathways to new approaches to their treatment. This new knowledge has led to the understanding that ulcerative colitis and Crohn’s disease are driven by very different sets of cytokines and this, in turn, accounts for the very different pathologic pathways that are evident in the histologic and clinical manifestations of these diseases.

Addressing ulcerative colitis first, we now know from both studies of murine models and from human studies that this disease is associated with an atypical Th2 response characterized by the presence of NKT cells that produce IL-13. In the murine model, oxazolone-colitis, it was shown that this mechanism is the cause of the disease since the disease could be prevented by the administration of two agents that block IL-13 activity and two agents that delete NKT cells including an anti-NK1.1 antibody and an IL-13-pseudomonas exotoxin fusion protein that deletes NKT cells via binding to a high affinity IL-13 receptor expressed by NKT cells known as the IL-13Rα2 receptor. Recently, we developed a model of chronic oxazolone-colitis in BALB/c mice which is also marked by the presence of increased NKT cells and IL-13 and which is reversed by agents that either delete NKT cells or block IL-13. Thus, oxazolone-colitis is both prevented and treated by these agents. Is human ulcerative colitis also due to NKT cells and IL-13? The answer will only come from studies of the treatment of this disease with NKT cell-deleting agents or IL-13 blocking agents that are currently being planned but have not yet been carried out. We have, however, conducted a study in which UC patients were treated with IFN-β and found that positive responses observed in some 70% of the patients were strongly correlated with decreased ex vivo IL-13 production by lamina propria mononuclear cells. This study thus provides a strong hint that IL-13/NKT cells do in fact drive ulcerative colitis. Finally, the question can be raised as to how NKT cells/IL-13 actually mediate disease. We have reported that IL-13 is itself toxic to epithelial cells and disrupts epithelial layer integrity. However, there is evidence that this cannot be the only mechanism of damage involved since we have recently studied a model of murine colitis in mice bearing a TL1A transgene who manifest increased IL-13 production in the absence of epithelial cell layer ulceration. On this basis, we believe that NKT cell targeting of epithelial cells shown previously in in vitro studies plays a major pathogenic role in ulcerative colitis. This view is strengthened by recent studies showing that numerous NK T cells can be found in the sub-epithelial areas of UC tissue.

With respect to Crohn’s disease, initial studies of both numerous murine models of the disease as well as the human disease established that IL-12p70 driving a Th1 cytokine response is occurring and is mediating disease. The fact that effective
treatment of mouse models of colitis, starting with TNBS-colitis, with anti-IL-12p40 and later treatment of humans with Crohn’s disease with a similar antibody seemed to confirm this view. However, the later discovery that a Th17 response resulting in both IL-17 and IL-22 production and sustained by IL-23 production accounted for some types of murine colitides rather than a Th1 response raised the question of whether a Th17 response rather than a Th1 response was the major driver of Crohn’s disease. This possibility was supported by the finding that IL-17 is indeed produced by cells in inflamed Crohn’s tissue and by the fact that the success of anti-IL-12p40 could be due to the fact that this antibody also targets IL-23 which, like IL-12, contains a p40 chain. More recent studies have clarified this issue to some extent. First they show that the Th17 response negatively regulates the Th1 response so that mice that cannot mount a Th17 response because they lack IL-23, exhibit much more severe TNBS-colitis; in addition, they show that IL-17 itself has a down-regulatory effect on IFN-γ-producing cells by direct interaction with IL-17. Second, they show that in accord with the regulation of Th1 responses by IL-17, Th1 and Th17 responses may be sequential so that the inflammation in Crohn’s disease (and in other autoimmune states) is a compound evolving lesion that begins as a Th1 response and merges into a Th17 response. Evidence for this comes from studies of chronic TNBS-colitis which is characterized by an initial Th1 response that morphes into a Th17 response. Whether or not this scenario is true, it is important to remember that IFN-γ is a major effector cytokine in Crohn’s disease and can arise from both a Th1 and a Th17 responses; in addition, with respect to tissue damage, it may be more potent than IL-17. How does this information inform our approach to the therapy of Crohn’s disease? The answer is that logically, anti-IL-12p40 is still the best single treatment possibility since it addresses both the Th1 and the Th17 response; in addition, it’s effect are persistent because like anti-TNF is induces apoptosis of effector cells. However, this probability needs to be proven by clinical studies of several different effector cytokines.

Other cytokines, such as those associated with regulatory cell induction and effector function, also contribute to the inflammations in IBD. These can only be glancingly considered here, although they undoubtably play an important role in both preventing onset of inflammation and resolving inflammation that has already begun.
Cytokines and chemokines in IBD: What are the most interesting targets and why?

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Inflammatory bowel diseases (IBD) are caused by an unbalanced activation of the mucosal immune system. This process is characterized by an activation of T cells and antigen-presenting cells such as lamina propria macrophages and dendritic cells. Recent studies have shown an important role of cytokines and chemokines in orchestrating the mucosal immune response in patients with IBD. Furthermore, in vivo studies in mouse models of colitis revealed that inactivation of certain cytokines and chemokines is beneficial for therapy of established disease.

In this presentation, we will review recent data on the role of chemokines and cytokines in IBD and describe interesting targets for novel therapeutic approaches.
IBD results from a continuum of complex interactions between a quartet of host-derived and external elements that involve various aspects of the intestinal microbiota, the immune system, the genetic composition of the host, and specific environmental factors. Recent studies into the complexity of these arrangements increasingly support not only the syndromic nature of this disorder, but also the need for systems-based approaches in understanding the biologic pathways involved and the correlation of these arrangements with specific phenotypic outcomes that go beyond the assigned clinical descriptors currently in practice, namely UC and CD. Studies of the microbiota, immune system, and genetics have revealed more similarities than differences between these two extreme phenotypes, suggesting this continuum of interactions is similarly reflected in a continuous lineage of functional pathways and, consequently, phenotypes. Genetic studies, for example, increasingly support the concept of familial and sporadic forms of IBD whose inheritance likely ranges from monogenic to polygenic and involve a wide range of biologic pathways that affect innate immunity, adaptive immunity, ER stress and autophagy as well as metabolic pathways associated with cellular homeostasis and the regulation of inflammation per se all of which may potentially intersect with a variety of yet to be defined environmental factors. Moreover, these genetic observations, together with immunologic studies, emphasize the particularly important role played by abnormalities of the innate immune functions of hematopoietic and nonhematopoietic cells, especially within the intestinal epithelium and its unique relationship with the commensal microbiota, in influencing and being influenced by the adaptive immune system. Given these considerations, it can be anticipated that environmental factors that modify the risk for development of IBD have the common attribute of affecting the relationship between the commensal microbiota and the immune system in a manner that intersects with the functionally relevant immunogenetic pathway(s) that are uniquely operative within a particular context of IBD.
Session II

New keys to diagnostic procedures: Laboratory markers
New insights into IBD epidemiology – Are there any lessons for treatment?

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The epidemiology of IBD has evolved. Western nations had a head start with Crohn’s disease and ulcerative colitis emerging through the mid to latter half of the twentieth century. Canada and New Zealand have had the highest incidence rates of Crohn’s disease while Denmark has continued to have the highest incidence rate of ulcerative colitis. However, over the past two decades these diseases have emerged in developing nations as well as in the developed nations of Asia such as Japan and South Korea. When IBD emerges as in the West 60 years ago, and in developing nations more recently, ulcerative colitis is the predominant form. But over the past several years in the West, Crohn’s disease has become the predominant form. Furthermore, while the sex ratio has remained equal in ulcerative colitis, the female predominance in Crohn’s disease has given way to equality between the sexes or even a male predominance. While these trends are interesting and potentially provide etiologic clues, no definitive etiologic clue has emerged. So are there environmental clues that might be harnessed for therapy?

Smoking has consistently been shown to be associated with Crohn’s disease. This and the fact that smokers consistently have been shown to have a worse course of disease, it could be argued that a compound that neutralizes smoking components might have therapeutic value. That having been said the countries with the highest smoking rates in the world have among the lowest rates of Crohn’s disease and countries with relatively high incidence rates such as Canada and Sweden have relatively low smoking rates among adult males. Quitting smoking though seems to have potential benefit, since quitters likely have a better course after medically or surgically induced remissions than continued smokers. Smoking cessation strategies need to be more fully explored with Crohn’s disease subjects and more successful smoking cessation strategies need to be discovered. In ulcerative colitis smokers seem to have a better course and quitters seem to be more likely to exacerbate. With this in mind nicotine enemas and patches have been tested therapeutically in ulcerative colitis without any enhanced benefit over placebo (enemas) or standard therapy (patches).

Recently, there has been emerging interest in the association of adherent invasive E coli (AIEC) and Crohn’s disease. At least 7 groups in North America and Europe have reported on this association. If this organism should prove to be etiologic it raises the issue as to why quinolone antibiotics, generally bacteriocidal for AIEC and widely used in Crohn’s disease are not particularly effective for luminal disease. Is insufficient antibiotic reaching the site of disease? Does antibiotic resistance develop too quickly? Or is the absence of response, an indication that AIEC are not causing inflammation? It is unclear how AIEC emerge within the bowel of patients with Crohn’s disease. In fact it is unclear how the balance of flora within the gut of subjects with Crohn’s disease becomes altered such that Firmicutes are reduced,
while Bacteroidetes and Proteobacteria are increased. Could administration of probiotics improve this balance? To date the data on probiotics in IBD have failed to show a benefit in Crohn’s disease. E coli Nissle is no more effective than low dose 5-ASA in ulcerative colitis. VSL#3 may have some benefit in pouchitis, an IBD-associated condition that does seem to consistently respond to antibiotics as well. Interesting data from a French group have shown a higher postoperative recurrence rate in Crohn’s disease in patients who harbor less Fecalbacterium prausnitzii (a member of the Firmicutes phylum). Further, less F. prausnitzii has been reported in the stool of patients with active colitis of either IBD or infection. This type of focused approach to finding a potential probiotic to administer based in evidence of its absence or reduction during pathologic states makes more sense than guessing as to which probiotics might be beneficial.

While patients are often craving dietary advice in terms of managing their IBD there is little evidence that there are specific diets or foodstuffs that predispose to developing the disease. One study from Japan previously showed an association between Crohn’s disease and consumption of total animal protein and intake of total animal fat, particularly ω-6 polyunsaturated fatty acids (and a high ratio of intake of ω-6 to ω-3 fatty acids). A second study suggested that a higher consumption of sweets was positively associated with ulcerative colitis risk and the consumption of sugars and sweeteners, fats and oils, fish and shellfish were positively associated with Crohn’s disease risk. In Crohn’s disease even the intake of ω-3 fatty acids positively correlated with disease as did the intake of ω-6 fatty acids.

In a pediatric survey study from Quebec higher amounts of dietary vegetables, fruits, fish, and fiber was protective against Crohn’s disease. Consumption of long-chain ω-3 fatty acids was negatively associated with CD and a higher ratio of ω-6/ω-3 fatty acids was significantly associated with higher risks for CD. In this study, sucrose consumption was not associated with an increased risk for Crohn’s disease.

Can we learn anything from these data about dietary advice and management once disease is diagnosed? Two important studies have shown that fish oil does not have a protective effect against disease recurrence once Crohn’s disease has been diagnosed. However, much like smoking avoidance among persons considered at high risk for disease (strong family history) it may also be prudent to encourage an increased diet of vegetables, fruit and fish. The data on ω-6 and ω-3 fatty acids seem conflicting and I would not recommend getting more specific in recommendations regarding these fatty acids and diet.

While there has been debate as to whether NSAIDs, antibiotics, infections or stress may trigger IBD, a recent review supports that the most robust data support a role for stress and more specifically the perception of stress as opposed to simply an accounting of stressful events. It has been shown that patents with IBD are more likely to have an antecedent diagnosis of depression than community based controls and that those with depression present at a younger age than those without. A series of elegant studies in an animal model of depression and colitis has shown that depression can exacerbate colitis and antidepressants can ameliorate the colitis. Hence, it is rational for IBD management to incorporate stress management and even to consider antidepressant therapy. While I would not recommend antidepressant therapy at this stage solely to treat active disease in the absence of clinical trials
proving their efficacy, these agents should be considered in patients who are depressed and who have chronic abdominal pain. Clinicians must ensure that they inquire of their patients as to their stress levels and for the presence of depression and other mood disorders. Identifying these issues in IBD patients so as they can be treated before the disease is flared may be of value.

**Selected references:**


www.nationmaster.com/graph/hea_tob_adu_mal_smokers


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Smoking, physical activity, nutrition and lifestyle: Environmental factors and their impact on IBD

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Current smoking protects against ulcerative colitis and after disease onset improves its course, decreasing the need for colectomy. On the contrary, smoking increases the risk of developing Crohn's disease and worsens its course, increasing the need for steroids, immunosuppressants, and re-operations. Smoking cessation aggravates ulcerative colitis and improves Crohn's disease. The effect of smoking in one individual may be the sum of contradictory effects of various substances, including nicotine and carbon monoxide, and may be modulated by gender, genetic background, disease location and activity, concomitant use of immunosuppressants, cigarette dose and nicotine concentration. Physical activity improves quality of life without detrimental effect on disease activity. Regarding nutrition, a western diet may be associated with an increased risk of IBD, and a case-control study revealed an increased consumption of linoleic acid before diagnosis of ulcerative colitis. However, with the exception of liquid diets which may improve Crohn’s disease flares, diet cannot be used as therapy. There are no defined diets able to improve the disease course, and in Crohn’s disease, supplementation with omega-3 PUFA did not show a significant benefit.
New serologic markers for IBD diagnosis

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Inflammatory bowel diseases (IBD) are chronic intestinal disorders where in genetically susceptible hosts an intestinal microorganism triggers an over reactive immune response. Antibodies against luminal antigens are specifically associated with Crohn’s disease (CD). In addition to the previously described antibodies ASCA, OmpC, I2 and CBir1 Flagellin, new anti-glycan antibodies were recently added to the armamentarium of serologic markers in IBD.

Glycans are sugars associated to proteins, abundant on many living cells. The anti-glycan antibodies are directed against laminaribioside, chitobioside, mannobioside and mannan residues and are designated anti-laminaribioside carbohydrate antibodies (ALCA), anti chitobioside carbohydrate antibodies (ACCA), anti mannobioside carbohydrate antibodies (AMCA) and gASCA, respectively. Anti-laminarin IgA (Anti-L), and anti-chitin IgA (Anti-C) are new members of this family.

Laminarin and chitobioside are capable of stimulating the innate immune system, thus the finding of antibodies against these glycans suggests a connection between the adaptive and innate arms of the immune response in CD patients.

The contribution of serologic markers, specifically the anti-glycan antibodies to IBD diagnosis may be in differentiating IBD patients from other gastrointestinal diseases, and between CD and ulcerative colitis (UC), in better classifying undetermined colitis and for decision making prior to proctocolectomy in UC patients. The anti-glycan antibodies are specifically important in ASCA negative CD patients. Correlation between serologic markers and genetic variations may contribute to reclassifying IBD into new and more homogeneous subclasses. Their significance in diagnosing populations at risk such as unaffected relatives of IBD patients and CD patients prior to diagnosis will be discussed.
Can serologic markers help determine prognosis and guide therapy?

M.C. Dubinsky, MD
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Physicians rely heavily on the presence of disease biomarkers to support or even at times modify their clinical impression of IBD. The search has intensified for biologic markers that can assess the natural history and predict the course of individual’s disease including response to treatments up front and sustainability over time. Both genetic and immune markers have been shown to be important predictors of the natural history of IBD. These markers have been shown to be associated with a more rapid disease progression, predicting patients who will develop a complication that results in surgery. Prognostic markers at the time of diagnosis may prove to be important in helping clinicians risk stratify and customize treatments accordingly based on risk of the underlying disease. This knowledge can help frame the conversation clinicians can have with patients so to put risk of medications into perspective keeping in mind the risk of the disease itself. Moreover these markers may prove helpful in predicting which patients may respond to which therapeutic class. This will be particularly important when multiple pathways are available for IBD patients so to choose the right therapy for the right patient.
Molecular predictors of prognosis and therapy: Are they the future?

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Progress in the field of inflammatory bowel disease (IBD) genetics has been rapid in recent years, and these advances have provided more urgent impetus to investigating the role of molecular tests in IBD. This lecture will summarize the current state of molecular testing available for IBD, and the potential utility of such tests in the future. Despite established uses of such tests in the oncology field, their integration into complex diseases has not been widely evaluated. Therapeutic decision making in IBD often hinges on some estimation of the prognosis and likely response to therapy. Since currently available clinical and laboratory markers are insufficiently helpful to be used in decision making, investigation and discovery of molecular biomarkers are of prime importance in the current and future management of IBD.

The newly discovered genetic markers are prime candidates for future analyses to assist with risk modeling in IBD for prognosis. They may also potentially have predictive value for therapy response. Thus far, there are insufficient data to justify utilizing a genetic panel of markers in clinical decision making but the field is evolving very rapidly and as new genetic markers are discovered, further work on genetic diagnostic and prognostic approaches will be carried out that may potentially bring such a panel to clinical use.

Concurrently to exploring genetic biomarkers, an effort has been made to understand how gene expression differs in affected individuals. Transcriptional changes can be induced by environmental triggers without underlying mutations in the genome. In addition, a mutant allele does not necessarily have altered expression, but it may cause transcriptional changes in downstream wild-type alleles of other genes by acting on their transcription factors. This field of “transcriptomics” is at an early stage but already some attempts have been made to study IBD outcomes by transcriptional inquiries on a genome-wide scale.

Most of these molecular approaches are not yet ready for clinical application to individualized patient care. However, it is clear that all of the ‘-omic’ approaches have exceptional potential for advancing patient care in the areas of differential diagnosis, disease prognosis, and therapy response. Molecular approaches to IBD will result in vastly improved diagnostic and prognostic methods and improved treatment decision making. Importantly, such developments will also aid in the discovery of novel therapies and, ultimately, to identification of the etiology of IBD. In order to achieve these goals, concerted and collaborative approaches by the scientific community will be required in order to perform large-scale studies for disease prognosis and therapy response such that the results are transferable across populations. If these occur, a systems biology approach of combining genetic, gene expression, and proteomic information in IBD will likely become standard within the next decade.
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Session III

New keys to diagnostic procedures: MRI, CT and endoscopy
CT enterography: Is it the current state-of-the-art for small bowel diagnostics?

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CT enterography has rapidly emerged as the preferred small bowel imaging modality at several tertiary care medical centers. It utilizes negative or neutral oral contrast agents to enhance small bowel mural assessments. A high sensitivity and specificity for active inflammation and its ability to detect extraintestinal disease set CT enterography apart from more traditional imaging methods. Robust data now support its use as it detects occult penetrating disease, changes physician level of confidence, and alters management plans in a large proportion of patients. Concerns regarding radiation exposure will become less of an issue with new dose reduction techniques. CT enterography has begun to revolutionize Crohn’s disease evaluations for luminal and extraluminal disease, and its role will likely continue to expand in diagnostic algorithms.
MR enterography: Is it the future of small bowel diagnostics?

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For imaging in small bowel diagnostics there is ultrasound, CT, MRI as well as capsule endoscopy and double balloon endoscopy as an endoscopic modality. There are several advantages of MR enterography and MR enteroclysis (which uses a duodenal sonde for continuous bowel contrast):

- MRI is not as operator dependent as ultrasound
- There is no need for ionizing radiation for the mostly young patient suffering from IBD, who frequently have multiple follow up examinations
- There is a need to exclude a relevant stenosis before applying capsule endoscopy – additionally it is not clear if the capsule endoscopy, which is a time consuming and expensive examination, is really specific enough
- Double balloon endoscopy is invasive and time consuming with a low patients acceptance and comfort for a routine application

For a MRI of the small bowel there is a need for an adequate contrast and distension of the bowel. Currently this is achieved by applying water add on such as mannitol. Image quality looks better when applying the contrast using a nasoduodenal sonde – still it is not really sure, if this adds diagnostic value for assessing Crohn's disease (CD). A recently published meta-analysis of prospective studies assessing CD by ultrasound US, MRI, CT and PET found no statistically significant different sensitivities among the image modalities on a per-patient base (US: 89.7%, MRI: 93%, scintigraphy: 87.8%, CT: 84.3%). Limitations of MRE are superficial lesions located within the mucosa. MRI is able to assess extraluminal lesions such as creeping fat, fistulas or an abscess. Additionally perianal fistulas can be assessed by MRI.

In patients with CD there is a probability of an exclusive small bowel affection in less then 10%. Therefore if a patient has the primary diagnosis of CD, the small bowel has to be evaluated completely. Currently MRI of the small bowel represents the best method with the fewest disadvantages: it is objective, non operator dependent, no ionizing radiation, patients comfort. Several national guidelines currently recommend MRI as the method of choice for small bowel assessment.
Capsule endoscopy and double balloon: When do we really need it?

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The choice of small bowel imaging is mostly dependent on local expertise, costs and availability of specific techniques. Only a few studies have compared the value of more than two different imaging techniques and capsule endoscopy (CE) for the diagnostic approach of small bowel lesions in patients with suspected or proven IBD. The consensus of these studies seem to be that the combination of endoscopic and radiologic techniques are more reliable than a single imaging modality for the first line approach of a patient with suspected IBD.

CE demonstrates a superior sensitivity compared to the radiological approach and a normal CE has a high negative predictive value for active small-bowel Crohn's disease. Before conducting CE in patients with suspected or proven IBD, an imaging study such as SBFT, CT or MRI should be performed, given the significant risk of capsule retention in this patient group. However, in a patient with suspected IBD and positive capsule findings only, a diagnosis of Crohn's disease should not be based on the appearances at CE alone.

The diagnostic yield of double or single balloon endoscopy (BE) is probably comparable to CE, but has not yet been evaluated in larger prospective studies. Theoretical BE is superior to CE since it can be used to diagnose Crohn's disease, because histological corroboration is available. However, it is an invasive and for the patient less pleasant procedure compared to CE, since most often both routes (oral and anal) are necessary to attempt to evaluate the entire small bowel. Additionally, BE can be employed to treat short strictures in patients with established Crohn's disease. However, the so far available few clinical data indicate that a superior yield and a therapeutic success of BE can be only achieved if a proper introduction route can be defined based on previous diagnostic procedures.

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Chromoendoscopy: What is the true value for UC surveillance?

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Chromoendoscopy in ulcerative colitis
Patients with extensive, longstanding, chronic ulcerative colitis have a greater risk of developing colorectal cancer than the general population. Risk factors for colorectal cancer in these patients include the extent and duration of the colitis, backwash ileitis and the presence of primary sclerosing cholangitis. Patients with longstanding ulcerative colitis are, therefore, recommended to undergo annual surveillance colonoscopy to identify mucosal abnormalities that may be indicative of colorectal cancer. Current guidelines for surveillance colonoscopy in patients with ulcerative colitis recommend that 30–50 random biopsies be sampled throughout the colon. Colitis-associated lesions, however, frequently grow flat and are multi-focal; therefore, these lesions are often missed by routine white-light endoscopy with random biopsies. There is clear evidence that chromoendoscopic guided surveillance improve the diagnostic yield of colitis associated dysplasia (per lesion and per patient) in patients with long standing ulcerative colitis.

In fact, the use of chromoendoscopy for cancer surveillance has now been investigated in more than 840 patients with ulcerative colitis in the past 5 years. The combined findings of these controlled studies indicate that the number of lesions detected by chromoendoscopy is greater than fourfold the number of lesions detected by white-light endoscopy and random biopsy sampling.

Narrow band imaging and autofluorescence for surveillance
The advantage of using chromoendoscopy in the upper gastrointestinal tract for the detection of pre-malignant and malignant changes has been challenged by the emergence of narrow-band imaging (NBI). However, no studies could proof so far any benefit for NBI for the detection of colitis associated dysplasias. However, there is an initial report available, which describes a value of autofluorescence combined with NBI to increase the diagnostic yield of intraepithelial neoplasias in UC. However, studies that directly compare NBI and/or autofluorescence imaging and chromo-endoscopy are required to assess the true value of endoscopic trimodal imaging for cancer surveillance in patients with ulcerative colitis.

Confocal laser endomicroscopy for surveillance
Confocal laser endomicroscopy is a new imaging modality for gastrointestinal endoscopy. It offers in vivo imaging of the mucosal layer at cellular and even sub-cellular resolution. Thus, in vivo histology becomes possible during ongoing endoscopy.
It was shown that chromoendoscopy can be combined to detect and diagnose intraepithelial neoplasias with high accuracy with increased diagnostic yield and significant reduction of mucosal biopsies.
In summary, chromoendoscopy is able to reveal circumscribed lesions, and confocal laser microscopy can be used to confirm intraepithelial neoplasias with a high degree of accuracy. Biopsies can therefore be limited to targeted sampling of relevant lesions. In vivo histology with endomicroscopy may lead to significant improvements.
in the clinical management of patients with ulcerative colitis, with reduced numbers of biopsies being needed for confirmation of the condition and time being gained for immediate therapeutic intervention. However, further studies are needed to clarify the value of endomicroscopy for the surveillance in IBD.

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Session IV

General treatment considerations
What is “early IBD”? How does time from diagnosis and the presence or absence of complications and previous surgery influence the response to therapy?

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Post hoc analyses of several clinical trials revealed that patients with a short Crohn’s disease history usually experience a better therapeutic response than patients with a longer disease history. This was particularly true for anti-TNF-antibodies, but similar observations have been made with antimetabolite therapy (1, 2). In a study where patients with a recent diagnosis of Crohn’s disease were treated with a combination of infliximab and azathioprine, less than 10% of the patients failed to respond to this combination, which is significantly less than the failure rates in other study populations with more ‘established disease’ like in the Accent or the CHARM trials (3–5). Likewise, children with newly diagnosed Crohn’s disease had a higher remission rate on the combination of 6-mercaptopurine and corticosteroids than adult patients with Crohn’s disease in e.g. the study by Candy and Wright (6, 7). This trend has not been observed consistently in ulcerative colitis (8).

Kugatashan and colleagues from Cleveland suggested a possible explanation for these observations, demonstrating that mucosal T cells isolated from the gut of children with early Crohn’s disease express a strongly polarised Th1 type response with excessive production of IFN-γ (9). This profile was lost with progression to late Crohn’s disease, suggesting a variable type of immunoregulation as the disease becomes ‘chronic’. An additional explanation is the presumable ‘absence’of fibrosis in earlier phases of the disease. The therapeutic agents that are usually administered to these patients probably have a limited impact on fibrogenesis. As a consequence, with the presence of more fibrosis (and a fortiori ‘stenosis’), the likelihood of a satisfactory therapeutic response will be lower.

Given the chronicity of transmural inflammation in Crohn’s disease, fibrosis gradually leads to stenosis in the absence of sufficient control of the disease and leads to the need for surgery, even despite treatment. Fibrosis and other complications such as perforation and fistula formation should hence be considered ‘late phases’ and less reversible disease states of Crohn’s disease. The fact that the inflammation in ulcerative colitis usually remains limited to the mucosa, may offer an explanation why fibrosis is less pronounced and disease duration has no impact on response to therapy.

In the postoperative setting of Crohn’s disease, all diseased segments are essentially removed and macroscopically healthy segments are anastomosed. This leads to, at least initially, absence of any fibrosis or other complications in the first months following surgery. This stage of Crohn’s disease appears to be extremely sensitive to anti-inflammatory treatment with anti-TNF agents, as it was demonstrated by the recurrence prevention trial by Regueiro et al. (10).
In summary, purely inflammatory disease states in IBD can usually be treated sufficiently with the agents that we have at our disposal. The presence of fibrosis, stenosis and fistulae invariably leads to a poorer therapeutic response. These elements favour early diagnosis and strong antiinflammatory treatments, in particular in patients with a poor disease prognosis.

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What is “accelerated step up” treatment – What are the time parameters for advancing conventional therapy?

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Ulcerative colitis (UC) and Crohn’s disease (CD) are chronic relapsing and remitting disorders of the gastrointestinal tract. During relapses or flares of disease pharmacological or surgical intervention is often needed to re-establish remission. Ideally, strategies would be employed to maintain patients in long-term remission while minimizing steroid dependence, reducing therapy related toxicity, hospitalizations, and surgeries.

Many patients with UC or CD may not receive effective therapy and their disease remains moderately active, leading to uncontrolled inflammation and potentially the development of complications due either to the underlying disease or to steroid-dependency. Although indications and goals of treatment exist, optimal treatment outcomes are not often well defined and the duration of treatment is not addressed. As a consequence, patients undergo repeated cycles of corticosteroids (with or without immunosuppressive agents) without success as their disease remains active and progresses towards complications and the need for surgery. Therapy is often continued for a long periods of time without structured reassessment to ensure that therapeutic goals are achieved. Symptomatic treatment success in the treatment of Crohn’s disease or ulcerative colitis should be defined as a return to the patients normal bowel function for that individual prior to disease flare. Setting specific time limits (i.e. time bound strategies or accelerated step up) for evaluation of the success of therapy may lead to improved patient outcomes and reduced side effects. A strategy that includes restricting overall exposure to corticosteroids and encouraging earlier use of immunosuppressive agents and anti-TNF therapies in steroid-dependent and steroid-refractory patients should be adopted in these patients to avoid complications leading to surgery and impairment of QoL. More recently, treatment goals beyond symptoms have been proposed which include mucosal healing and the return to structural normality. Although in theory, treating to mucosal healing appears to be attractive and should logically lead to improved outcomes, this is not currently common practice. It is likely that future investigators will reveal to what degree mucosal healing impacts patient outcomes and how current treatment strategies may need to be modified to achieve this goal. Structured algorithms for the treatment of moderate to severe CD and UC with corticosteroids, immunosuppressive agents and biologic agents, with the goal of maximising remission and minimising corticosteroid dependency will be presented.1,2

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Supportive care in inflammatory bowel disease

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The past decade has witnessed tremendous advances in medical and surgical strategies to treat inflammatory bowel disease (IBD), particularly those patients with moderate to severe manifestations of its two major forms, Crohn’s disease and ulcerative colitis. Widespread use of immunomodulator maintenance therapy with purine analogs and methotrexate and the advent of biologic therapy has dramatically improved the ability of patients with more severe disease to achieve and maintain remission. Surgical advances have offered minimally invasive, laparoscopic approaches for the treatment of IBD complications with improved cosmesis and diminished post-operative pain and recovery time. New understanding of how to utilize medications in the post-operative time period may also provide an ideal approach to prevent damage and achieve optimal remission in patients at risk for significant post-operative recurrence. However, the optimal care of patients suffering from moderate to severe IBD remains complex, and must take into account numerous additional clinical factors and patient issues to achieve optimal results.

Foremost in the area of IBD supportive care, is the identification and treatment of complicating factors, specifically gastrointestinal infections (i.e. Clostridium difficile) which can both mimic and worsen an IBD flare if not recognized and treated effectively. Likewise, the ability to optimally treat patients requiring hospitalization will also require attention to nutrition, prophylaxis targeting thromboembolic complications and safe and effective pain management. Finally, there is resurgent interest in addressing the psychological aspects of caring for severely ill IBD patients, particularly hospitalized individuals those facing surgery. Providing supportive psychotherapy for patients facing the prospects of an ostomy is an issue which has received little formal attention on the part of treating clinicians, but represents one of the most pressing concerns among colitis patients. Along these same lines, the severely ill colitis patient who fails to accepts these body-image issues and refuses colectomy faces life-threatening complications if they refuse emergent surgery. Patients who fail to adjust to the reality of an ostomy after colectomy may take extreme action and suicide has been witnessed in this setting. Addressing psychological complications of severe illness, particularly the adverse effects of corticosteroids which can exacerbate depression as well as recognizing the adverse effects of sleep deprivation associated with both hospitalization and active IBD flare are important and often overlooked areas which can help patients adjust, heal and successfully recover from severe disease.

This review will provide an overview of supportive care for patients with moderate to severe IBD, with particular focus on approaches for patients facing hospitalization and surgery. Effective supportive care will address complicating factors, prophylaxis strategies, nutrition, pain control and psychological aspects of illness in patients with moderate to severe IBD.
Inflammatory bowel diseases (IBD) are known to influence physical, psychological, familial and social dimensions of life. Over the past two decades, attention has been focused on the ability of IBD to alter patients’ quality of life. A number of general and disease-specific scales have been used to assess quality of life in patients with IBD. The Inflammatory Bowel Disease Questionnaire (IBDQ) is the most widely disease-specific tool used in clinical trials. Forty to fifty million individuals in the US now live with potentially disabling conditions. Disability usually refers to an individual’s inability to perform a task successfully. Disability refers to the problems that you have in different areas or health domains, whereas quality of life refers to how you feel about these limitations and restrictions. Data about disability are objective descriptions that differ from subjective appraisals such as quality of life, well-being, and personal satisfaction with life. For instance, difficulties in walking (disability) may be in stark contrast to how do we feel about this difficulty (quality of life). It should be emphasized that the concepts of health-related quality of life and disability are different but not mutually exclusive. When compared to quality of life, disability remains poorly investigated in IBD. Work is the only dimension of disability that has been widely assessed in IBD. Similar to multiple sclerosis and rheumatoid arthritis, developing a specific instrument capable of evaluating disability in IBD is a prerequisite to undertaking clinical trials aimed at identifying therapies capable of changing their clinical course.
Evolving concepts in IBD therapy: What should be studied in the future?

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Recently the goals of treatment in IBD have been shifting in analogy to rheumatoid arthritis towards avoiding structural damage, long-term functional deficits and complications limiting quality of life in patients with a life-long disorder. This implies the avoidance of surgery and/or scaring due to continuous inflammation. The ultimate goal is obviously the healing of the disease, which would mean elimination or neutralization of susceptibility factors, which are mostly not yet even known. Since it is not possible to change genetics an approach to change the environmental factors would be reasonable but is probably not possible.

Thus far sufficient success has been achieved regarding the long-term course of the disease in 40 to 50% of patients with Crohn's disease and 60% of patients with ulcerative colitis. This implies that still quite a number of patients has continuous problems and faces long-term structural damage and complications. The results may be improved by just optimizing the currently available therapies using better modes of application or combinations of available principles. The improved effect of a combined oral and rectal application in ulcerative colitis or the improvement by using a combination of azathioprine and infliximab in patients with need of more aggressive immunosuppression may serve as an example.

Thus far most generally accepted therapies are based on the immunosuppression paradigm. This concept is more than 50 years old and has been somewhat successful in treating active disease using corticosteroids and later-on other fast acting immunosuppressants such as the TNF antibodies. It was based on the idea that an overactivity of the adaptive immune system may be the primary or the secondary mainstay of pathophysiology. The overall success rates of such treatment in particular in the long-term, however, have raised doubts about the validity of this concept and this approach. This can particularly be shown in the recent SONIC trial where the long-term remission rate is far below what we would need for all 3 arms. This may be due to the fact that we have a syndrome of inflammation in the gut due to a wide variety of causes needing different approaches and to the fact that all concepts of immunosuppression neglect the finding that more recently the defective barrier and in particular deficiencies of the innate immune system have been shown to be major players in the etiology and pathogenesis of this syndrome.

Therefore the concept of the defective barrier needs to provide targets for future treatments. For those patients showing a defect of their innate immune system (which is part of this barrier) approaches supporting rather than suppressing immune responses need to be tested. This has shown to be effective in animal models but needs to be tested in humans.
In a similar way modulation of the bacteria in the gut, which are the primary players on the other side of the barrier needs to be tested more vigorously. Thus far probiotics, helminths and others have been studied but may need to be more refined in the approaches.

While defensins may be overstated as single major cause of IBD the idea of somehow improving this component of the barrier may be reasonable in a group of patients as well.

Furthermore luminal components such as bile acids or biliary constituents, nutritional components and others need to be tested or manipulated in order to analyze their role in the barrier defects.

Some simple measures to improve barrier tightness such as components of the mucus layer (i.e. phosphatidylcholine and others) may prove to be effective treatments in some or even a larger group of patients as well.

In summary, the shift of etiological and pathophysiological thinking from general principles of inflammation and hyperimmune reaction towards more focused barrier concepts leads to novel treatment approaches, which need however to be tested in appropriate trials. Animal data and pilot results are promising and seem to be more rational than the further development of immunosuppressive strategies, which have been used for more than 50 years with some but not overwhelming success.
Session V

New keys to the treatment of ulcerative colitis
Does treatment schedule matter? Once daily vs. divided doses of 5-ASAs

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Sulfasalazine was the first 5-ASA product used to treat ulcerative colitis (UC). Because of tolerability issues, it was administered in a three times a day schedule in order to try to minimize side effects. With the development of sulfa-free 5-ASA products, the controlled trials used historical clinical experience and in vitro pharmacokinetic studies to dose their therapies to perhaps be in the most favorable light possible. However, it became clear over the years that outside of the context of a clinical trial, tid or even qid dosing as in the case of time-released mesalamine, patient satisfaction and overall adherence to therapeutic regimens was low. Research demonstrated that upwards of 40% of patients were not taking their maintenance 5-ASA, and many cited unintentional forgetfulness as the reason. Pediatric patients felt encumbered by having to take medicines at school and regularly missed their mid-day doses. It became clear that simplifying the regimen was paramount for acceptable outcomes. Early pilot data and then controlled trials demonstrated the efficacy and safety of twice daily 5-ASA for active and quiescent UC. Now several large controlled trials demonstrate the non-inferiority and increased patient adherence and satisfaction with once daily dosing. MMX mesalamine was the first 5-ASA to receive US FDA approval in a once daily regimen. Results from the PODIUM, QDIEM and SIMPLE studies have all demonstrated acceptable effectiveness rates with favorable side effect profiles. Adherence rates remain high in real-world settings when medication is given once daily and data now suggest that once daily is more effective than once daily. It thus appears that the majority of patients with UC, whether with active or quiescent disease, can be treated with once daily 5-ASA.
New keys to maintenance treatment in ulcerative colitis

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Maintenance treatment in ulcerative colitis often unnecessarily fails to prevent flares and long term complications. The first key is to use effective maintenance therapy, even when patients become asymptomatic. The second key is to communicate the importance of adherence to your patients, and to help them achieve long term adherence. Simplified dosing schedules are of some benefit, but the bond between patient and doctor, and the patient’s belief in the efficacy of the therapy are essential. Decreased copays have been associated with increased adherence, and incentives for patients may be a cost-effective approach to improving adherence. While the most substantial data on the association between adherence and clinical outcomes is in 5-ASAs, nonadherence also limits the efficacy of thiopurines and biologics.

The third key to maintenance treatment is monitoring and maintaining control of inflammation. Decreased histologic and endoscopic damage to the colon has been associated with decreased risk of colon cancer. The most cost-effective way to monitor smoldering inflammation is not known, but endoscopy, structured symptom indices, and biomarkers may be valuable approaches. The fourth key to maintenance treatment is optimizing immunomodulator therapy with thiopurines, and possibly methotrexate in the future. The fifth key to maintenance treatment in ulcerative colitis is maintaining biologic efficacy by avoiding low trough levels and being vigilant for symptom recurrence at the end of dose intervals. Combination therapy with immunomodulators improves trough levels in Crohn’s, and may prove to have benefits for maintenance of biologic efficacy in UC.
Phosphatidylcholine (lecithin) and the mucus layer: Evidence of therapeutic efficacy?

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Colonic mucus serves to protect against attacks from the bacterial flora in stool. Phospholipids are one of the major components of the mucus, which consists of up to 90% of phosphatidylcholine (PC) and lysophosphatidylcholine (LPL). PC is found as a continuous lamellar layer in the apical mucus and is thought to be responsible for establishing a protective hydrophobic surface. This “intestinal surfactant” appears to play a key role in mucosal defense. A defective PC layer is thought to contribute to the development of inflammation and ulceration. Analysis of rectoscopically acquired mucus aliquots revealed a 70% decrease in PC and LPC contents in ulcerative colitis (UC) in comparison to Crohn’s disease (CD) and healthy controls. This was independent of disease activity. PC secretion measured in ileal mucosal biopsies was significantly reduced in UC. In murine intestinal perfusion studies PC was found to be actively secreted in the jejunum and ileum, but only marginally secreted in the colon. As PC can be found in colonic mucus, we postulate that it moves with the mucus along the intestinal wall from cecum to rectum, revealing the lowest content in rectum (“the last lawn”). The consequent clear reduction of surface hydrophobicity in UC was determined by contact angel measurements and indicates a higher permeability for colonic bacteria to attack the mucosa and to trigger inflammation. Thus, we propose the lack of mucus PC as key pathogenetic factor in UC. Accordingly we developed a delayed release oral PC preparation to supplement PC in colonic mucus. In a first proof of concept study in non-steroid-treated chronic-active UC, delayed release PC was found to substitute the PC depletion in the rectal mucus. Patients had a clear benefit from the treatment. Sixteen of 30 PC patients (53%) reached remission (CEA ≤ 3) compared to 3/30 (10%) placebo patients (p ≤ 0.001). Endoscopic and histologic findings as well as life quality improved, concomitantly. A second trial with 60 chronic-active, steroid-dependent UC patients was conducted to test for steroid sparing effects. The main outcome measure (complete steroid withdrawal with a concomitant achievement of remission (CAI ≤ 3) or clinical response (≥ 50% CAI improvement) was reached in 15 PC-treated patients (50%) but only in 3 (10%) placebo patients (p = 0.002). A dose finding study confirmed these results and demonstrated clinical efficacy at doses of 1–4 g daily. Doses above 1 g, however, were significantly superior in inducing remission while having a similar safety profile. A recent follow-up evaluation of all patients treated in our PC studies and were maintained on open label PC at our centre revealed that 33% of PC patients remained in continuous remission, compared to 10% of the patients in the control group.

Conclusion: The intrinsic significant reduction of colonic mucus phosphatidylcholine (lecithin) may be a key pathogenetic feature of ulcerative colitis. Topical supplement of PC by a delayed released oral PC preparation is effective in resolving inflammatory activity of UC and may develop to a first choice therapy for this disease.
Positioning biologics in ulcerative colitis

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While the evidence base for biologic agents in UC is less developed than the clinical data for Crohn’s disease, there remains a clinical need for improved therapeutic algorithms; in particular for patients who are refractory to therapy with aminosalicylates or as steroid-sparing agents.

At present, data for biologic therapy in UC is limited to: the two large ACT trials with infliximab for patients with moderate-severe activity despite aminosalicylates, corticosteroids and/or immunosuppressives; a large multicenter clinical trial in a similar population of patients using adalimumab, and; a number of small series of patients treated in hospital for severe colitis or outpatients with refractory pouchitis. The ACT trials have demonstrated that patients with moderate-severe refractory colitis are likely to respond to infliximab induction and maintenance therapy. Approximately two-thirds of patients responded within the first 8-weeks to induction regiments of 5 or 10 mg/kg at weeks 0, 2, and 6 (compared to less than 30% of patients receiving placebo and over one-half of patients maintained their response for a full year. Approximate one-third of patients were in clinical remissions at 8-weeks, and two-thirds achieved “mucosal healing”. Twice as many patients achieved a prolonged, steroid-free remission at one-year compared to patients receiving placebo (approximately 20–25% vs. 10%) (1). Subsequent analysis also demonstrated a “colectomy-sparing” benefit from infliximab in the clinical trial population (10% with infliximab vs. 17% with placebo) (2).

In the setting of hospitalized patients with severe colitis, infliximab has also been reported to have colectomy sparing benefits in smaller clinical trials and observational series; however, the subjectivity of end-points and lower “quality” evidence provide less conclusive, though positive outcomes (3).

Anti-TNF biologic therapy has also been explored in the setting of pouchitis, in particular for patients with “Crohn’s-like” pouch or ileal complications (4–6).

With respect to the positioning of biologics in UC, there is also some concern regarding adverse effects, in particular, operative complications and infections (7).

In addition to biologic therapy directed at TNF, early trials using anti-adhesion molecule therapy have led to ongoing phase III trials with vedolizumab (8). Meanwhile, strategies assessing inhibition of T cell activation with visilizumab, abatacept, basiliximab and daclizumab have been abandoned.

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Total proctocolectomy (TPC) cures a patient of the intestinal manifestation of CUC. The timing of surgery during the illness will influence the choice of operation, the frequency of post-operative complications, and the long-term functional outcomes. Surgery is divided into: emergent, urgent, and elective procedures. Emergent cases are performed for complications of fulminant colitis: hemorrhage, perforation, toxic megacolon or sepsis. A subtotal colectomy (STC) with an end ileostomy (EI) is the procedure of choice. A STC removes the bulk of the disease, allows the patient’s health to be restored, medication to be withdrawn, and permits a future restorative operation. Urgent operations occur in hospitalized patients with continued symptoms after 7 days of maximal medical therapy. Once again the preferred operation is a STC with EI. Indications for elective colectomy include: persistent symptoms despite maximal therapy, medication side-effects, persistent chronic disease state, dysplasia/malignancy. Elective surgical options include TPC with EI, TPC with ileal-pouch anal anastomosis (IPAA), or STC with EI. The choice of operation is based upon patient preference and preoperative physiologic and functional status. Factors associated with increased post-operative complications are weight loss > 10%, multiple preoperative blood transfusions, albumin < 3.0 gm/dl, and degree of immunosuppression. In high-risk patients, a STC with EI should be performed. IPAA can be performed later after the patient’s health is restored. In conclusion, numerous factors affect the timing and choice of operation patients with CUC. Avoiding complications especially in IPAA patients is essential as they negatively impact the long-term function and durability of the IPAA.
Session VI

New keys to immunosuppression
Surveillance strategies in IBD patients – A dermatologist’s sight

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A certain percentage rate of patients with inflammatory bowel diseases (IBD) require long-term immunosuppressive therapy (IS). Though immunosuppressive therapies are nowadays comparably well adapted to the patients’ individual tolerance and therapeutic need, iatrogenic immunosuppression has been associated with subsequent infectious diseases and malignancies. While it is well established that other groups of patients in need of chronic immunosuppression, such as organ transplant recipients (OTR), have a predominant increase of non-melanoma skin cancers little is known about dermatologic side effects in patients with IBD requiring chronic IS. With an annual incidence greater than 1,000,000 patients in the USA, invasive skin cancers are already the most frequent types of any invasive malignancy in immunocompetent subjects with Caucasian skin types. However, in organ transplant patients the incidence after only 3 years of immunosuppression is more than 20 fold increased as compared to age matched, immunocompetent control persons. Interestingly non-melanoma skin cancer and especially invasive squamous cell carcinomas seem to be benefitted from chronic IS. Ten years ago, an international network started to explore the incidence of skin disorders in OTR, define relevant risk factors for the high skin cancer burden in this group and evaluate mechanisms for primary and secondary prophylaxis for this delicate group of patients. Studies regarding the incidence of skin cancer in IBD are rare and still inconsistent but appear to confirm the trends shown in OTR before. The lesions learnt in OTR and other patient groups with chronic iatrogenic immunosuppression should benefit aftercare programs for IBD patients. Similar preventive techniques and therapeutic strategies embedded into interdisciplinary, international networks may help to prevent morbidity and potential mortality due to skin cancers but also skin infections in IBD.

Skin cancers are the most frequent malignancies in organ transplant recipients (OTR), 95% of them being keratinocytic cancers (KSC), especially squamous (SCC) and basal cell carcinomas. Most OTR with a first SCC develop subsequently multiple KSC within 5 years, highlighting the concept of “field cancerization”, and are also at high risk for non-cutaneous cancers. In order to reduce the tumoral burden of these patients, their management requires an interdisciplinary approach including revision of immunosuppression, new dermatological treatments and adequate patient education about photoprotection in specialized dermatology clinics for OTR. Whereas surgery remains the gold-standard therapy for KSC, non-invasive methods have shown promising results to treat superficial keratoses and subclinical lesions on large areas. Although the threshold of skin cancer necessitating revision of immunosuppression is controversial, this measure should be discussed at the occurrence of the first SCC or in case of multiple non-SCC KSC. If the role of immunosuppressants in the occurrence of KSC is widely recognized, the best immunosuppressive strategies remain to be defined. Presently, randomized prospective studies assess the burden of new skin tumors, as well as graft and patient survival, in patients with one or several KSC after the introduction of mTOR inhibitors.
Keywords: Inflammatory bowl diseases, organ transplantation, skin cancer, skin cancer prophylaxis, sun-screen, immunosuppression, mTORi

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Hepatotoxicity of IBD therapy: A hepatologist’s viewpoint

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Hepatobiliary disease in IBD must be viewed from the perspective of the primary or secondary disorders that are commonly associated with IBD (such as PSC, cholangiocarcinoma and autoimmune hepatitis); the acute and chronic hepatic injury directly attributable to the drugs used to treat IBD (sulfasalazine, mesalamine, thiopurines, methotrexate, TNF antagonists, quinolone antibiotics); liver toxicity from the drugs used to treat complications of immunomodulators and TNF antagonists (such as from isoniazid for the treatment of reactivated tuberculosis); and exacerbation of underlying chronic viral hepatitis B (and possibly C) with infliximab and other TNF antagonists. Finally, on a related note, there have been instances of ulcerative colitis being exacerbated by interferon used to treat chronic viral hepatitis C.

General references of the hepatobiliary diseases and DILI in IBD:
(a) Bashir and Lewis. Gastroenterol Clin North Am 1995;24:647
(b) Davern. In Kaplowitz & DeLeve, eds. Drug induced liver disease 2008, p. 666
(e) Saich and Chapman. World J Gastroenterol 2008;14:331

I Hepatobiliary disease associated with IBD

1) Primary sclerosing cholangitis (PSC)
- PSC is found in 5% of patients with UC and in 3–4% with Crohn disease (CD); and conversely, approximately 90% of PSC patients have IBD. Cholangiocarcinoma complicates 10–15% of PSC patients [Saich and Chapman. World J Gastroenterol 2008;14:331]
- Elevated serum alkaline phosphatase (AP) is found in 5% of UC patients (85% of whom had PSC on ERCP in a Swedish study [Olsson et al. Gastroenterology 1991;100:1319]; more common in men with pancolitis
- Common symptoms include pruritus and lethargy but 40–50% are asymptomatic at time of diagnosis (at mean age 40–45); men outnumber women by 2:1
- Norwegian study of CD patients found 15% had abnormal liver associated enzymes (LAEs), and ERCP diagnosed PSC in 3–4% [Scand J Gastroenterol 1997;32:604]
- pANCA positivity in 80% of PSC patients and HLA B8/DR3 more common in those with associated IBD compared to PSC alone [van Milligan et al. Am J Gastroenterol 1995;90:893]
- variant of “small duct PSC” recognized in small percentage with characteristic clinical and biochemical findings but normal cholangiogram; requires biopsy to identify the typical concentric fibrosis around bile ducts (“onion-skin appearance”); may have a more favorable long-term prognosis but may progress to large duct disease [Bjornsson et al. Gut 2002;51:731]
2) Autoimmune hepatitis (AIH)

- UC found in up to 16% of patients with autoimmune hepatitis and overlap syndromes [Perdigoto et al. J Hepatol 1992;14:325; Saich and Chapman. World J Gastroenterol 2008;14:331]
- Usually associated with autoantibodies (anti-nuclear, anti-actin or smooth muscle antibodies)
- Swedish registry reported familial association of IBD with other autoimmune disorders in 5% of UC and 6.5% of CD patients [Hemminki et al. Am J Gastroenterol 2010;105:139]
- Overlap of AIH found in 7–54% of PSC patients – suspected in those with positive autoantibodies, lower alk phos, elevated IgG and interface hepatitis on biopsy [Gregorio et al. Hepatology 2001;33:544]
- Steroid therapy may exacerbate underlying chronic hepatitis B and C

II Drug-induced liver injury due to agents used to treat IBD

1) Sulfasalazine and other aminosalicylates

*Sulfasalazine* can cause two main forms of hepatic injury:

(a) acute hepatocellular damage as part of a generalized hypersensitivity reaction due to the sulfapyridine moiety, accompanied by fever, rash, lymphadenopathy, hepatomegaly, atypical lymphocytosis and eosinophilia; usually well within two months of starting therapy (with a shorter latency on reexposure)

- frequency of severe DILI estimated at 0.4% in a local UK series [Jobanputra et al. BMC Musculoskelet Disord 2008;9:48]
- incidence in a large UK survey was 6 cases of DILI per million prescriptions [Ransford and Langman. Gut 2002;51:356]

(b) acute granulomatous hepatitis, often presents with high fever, malaise, RUQ pain, elevated ALT and bilirubin (but normal alk phos), with non-caseating granulomas on biopsy; treatment with corticosteroids [Namias et al. J Clin Gastroenterol 1981;3:193]

*Mesalamine* only rarely causes acute DILI – the incidence was 3.2 cases per million prescriptions in the UK audit [Gut 2002;51:356]; cholestatic injury has been reported [Stoschus et al. J Hepatol 1997;26:425] with non-immunoallergic features in some cases [Barroso et al. Gastroenterol Hepatol 1999;22:176] but and an apparent cross-reactive hypersensitivity reaction was seen with mesalamine after a prior hypersensitivity reaction to sulfasalazine [Hauketeete et al. Gastroenterology 1992;103:1925]
2) Thiopurines

Azathioprine (AZA), 6-mercaptopurine (6MP) and 6-thioguanine (6-TG) produce a range of DILI including asymptomatic LAEs, hepatocellular necrosis, cholestasis and mixed injury. In addition, hepatic vascular endothelial injury is also seen as sinusoidal dilatation, peliosis hepatis, nodular regenerative hyperplasia (NRH) and veno-occlusive disease (sinusoidal obstruction syndrome, SOS).

(a) Acute liver injury:
- overall prevalence of 3.4% with annual incidence of 1.4% cited on literature review by Gisbert et al. (Am J Gastroenterol 2007;102:1518) using definition of LAEs > 2 x ULN; liver injury being ALT > 2 x with bilirubin > 2 x with little difference in DILI incidence between AZA (2.1%) and 6-MP (2.7%)
- prospective study in 161 patients treated for mean 9 months found elevated LAEs in 13% [Bastida et al. Aliment Pharmacol Ther 2005;22:775]
- acute hypersensitivity with cholestatic hepatitis occurs within 2–3 weeks with cholestatic injury pattern and is felt to be idiosyncratic, not related to the dose, associated with rash, fever, arthragias, and sometimes pancreatitis
- Most cases of non-allergic AZA or 6-MP induced cholestasis occur within 2–5 months of use, with men at higher risk than women; in contrast to acute hepatocellular injury, some instances of cholestatic jaundice DILI may not regress despite drug withdrawal
- DILI appears to be related to the concentration of thiopurine metabolites mediated in part by genetic polymorphisms of thiopurine (S)-methyltransferase (TPMT) [Gardiner et al. Eur J Gastroenterol Hepatol 2008;20:1238]
- All 3 agents are prodrugs that must be metabolized in order to be active. AZA is rapidly converted to 6-MP in the liver which is then metabolized by TPMT into 6-methyl mercaptopurine (6-MMP); by xanthine oxidase into 6-thiouric acid and by hypoxanthine phosphoribosyl transferase (HPRT) into 6-thioinosine-5'-monophosphate (6-TIMP) and then into 6-thioguanine nucleotides (6-TGNs)
- TMPT catalyzes thiopurine S-methylation under genetic control with poor methylator phenotypes at risk for severe myelotoxicity via higher levels of 6-TGNs; in contrast, high TMPT activity leads to lower 6-TGN levels associated with a poor clinical response and higher levels of 6-MMP concentrations associated with hepatotoxicity
- Retrospective study of 173 adults with IBD in LA (90% receiving 6-MP for a mean of 20 months, 107 with CD) reported that 4.6% developed hepatotoxicity (mean ALT 178, AST 117, bili 1.1, with normal alk phos) that normalized with dose decrease or discontinuation. Levels of 6-TGN was higher (277 pmol vs. 214 p < 0.05) in the DILI group as were levels of 6-MMPR (10,537 pmol vs. 3452 p < 0.001 [Shaye et al. Am J Gastroenterol 2007;107:2488]
• Study of 92 pediatric patients on 6-MP/AZA found 17% had DILI, associated with higher 6-MMPR levels (risk was 3x higher when the level was > 5700 pmol) [Dubinsky et al. Gastroenterology 2000;118:705]. Same group also found higher 6-MMPR levels correlated with DILI among adults vs. those without DILI [Dubinsky et al. Gastroenterology 202;122:904]; although not all studies have shown a close correlation of DILI to 6-MMPR levels [Gupta et al. J Pediatr Gastroenterol Nutr 2001;33:450]

• Switching from once daily dosing to twice daily has been proposed as a means of decreasing 6-MMPR levels and reducing the risk of DILI; conversely, if LAEs are normal but clinical response is suboptimal, dose escalation is warranted with monitoring of 6-TGN levels to ensure they rise appropriately (Shaye et al. AJG 2007;107:2488)

(b) Vascular endothelial lesions (NRH, VOD, peliosis)

• NRH has been seen in a variety of hematologic, rheumatologic and lymphoproliferative disorders, and more recently as a result of certain drugs and chemotherapeutic agents, including 6-TG and AZA

• Incidence from 6-TG in IBD studies ranges from 27–61.5% [Teml et al. Clin Pharmacol Ther 2006;44:503]; occurs after 3 months to > 3 years on therapy

• Geller et al. (Am J Surg Pathol 2004;28:1204) found NRH changes in 53% of 38 liver biopsies from patients receiving 6-TG for 1–3 years

• Large survey found 29% of biopsies showed NRH (number needed to harm with high-dose 6-TG only 3–4), but very few patients discontinued therapy due to hepatic biochemical abnormalities

• NRH appears to be dose-related – rarely seen with low-dose regimens of 20 mg/day [de Boer et al. Liver Transplant 2005;11:1300]

• Recognized pathologically by the presence of small hepatic nodules (usually < 3 mm) separated by atrophic tissue and (in contrast to cirrhosis) the absence of fibrosis [Wanless et al. Hepatology 1990;11;787]

• Clinical course is usually indolent, but it may lead to noncirrhotic portal hypertension, including varices, and has led to liver transplant [Krasinskas et al. Liver Transplant 2005;11:627] but is usually asymptomatic with mild elevations of alk phos and aminotransferases that is potentially reversible [Seiderer et al. Eur J Gastroenterol Hepatol 2006;18:553]

• Natural history data of NRH are limited, but changes of portal hypertension have resolved after discontinuation [Herrlinger et al. Aliment Pharmacol Ther 2003;17:1459]

• MRI appearance of multiple fine nodules without overt changes of portal hypertension may be suggestive [Seiderer et al. J Hepatol 2005;43:303]

• Etiopathogenesis thought to be a compensatory hypertrophic response to the effects of hepatocyte atrophy caused by obliteration of portal venules (by platelet aggregates and/or thrombi); endothelial damage leads to extravasation of RBCs into the space of Disse which may eventually narrow the lumen of the small venules and contribute to portal hypertension
Hepatic hemodynamics studied in 26 pts on 6-TG for IBD (mean treatment duration 38 mo); 6 [4F, 2M] of 24 (25%) had NRH on biopsy and hepatic venous pressure gradient was elevated in all 6 [with thrombocytopenia and mean ALT 100]; 2 of 6 had clinically significant portal hypertension; HVPG decreased one year after 6-TG discontinued [Ferlitsch et al. Am J Gastroenterol 2007;102:2495]

Peliosis hepatic has been described after 6-TG therapy of acute leukemia (Larrey et al. Gut 1988;29:1265), and probably shares an etiopathogenesis with sinusoidal dilatation, NRH, and VOD. Alcohol binging was associated with peliosis in a pt taking AZA [Elsing et al. World J Gastroenterol 2007;13:4646]

Acute sinusoidal obstruction syndrome (Veno-occlusive disease) has been described in CD after 14 months on 6-TG [Kane et al. Inflamm Bowel Dis 2004;10:652]. The mechanism of SOS may be marked depletion of glutathione by AZA on sinusoidal endothelial cells [DeLeve et al. Hepatology 1996;23:589]

(c) Management and prevention of thiopurine-related DILI


- Monitor LAEs, WBC and clinical symptoms at week 2, 4, 8 and every 3 months thereafter for AZA or 6-MP (and more frequently if 6-TG used)
- Liver biopsy recommended after 6-12 months and q 3 years for patients on 6-thioguanine [de Boer et al. World J Gastroenterol 2006;73:25–31]; add EGD to look for varices if clinically apparent portal hypertension from NRH suspected
- Utility of 6-MP metabolite monitoring (e.g. 6-MMP levels) is increasingly recognized to identify patients at risk of hepatic injury and other toxicities [Gearry and Barclay. J Gastroenterol Hepatol 2005;20:1149; Kwan et al. Dig Liver Dis 2008;40:425]
- Split dosing of AZA or 6-MP to decrease 6-MMP levels while maintaining clinical efficacy and 6-TGN levels [Shaye et al. Am J Gastro 2007;102:2488]
- Allopurinol, a xanthine oxidase inhibitor, has been utilized to reduce the adverse effects of AZA/6-MP, including hepatotoxicity [Sparrow et al. Clin Gastroenterol Hepatol 2007;5:209; Leong et al. Expert Opin Drug Safety 2008;7:607]
• Allopurinol 200mg/day was given in combination with AZA or 6-MP in a dose reduced by 25% after LAEs had returned to normal in 11 pts (UC = 8, CD =3) with DILI on their original doses of AZA/6-MP. Nine of the 11 tolerated the low-dose regimen long-term without recurrent DILI [Ansai et al. Aliment Pharmacol Ther 2008;28:734]

3) TNF-alpha antagonists

Infliximab (Remicade) and Adalimumab (Humira) are both approved for use in IBD. Relatively few cases of DILI have been reported with these biologics, with clinical trials of infliximab having elevations in aminotransferases similar to placebo recipients, without jaundice or impaired liver function [Hanauer et al. Accent I trial. Lancet 2002;359:1541]

• The FDA has issued warnings regarding the potential risk of serious liver injury based on postmarketing surveillance
• While some cases have features of autoimmune hepatitis, the meaning of autoantibodies that frequently accompany use of these biologics is uncertain
• As TNF-alpha signaling is considered important for self-tolerance, it is postulated that hepatotoxicity appears to be idiosyncratic, mediated by aberrant immune response induced by blocking TNF in a susceptible host [Davern. In: Kaplowitz and DeLeve, eds. Drug-induced liver disease 2008, pp. 672–3]
• Hepatosplenic T-cell lymphoma (HSTCL) associated with biologics may be confused with liver disease from other causes (e.g. elevated LAEs with hepatosplenomegaly, malaise, fever, thrombocytopenia, etc) [Thayu et al. J Pediatr Gastroenterol Nutr 2005;40:220]

4) Other Agents

(a) Methotrexate has been linked to severe fibrosis and cirrhosis when used in frequent high cumulative dose regimens in rheumatoid and psoriatic arthritis [Lewis & Schiff. Am J Gastroenterol 199 ], but less so when used in IBD

• In 20 pts with refractory IBD on MTX who had liver biopsies at the University of Chicago, the mean cumulative methotrexate dose was 2633 mg (range, 1500–5410 mg), given for a mean of 131.7 wk (range, 66–281 wk). Nineteen of 20 patients (95%) had mild histological abnormalities (Roenigk's grade I and II), and one patient had hepatic fibrosis (Roenigk's grade IIIB). Abnormal liver chemistry tests, present in 6 of 20 (30%) patients, did not identify the patient with Roenigk's grade IIIB hepatotoxicity. The authors concluded that cumulative methotrexate doses up to 5410 mg given up to 281 wk in patients with inflammatory
bowel disease are associated with little hepatotoxicity. Surveillance liver biopsies based on cumulative methotrexate doses are not warranted in these patients [Te et al. Am J Gastroenterol 2000;95:3150]

- Elevated aminotransferases may correlate with low serum albumin levels

(b) Quinolones (e.g. ciprofloxacin) have been reported to cause acute DILI (often cholestatic) and have done so in IBD patients [Bataille et al. J Hepatol 2002;37:696]

III. DILI from agents used to treat complications of IBD therapies

1) Drugs used to treat tuberculosis reactivated or induced by biologics
   - Isoniazid produces acute hepatocellular injury in an age dependent manner that may be fatal or lead to liver transplant; ALT and clinical monitoring should be continued for at least 6–9 months
   - Belgian series of 8 pts (with RA) treated with TNF inhibitors treated with INH reported 4 with moderately severe DILI; 3 had to discontinue Tx [VanHoof et al. Ann Rheum Dis 2003;62:1241]; although other series have reported less toxicity [Mor et al. Ann Rheum Dis 2008;67:462; Zabana et al. Inflamm Bowel Dis 2008;14:1387]
   - Risk of DILI is higher when given in combination with rifampin or pyrazinamide
   - Pyrazinamide is no longer considered appropriate as prophylaxis due to risk of severe DILI

IV. Hepatic injury from reactivation of viral hepatitis on IBD therapies

- Only limited anecdotal data about the risk of HBV reactivation with TNF inhibitors in IBD patients [Shale et al. Aliment Pharmacol Ther 2010; 31:20] – most reports from pts receiving cancer chemotherapy [Khokhar, Lewis et al. Chemotherapy 2009] or TNF inhibitors for RA or other rheumatic or dermatologic disorders [Stine, Lewis et al. 2010]
- DMARDs including sulfasalazine and methotrexate (for RA) were associated with a high incidence of hepatotoxicity in a Chinese population with chronic viral hepatitis [Mok et al. Clin Exp Rheumatol 2000;18:363]
- Risk of reactivation of chronic Hepatitis B (which can fatal) mandates screening for HBsAg in all IBD patients receiving immunomodulatory agents, including infliximab and other TNF inhibitors based on AASLD and other societal guidelines [Esteve et al. Gut 2004;53:1363; Ojiro et al. J Gastroenterol 2008;43:397; Chung et al. J Rheumatol 2009;36:2416]
- Prophylactic antiviral therapy (e.g. entecavir, tenofovir) warranted if HBsAg positive with or without HB viremia [Colbert et al. Inflamm Bowel Dis 2007;13:1453]
- Risk of Hepatitis C reactivation if pegylated interferon discontinued due to exacerbation of UC [Watanabe et al. Gut 2006;55:1682]
EBV, lymphoma-risk and the potential role of HIV-infection for IBD patients undergoing immunosuppression

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Based on a series of observational and case-control studies, it appears that patients with inflammatory bowel disease (IBD) have an increased risk for developing lymphoma, compared with the general population. Multiple factors may contribute to this increased risk but vary widely between patients with IBD. Among the factors, type and duration of immunosuppressive therapy, HIV infection, primary EBV seroconversion, and possibly severity of IBD, may directly affect risk. Over 40 subtypes of Hodgkin and non-Hodgkin lymphoma have been reported in patients with IBD, and each subtype has its own, often poorly-understood, pathogenesis and risk factors. Thus, the relationship between IBD and any particular lymphoma remains obscure. I will discuss the epidemiology, pathogenesis, monitoring and treatment of lymphoma in patients with IBD, with a particular focus on recent data related to risk from novel therapies.
**Vaccination and IBD**

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IBD patients are immunocompromised both from their disease process and from the immunosuppressive medications used to control their disease. This immunocompromised state leaves them vulnerable to infection, which can be life threatening. Vaccination has been a very successful modality in preventing infection and has saved more lives than any other medical intervention, but is less likely to be effective in immunocompromised hosts. Response to vaccination can be augmented by optimizing timing, dose, route, boosters, and altering immunosuppression. In general, when possible, IBD patients should be vaccinated prior to undergoing immunosuppressive therapy; when this is not possible, they should be vaccinated during periods of lighter immunosuppression. The influence of more traditional immunosuppressive agents has been studied in different patient populations over the years. Data are emerging on the impact of biologic therapy on response to vaccination. Routine vaccines should be kept up to date, live attenuated vaccines avoided (with specific recommendations for the varicella and zoster vaccines), and travel vaccines used as needed. Household and community contacts may also have an impact on vaccination practices. Opportunities to optimize the use of seasonal (influenza) and occasional (Pneumovax, hepatitis B, tetanus) vaccines are often missed in this population. General recommendations for optimal vaccination of this vulnerable population should be understood and implemented to decrease the risk of infection, and will be covered during this lecture.

**References:**


Azathioprine and 6-mercaptopurine are orally administered immunomodulatory drugs which are effective for the treatment of Crohn’s disease (CD) and ulcerative colitis (UC). Azathioprine is rapidly converted to 6-mercaptopurine after administration. 6-Mercaptopurine is then either converted to the putative active metabolites, the 6-thioguanine nucleotides, or inactivated by xanthine oxidase to 6-thiouric acid or alternatively inactivated to 6-methylmercaptopurine by the enzyme thiopurine methyltransferase. Thiopurine methyltransferase activity is genetically determined, with 1 in 300 patients having low or absent enzyme activity, 1 in 10 patients having intermediate enzyme activity, and 9 in 10 patients having normal enzyme activity. Patients with intermediate or low thiopurine methyltransferase activity are at risk for early leukopenia. Higher erythrocyte 6-thioguaine nucleotides concentrations are associated with a greater likelihood of clinical response. Azathioprine is modestly effective for CD and UC. Toxicity associated with azathioprine includes infection and lymphoma. Anti-tumor necrosis factor (TNF) therapy with infliximab, adalimumab, and certolizumab pegol is effective for induction and maintenance treatment of CD, and infliximab is effective for UC. Toxicity associated with anti-TNF therapy includes infection and lymphoma. Combination therapy with infliximab and azathioprine is more effective for inducing and maintaining steroid free remission and mucosal healing than monotherapy with either drug alone. Strategies to reduce immunogenicity of anti-TNF agents include combination therapy with azathioprine and administration of a loading dose followed by systematic maintenance dosing. Higher serum trough concentrations of infliximab occur more frequently in patients receiving combination therapy with azathioprine and are associated with better clinical outcomes. Combination therapy is associated with an increased relative risk of opportunistic infection, but is not associated with an increased absolute risk of serious infection. Clinical practice should change such that combination therapy with an anti-TNF agent and azathioprine replace azathioprine in patients failing first line therapy with mesalamine and/or steroids.
Session VII

New keys to CD therapy I
What options do we have for induction therapy?

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The first goal of Crohn’s disease treatment is in inducing a response. The choice of induction therapy depends on a number of factors. First, disease severity will dictate the level of intensity of treatment. Moderate to severely active Crohn’s disease needs to be treated more aggressively than mild disease. Second, it is important to consider the disease distribution, since some medications (e.g., 5-ASAs, budesonide, antibiotics) are more effectively delivered to the small bowel or colon. Third, prior medications need to be considered. A patient naïve to immunomodulators and anti-TNF agents will be managed very differently than a patient who has already failed two anti-TNF drugs. A fourth critical factor is considering the individual patient. The balance of benefits and risks will depend on the patient’s expected future disease course, and how much risk they are at personally for serious adverse events from treatment. In addition, patients’ preferences for treatment need to be addressed since they will chose therapies differently based on their personal experience with symptoms, thresholds for risk taking, and fears about their disease and treatment.

The basic armamentarium for induction therapy for Crohn’s disease includes: 5-aminosalicylates, antibiotics, budesonide, systemic corticosteroids, thiopurines, methotrexate, anti-TNF agents and natalizumab. These drugs can be used alone or combined in difference treatment algorithms to optimize therapy. Predictive models can help guide physicians and patients, but the art of treating the IBD patient is in understanding your choices and being able to apply an individualized regimen based upon unique patient and disease factors.
What options do we have for maintenance therapy?

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Maintenance therapy is the cornerstone of current treatment strategies and the most difficult to achieve in a satisfactory fashion for the patient. The algorithm depends on the current clinical situation (relapsing disease, steroid-dependent, postoperative) as well as prior treatment response.

Relapsing Crohn’s disease
Unfortunately, mesalamine treatment has failed to significantly impact on the short or long term course of Crohn’s disease. Steroids potently induce a remission but are ineffective in maintaining it. Frequent relapses therefore indicate early escalation to thiopurines like azathioprine or mercaptopurine. In case of ineffectiveness or intolerance methotrexate may be an option, although studies are limited. This time honored approach is successful in a significant proportion of patients, although clearly some patients require further escalation to anti-TNF antibodies due to frequent recurrence of clinically active disease. In every case the potential benefit of this therapy has to weighed against the possible side effects associated with more potent immunosuppression including opportunistic infections.

Steroid-dependent Crohn’s disease
If a patient achieves remission but promptly relapses upon gradual reduction of the steroid dose, again thiopurines or, in case of failure, methotrexate, are indicated. Similar to relapsing disease, alternative or additional anti TNF strategies are the next step, if required. Although none of the studies have focused on this particular population, current evidence is convincing that steroid reduction is often achieved. However, on the long run only a minority of patients experience long term quiescent disease and relapse within a year after achieving a remission is the rule rather than the exception. In this situation alternative therapies with the competing TNF antibodies, natalizumab or experimental approaches (cyclophosphamide, anti IL-17 etc.) should be discussed with the patient. Again, side effects may be a problem with all these medications, sometimes severe and even life threatening. Therefore, it is wise to include the surgical options early, particularly in case of limited but severe disease.

Postoperative Crohn’s disease
In the postsurgical patient there is a probably limited effect of mesalamine. Thiopurines are alternatives which, if tolerated, are at least partially effective in retarding relapse. The escalation to anti TNFs is hampered by expense and limited supporting data.
How rapid should a remission be achieved?

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The major goal of therapy in inflammatory bowel disease is to induce remission. Remission has multiple definitions – clinical remission where the patient's symptoms have remitted and endoscopic remission in which there has been complete mucosal healing. Mucosal healing is a harder endpoint of remission but may be harder to achieve. In clinical trials we are forced to use activity indices such as the Crohn’s disease activity index that may not completely reflect the endoscopic and histologic state of the bowel. Ideally we would like to see a remission as quickly as possible to improve patient’s quality of life. The time to remission varies between different therapeutic approaches. Steroids tend to have a rapid clinical effect with remission seen in some patients as early as 2 weeks. In early anti-TNF trials a single dose of infliximab lead to 27% remission at 2 weeks compared to 4% of placebo patients. Adalimumab and certolizumab have similar reports of early induction of remission. Mesalamine in Crohn’s disease has inconsistent and delayed remission rates whereas in ulcerative colitis response and remission rates are more consistent in the 3 week time frame. Azathioprine and 6-mercaptopurine have delayed onset of action but may induce remission as early as 6 weeks if dosing is optimized. In this presentation induction of clinical remission and mucosal healing in Crohn’s disease and ulcerative colitis will be discussed. The impact of early remission on disease course will also be reviewed.
Are there options for patients that failed to respond to biologicals?

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Anti-tumour necrosis factor (TNF) antibodies have made a significant impact on the management of Crohn's disease and ulcerative colitis. Anti-integrin antibodies are licensed in some countries for management of Crohn’s disease and these are also effective in ulcerative colitis. A number of other biologics such as ustekinumab and ABT-874 (anti-IL-12/23 antibodies) and other anti-integrin antibody molecules appear promising in managing inflammatory bowel disease (IBD). Biologics however may be ineffective (primary failure) or gradually lose response after initial efficacy (secondary failure) and currently such failure generally indicate failure of medical therapy for many patients with IBD. These patients may be extremely difficult to manage.

Management of patients with failure of biologic therapy is challenging and a number of questions require to be asked regarding such failure. These include:

1. Is the patient symptomatic due to a mechanical and not inflammatory problem: these include fibrostenotic strictures and long-standing fistulou s tracts without active inflammation?
2. Is the patient symptomatic due to post-inflammatory irritable bowel syndrome rather than active inflammation?
3. Is the patient symptomatic due to a correctable cause such as bacterial overgrowth or bile acid malabsorption rather than active inflammation?
4. Is the patient symptomatic due to iatrogenic causes such as 5-ASA induced diarrhea or intra-abdominal adhesion induced abdominal pain?
5. Is the patient symptomatic due to depression or other psychosomatic issues?
6. Is the patient symptomatic due to concurrent gastrointestinal infections such as C. difficile or cytomegalovirus?
7. Is the loss of response due to immunogenicity?

To resolve the above questions may require a panel of investigations, including inflammatory parameters in blood and stool, radiological and endoscopic investigations and other functional investigations (such as hydrogen breath tests and SeHCAT). Serum trough levels and antibody levels of biologics may be useful in analyzing biologics failure.

The mechanism of primary anti-TNF failure in actively inflamed IBD is unclear. In patients who are refractory to biologic therapies and have been proven to have active IBD the therapeutic options are currently limited but are likely to expand in future. These include oral anti-trafficking agents and anti-chemokine receptors, other signaling molecule inhibitors such as MAP-kinase inhibitors and JAK-3 inhibitors and novel immunosuppressive molecules such as everilimus. There is considerable interest in immune reconstitution therapies such as bone marrow transplantation, stem cell therapies using various types of stem cells and apheresis. In addition, the role of combination antibiotic therapy continue to be explored. The evidence for each
of these is accumulating. In addition pharmacokinetic interactions such as that between methotrexate and monoclonal antibodies can be utilized in selected patients. Viral or bacterial vectors to deliver pharmacoactive molecules are also at an experimental stage.

Finally the role of appropriate surgery cannot be overemphasized. Failure of response to biologics similar to failure of other conventional agents may also be temporary rather than permanent. The problem of failure of biologic therapy may be minimized by starting therapy early in patients with aggressive disease, using optimal dose and concurrent therapy, maximizing induction efficacy and modifying lifestyle such as smoking.
Does it make sense to avoid surgery in CD patients?

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Surgery is needed at least half of patients with Crohn’s disease (CD) during their lifetime. Newer agents including anti-TNFα and anti adhesion molecules agents have been developed for patients with refractory disease. However, patients who were refractory to conventional medical therapy don’t seem to benefit from newer treatments in the long-term. 44.9% of patients with CD maintained response to infliximab therapy at 108 weeks (1). With a median of 18 months follow-up after infliximab therapy for CD stricture, only 28% complete response rate was reported (2). Preoperative infliximab infusion did not affect overall healing rates in patients with CD undergoing perianal fistula surgery (3). It has been shown that infliximab availability did not reduce surgical requirements or the development of disease related complications (4). Infliximab was found to be effective in achieving clinical remission in refractory CD but may only delay and not avoid the need for surgery (5). Also, use of biologic therapies for all patients with CD leads to many being exposed unnecessarily to the risk of side effects. Infliximab use within 3 months before surgery was shown to be associated with increased postoperative sepsis, abscess, and readmissions in CD patients undergoing ileocolic resection (6). Following use of adalimumumab in the management of refractory CD, serious infective complications and development of cancer were reported (7). Hence, surgery continues to have a critical role in the treatment for patients with limited CD, refractory disease or those who suffer significant adverse reactions with medication and it should not be considered as a failure.

References:


Session VIII

New keys to CD therapy II
Fistula treatment: The unresolved challenge

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In population-based studies, up to 50% of patients with Crohn’s disease suffer from fistulas. Fistulas pose a considerable morbidity including permanent sphincter and perineal tissue destruction as well as professional and personal disabilities. However, treatment options have progressed and fistula closure and fibrosis of the fistula track is achieved in some patients. Depending on severity of symptoms and fistula location, different medical and surgical therapies can be chosen. Internal fistulas such as ileoileal or ileocecal fistulas are either asymptomatic and do not require intervention or they are symptomatic and need surgery alone. Simple disease can be treated with antibiotics (i.e. metronidazole and ciprofloxacin) for the first three months and immunosuppressant therapy (6-mercaptopurine or azathioprine) at the same time. More complex cases need additional anti-TNF therapies. Only few and preliminary data exist on cyclosporine A, tacrolimus or methotrexate in fistulising Crohn’s disease. Therefore, these therapies should only be used as second-line therapies. Surgery is reserved for the treatment of perianal sepsis in the presence of abscesses and refractory disease, or be used in combination with pharmacological approaches. The surgical interventions in perianal disease consist of surgical drainage with or without seton placement, transient ileostomy, or in severe cases, proctectomy. The classification of fistulas in patients with Crohn’s disease remains poorly defined and largely investigator-dependent. The unresolved challenges in fistula treatment are warranted randomized controlled trials for existing and future treatment strategies as well as a better classification system to compare available studies.
Drug monitoring of azathioprine and infliximab

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Azathioprine (AZA) and 6-mercaptopurine (6-MP) are effective medical therapy for Crohn’s disease (CD) and ulcerative colitis (UC) (1). Evidence from controlled trials supports the use of AZA/6-MP for mild-to-moderate inflammatory CD, as a steroid sparing agent in steroid-dependent CD, and for maintenance of remission (2–4). In ulcerative colitis, controlled trials demonstrate efficacy of thiopurines in active disease and for maintenance of remission (5–7).

AZA and 6-MP are metabolized by thiopurine methyltransferase (TPMT) and polymorphisms in TPMT, resulting in decreased enzymatic activity, are associated with a greater risk of myelotoxicity (8). A prospective study of 394 IBD patients showed that patients with intermediate TPMT activity had fourfold greater risk of myelotoxicity than patients with normal TPMT activity (9). Given that pharmacogenomic testing is available for 6-MP/AZA, many have advocated measuring TPMT activity prior to starting. Although genetics tests assaying for the common polymorphisms that occur in TPMT are available, measuring the enzyme activity in red blood cells gives a more accurate depiction of the variation in enzyme levels to permit accurate dosing.

Once the patient initiates therapy with AZA/6-MP, the next question is whether metabolite testing is of value. Ample retrospective cohort studies support the use of metabolite levels to optimize response to therapy. The first to show that there was a relationship between 6-MP levels and the response to therapy was performed by Marla Dubinsky in a pediatric population (10). She found that patients that had levels above of 238 were significantly more likely to be in remission compared to those that had lower levels. She also found a relationship between high levels of 6-thioguanine and myelosuppression. A recent meta-analysis that has looked at all the various studies published measuring metabolite levels and the relationship to maintenance and again corroborates the original findings (11). Weight-based dosing under-estimates the dose approximately 50% of the time (12). Because of that, it is generally not sufficient to only use weight-based dosing or only use routine blood test to determine whether or not a patient is therapeutic on their 6-MP/AZA.

The other important therapy for which drug monitoring is available is infliximab. Low or absent trough levels of infliximab correlate with a poor response to therapy (13). A recent abstract at UEGW found that mucosal healing correlated with higher blood levels of infliximab. The same is true for rheumatoid arthritis in which trough levels correlate with Sharp scores (14, 15). Although monitoring is not available for adalimumab or certolizumab, the expectation is that the same would be true for these other protein-based biologics.

References:


Pouchitis and pouch dysfunction

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Ileal pouch-anal anastomosis (IPAA) following proctocolectomy has become the surgical procedure of choice for the majority of patients with ulcerative colitis (UC) who fail medical therapy or develop dysplasia and for patients with familial adenomatous polyposis (FAP). While the procedure improves patients’ health-related quality of life and substantially reduced colitis-associated dysplasia, complications are common. Some of the complications can lead to pouch failure. The most common causes for pouch failure are pelvic sepsis, chronic pouchitis, and Crohn’s disease (CD) of the pouch.

Surgical Technique-Associated Complications

Anastomotic leak is often located at the pouch-anal anastomosis, the tip of the “J”, and the body of the pouch along the staple line. Soluble contrast enemas, pelvic MRI and examination under anesthesia can help detect the location and degree of the leaks. Immediate postoperative pelvic sepsis and pelvic abscess occurs in 5% to 20% of patients undergoing restorative proctocolectomy with IPAA, and approximately 30% of these patients will eventually have pouch failure. Pouch sinus is typically a later presentation of an initial anastomotic leak. The most common location of a pouch sinus is the pouch-anal anastomotic site. Sinus opening and sinus tract can be detected by pouch endoscopy, contrasted enemas, pelvic MRI, or examination under anesthesia. Treatment usually includes periodic incision and drainage of the chronically infected superficial sinuses to promote secondary healing and closure. It may take up to 9–12 months before these sinuses heal. Patients with a long sinus track which do not have complete healing following ileostomy closure, usually require a redo pouch procedure. Surgery-associated fistulae can originate at any levels of the pouch with the commonest location being at the anastomosis, and they can extend into any adjacent organs or to the skin. The distinction between surgery-induced fistulae and CD-associated fistulae can be difficult. Pouch-vaginal fistula is a unique and yet common condition with IPAA and a major source of morbidity, which is one of the most common causes for pouch failure.

Pouchitis

Pouchitis is the most common long-term complication in patients with IPAA. Reported cumulative frequency rates of pouchitis 10–11 years after IPAA surgery range from 23% to 46%, with an incidence of 40% within first 12 months after ileostomy closure. Reported risk factors for pouchitis include genetic polymorphisms of IL-1 receptor antagonist and NOD2/CARD15, non-carrier status of tumor-necrosis factor allele, extensive UC, backwash ileitis, precolectomy thrombocytosis, preoperative corticosteroid use, extra-intestinal manifestations, especially PSC, the presence of perinuclear anti-neutrophil cytoplasmic antibodies, being a non-smoker, and NSAID use. Pouchitis represent a disease spectrum with a wide range of clinical presentations, endoscopic and histologic features, disease course, and prognosis. Increased stool frequency, urgency, incontinence, nocturnal seepage, abdominal cramping, pelvic discomfort, and arthralgia are the most common presenting symptoms. The severity
of symptoms does not necessarily correlate with the degree of endoscopic or histologic inflammation of the pouch. Endoscopy is the most valuable tool to differentiate pouchitis from other anatomic or inflammatory disorders of the pouch and is a key to making an accurate diagnosis.

It is important to accurately classify the disease before initiating appropriate therapy, although there is no validated and universally accepted classification system. From various clinical perspectives, pouchitis can be categorized into: 1) idiopathic vs. secondary; 2) remission vs. active; 3) acute vs. chronic with a cut-off duration of 4 weeks; 4) infrequent episodes (e.g. < 4 episodes a year) vs. relapsing (≥ 4 episodes a year) vs. continuous course; and 5) antibiotic-responsive, antibiotic-dependent vs. antibiotic-refractory refractory. For patients with a disease course refractory to antibiotic therapy, secondary etiologies should be evaluated. In a subset of patients, pouchitis is associated with specific etiologic factors such as *Clostridium difficile*, *Candida* or cytomegalovirus infection, NSAID use, concurrent autoimmune disorders (autoimmune pouchitis), and ischemia.

The management strategies vary in different types of pouchitis. For antibiotic-responsive pouchitis, the first-line therapy includes a 14-day course of metronidazole (15–20 mg/kg/day) or ciprofloxacin (1000 mg/day). Patients with antibiotic-dependent pouchitis often require long-term maintenance therapy to keep disease in remission. Maintenance agents include probiotics (such as VSL#3®) and low dose of antibiotics (such as rifaximin). Treatment of antibiotic-refractory pouchitis is often challenging. Options could be combined ciprofloxacin (1000 mg/day) with rifaximin (2000 mg/day), metronidazole (1000 mg/day) or tinidazole (1000–1500 mg/day) for 4 weeks. However, maintenance of remission in this group of patients after the induction therapy with dual antibiotics remains challenging. Immuno-modulator therapy and oral budesonide may be beneficial in patients with autoimmune pouchitis.

**Cuffitis**

Cuffitis, a variant form of UC in the rectal cuff, is common in patients with IPAA, particularly in those with stapled anastomosis without mucosectomy. Clinical symptoms of cuffitis are similar to those in pouchitis. In addition, patients with cuffitis often present with bloody bowel movements. Cuffitis can be treated with mesalamine suppositories, or topical lidocaine/corticosteroid agents. Systemic agents are rarely needed. Patients with cuffitis refractory to topical mesalamine and/or corticosteroid therapy should be evaluated for other disease processes at or around the cuff, such as fistula and chronic anastomotic leaks. Refractory cuffitis can also be a sign of CD of the pouch or inflammatory process outside the anal transitional zone.

**Crohn's Disease of the Pouch**

CD of the pouch can occur after IPAA which is intentionally performed in a selected group of patients with Crohn’s colitis with no previous small intestinal or perianal disease. CD is also inadvertently found in colectomy specimens of patients with a pre-operative diagnosis of UC. *De novo* CD of the pouch may develop after IPAA for UC. Reported cumulative frequencies of CD of the pouch ranged from 2.7% to 13%. *De novo* CD of the pouch may represent a unique phenotype of CD in the setting of bowel reconstruction and fecal stasis. CD of the pouch can be classified into inflammatory, fibrostenotic, or fistulizing phenotypes. There are scant data on treatment of CD of the pouch. Patients should be encouraged to avoid cigarette smoking and NSAID use. CD can be treated with a
combined medical, endoscopic (e.g. balloon dilation of stricture), and surgical (e.g. stricturoplasty) therapies. Inflammatory CD of the pouch may be treated with topical and oral 5-aminosalicylate agents, oral or topical corticosteroids, antibiotics, and immunomodulators. Commonly used agents include oral mesalamines and budesonide. In patients whose disease is refractory to these agents, particularly when they have concurrent extra-intestinal symptoms, biological agents may be used. For fibrostenotic CD of the pouch, endoscopic therapy together with medical therapy is often needed. For patients with long and high-grade strictures, endoscopic needle knife “stricturoplasty” treatment may be attempted in experienced hands. The management of fistulizing CD of the pouch has been difficult. Antibiotics, immunomodulators, and biologics may be tried. Biologics such as infliximab and infliximab appeared to be effective in short-term induction for fistulizing CD of the pouch.

In summary, restorative proctocolectomy IPAA is a technically challenging procedure which requires appropriate skills and expertise. Adverse sequelae of IPAA are common. Accurate diagnosis and classification of pouch disorders and associated complications are important for proper management and prognosis and for improving long-term surgical outcome.

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Prebiotics and helminths: The “natural” solution?

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IBD probably results from an inappropriately vigorous adoptive immune response to contents of the intestinal lumen. Environmental factors strongly affect the risk for IBD. People living in less developed countries are protected from IBD. The “IBD hygiene hypothesis” states that raising children in extremely hygienic environments negatively affects immune development, which predisposes them to immunological diseases like IBD later in life. Helminths are parasitic animals that have evolved over millions of years to live in the intestinal track or other locations of their hosts. Colonization of humans with these organisms was nearly universal until the early-twentieth century. More than 1,000,000,000 people in less developed countries carry helminths even today. Helminths must quell the host immune system to successfully colonize. It is likely that helminths sense hostile changes in the local host environment and take action to control such responses. Helminths interact with both host innate and adoptive immunity to stimulate immune regulatory circuitry and to dampen effector pathways that drive inflammation. These powerful interactions have long-term effects on host immune reactivity. Modern day absence of exposure to intestinal helminths may be one important environmental factor contributing to development of these illnesses. The first prototype worm therapies directed against immunological diseases are now under study in the United States and various countries in Europe. Additional studies are in the advanced planning stage.
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POSTER ABSTRACTS

Poster Numbers 1 – 35
Diagnostic potential of volatile organic compounds in inflammatory bowel disease

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²Clinical Sciences, University of West of England, Bristol, UK

Introduction: Diagnosis of inflammatory bowel disease (IBD) requires invasive procedure. Non-invasive modalities are yet to be adopted. Volatile organic compounds (VOCs) are chemicals which emit in the faeces and give a characteristic odour. Understanding changes in concentration and pattern of these VOC could provide information about various bowel diseases.

Methods: We studied 205 individuals, 75 with active IBD (CD = 46, UC = 29), 70 with disease in remission (CD = 35, UC = 35) and 60 healthy controls. Diagnosis was confirmed histologically. Fresh samples were aliquoted in 10 mls vial and were heated at 60° C for an hour. VOCs were extracted using SPME (solid phase micro-extraction) fibre exposed to the headspace above faecal matter for 10 minutes and were analysed by gas chromatography/mass spectrometer.

Results: VOCs extracted in all 5 groups were compared to identify the combination that provided the best discrimination between the groups. Univariate analysis selected 35 VOCs out of 225 as statistical significant. These were used in a forward stepwise discriminant analysis to construct a predictive model comparing CD and UC with normal both of which achieved excellent discrimination. On cross validation using 80:20 split of data arbitrarily on 8 occasions and averaging the results, this approach appears to have excellent stability, the average area under the curve for the CD model is 0.95 test sets and 0.80 for the validation sets, and the UC models give 0.94 and 0.86 respectively.

Discussion/Conclusion: This preliminary data demonstrates that pattern analysis of faecal VOC in patients with IBD may provide a non-invasive method in the diagnosis of the disease.
Is folate measurement in inflammatory bowel disease an opportunity missed to reduce risk of colorectal cancer?

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Introduction: Colorectal cancer (CRC) is the third most prevalent malignancy in the world and is the second leading cause of cancer death worldwide. Epidemiologic and clinical studies indicate that dietary folate intake and blood folate levels are inversely associated with colorectal cancer risk (1–3). Folate is involved in the biological methylation and maintenance of intracellular DNA synthesis, therefore, a folate deficiency could potentially lead to cancer through disruption of these events. Patients with inflammatory bowel disease (IBD) have a higher risk of developing CRC and folate deficiency may synergistically add to this risk of CRC in these patients.

Methods: To assess the monitoring of the folate levels in IBD patients presenting to our associate teaching district general hospital (DGH).
A single centre, retrospective analysis of 212 consecutive patients with IBD in our DGH was performed. The data from patients with IBD were obtained from the endoscopy reporting system, EPR, hospital pathology database and clinical records. Blood serum folate levels were analysed and retrieved from the biochemical laboratory data and patients clinical records for the period 2006–2008. The normal levels of folate were 3–18 µg/l.

Results: 212 patients with IBD, 110 (47%) males and 112 (53%) females with age range from 20–100 years were assessed. 141 (66%) had ulcerative colitis, 49 (23%) Crohn’s disease, 2 (0.9%) indeterminate colitis and 20 had normal looking histology in patients known to have IBD. Of the 212 patients, folate levels were assessed in 164 (77.3%). Low levels were found in 12 of 164 patients with IBD (7.5%), all of which were corrected with supplementary folic acid. In 48 (22.6%) patients of which 21 (43.7%) females and males 27 (52.3%) serum folate levels were not assessed.

Discussion/Conclusion: Within the study period, 7.5% of patients with IBD had a low serum folate and in all these patients it was corrected. In 22.6% patients with IBD, serum folate levels were not measured on follow up. This may suggest a missed opportunity to reduce the CRC risk in these patients with IBD who do not undergo folate measurement. We recommend routine measurements of folate in all patients with IBD under follow up and supplementing those who are deficient in folate to further reduce the risk of CRC in these patients.

References:


Is anaemia a consistent clinical feature in IBD?


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Introduction: Anaemia has been recognised as a key symptom of inflammatory bowel disease (IBD). Both anaemia of iron deficiency (IDA) and anaemia of chronic disease (ACD) are frequently encountered in inflammatory bowel disease. However other causes include folic acid deficiency, vitamin B₁₂ deficiency, malnutrition, haemolysis and bone marrow suppression (drug induced and autoimmune) are also a cause. Improvement of anaemia improves quality of life in cancer patients detected at haemoglobin levels of up to 14 g/dl. As most IBD patients are young, they may have even higher physical and cognitive demands than cancer patients. Normalisation of haemoglobin level (12.0 g/dl in women and 13.5 g/dl in men) should be the aim, hence monitoring of IBD patients with complete blood counts is a routine measure.

Methods: To analyse the association between anaemia and IBD in patient diagnosed with IBD.

We analysed 212 patients with IBD in our associate teaching hospital from May 2007–March 2009. Data was obtained from the Unisoft software data, clinical records, haemoglobin (Hb) levels; mean corpuscular volume, erythrocytes’ indices, ferritin, vitamin B₁₂ and folic acid levels. The Hb levels according to gender was considered.

Results: 212 patients were assessed. 47% (110) males and 53% (112) females. Patients’ age ranged from 20–100 years. The normal Hb in females was (12–15.5 gm/dl and in males was 13.5–16.5 gm/dl). 41% (46) of female patients with IBD had anaemia and 56% (50) of males. In total 48% (102 patients) with IBD had anaemia. Most of our patients had IDA, Serum ferritin was low in 61% (130) and folic acid was low in 10% (21).

Discussion/Conclusion: Anaemia is a consistent clinical feature of IBD and is still a frequent complication that may affect the ability to perform normal daily activities. For patients, this can be the most debilitating aspect of their disease. In our study we found nearly half of our patients who presented with IBD had anaemia. When dealing with IBD patients part of the management is to treat the anaemia. Vigilance in investigating and treating patients with anaemia should be one of our prime goals in the optimising IBD patient’s management and normalisation of haemoglobin level should be paramount.

References:


Is there any correlation between endoscopic and histological findings in IBD?

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Introduction: Endoscopy plays an important role in the diagnosis, management and surveillance of Inflammatory Bowel Disease (IBD). Endoscopy allows for direct mucosal visualisation and biopsies, thereby facilitating the diagnosis and determination of colonic extent, activity and severity and helps in differentiating between the types of IBD. Accurate differentiation of type of IBD helps in the management of the condition (e.g. methotrexate/infliximab of proven use in Crohn’s, 5-aminosalicylic acid in ulcerative colitis). A previous study has suggested further differentiation of indeterminate colitis to ulcerative colitis (UC) in 33% of patients after 1–2 years of follow-up.

Methods: To assess the correlation between, endoscopic and histological findings, in patients with IBD in our associate teaching district general hospital (DGH).

Retrospective analysis of patients undergoing colonoscopy with a diagnosis of colitis in an associate teaching hospital in the period from May 2007–March 2009 was performed. Data was obtained from the Unisoft endoscopy software, histological, laboratory findings and clinical notes. Data was compared between the two modalities, endoscopic and histological findings, with regards to type of colitis (UC, Crohn’s and ID), disease activity (quiescent, mildly active, moderately active, severely active) and extent of disease.

Results: 212 patients, 47% (110) males with age range from 20–100 years were assessed. 192 of 212 patients were correlated to have histological correlation with endoscopic macroscopic appearances (correlation coefficient 0.97). The severity assessment of endoscopy and histology had a correlation coefficient 0.99. Comparison of endoscopy and histology finding are shown in table 1.
Table 1:

<table>
<thead>
<tr>
<th>Modality</th>
<th>Colonoscopy</th>
<th>Histology</th>
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</thead>
<tbody>
<tr>
<td>IBD type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>146 (68.6%)</td>
<td>141 (66%)</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>42 (19.8%)</td>
<td>49 (23%)</td>
</tr>
<tr>
<td>Indeterminate colitis</td>
<td>24 (11%)</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>20 (9.4%)</td>
</tr>
<tr>
<td>IBD Severity assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quiescent</td>
<td>116 (54.7%)</td>
<td>115 (54%)</td>
</tr>
<tr>
<td>Mild</td>
<td>45 (21%)</td>
<td>45 (21%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>37 (17.4%)</td>
<td>32 (15%)</td>
</tr>
<tr>
<td>Severe</td>
<td>14 (6.6%)</td>
<td>20 (9.4%)</td>
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</tbody>
</table>

Discussion/Conclusion: There is good correlation in the diagnosis of extent, severity and type of colitis between endoscopy and histology. Endoscopy assessment may allow speedier diagnosis on the extent, severity and type of IBD in order to tailor treatment prior to histology.
IBD: Some aspects of pathophysiology and treatment

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The phases of the endointoxication were discovered for children with IBD. There were observed five phases.

Introduction: Inflammatory bowel disease (IBD) is a collection of systemic diseases involving inflammation of the gastrointestinal tract. IBD includes three diseases of unknown causation: Ulcerative colitis (UC), which affects only the large bowel; Crohn’s disease (CD), which can affect the entire gastrointestinal tract; and, indeterminate colitis, which consists of large bowel inflammation that shows elements of both CD and UC.

Methods: We estimated quantitative and qualitative changes of metabolic status in accordance with LMMWP (low and medium molecular weight peptides – universal markers of intoxications) and OP (oligopeptides), defined in erythrocytes, plasma and urine.

Results: 80 children with IBD were examined. In the initial phase of intoxications, the increase of LMMWP only on erythrocytes is observed. In the second phase, the moderate increase of concentration of LMMWP in plasma and on erythrocytes is observed (a phase of accumulation of products from the center of aggression). In the third phase LMMWP on erythrocytes remains constant (a phase of full saturation), and in plasma concentration continues to accrue, reaching significant sizes. The fourth phase is characterized by decrease LMMWP on erythrocytes (probable changes of structure of membranes) and growth of maintenance LMMWP in plasma (a phase of an inconsistency of systems of a homeostasis). The fifth, terminal phase, is characterized by significant damage of the membranes, accompanied decrease LMMWP both on erythrocytes, and in plasma (full decompensation).

Discussion/Conclusion: Enhanced injured surface in IBD contributes to auspicious conditions for bacterium and toxin penetration in blood flow. The most prominent endointoxication was observed in children with total UC. On the base of these findings we calculated the adequate dose of enterosorbents.
Changes in Crohn’s disease phenotype over time (application of Montreal Classification)

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Given the heterogeneous nature of Crohn’s disease (CD), our aim was to apply the Montreal Classification (MC) to a cohort of patients with CD in order to identify potential predictive regarding the need for medical and/or surgical treatment.

**Purpose:** As Crohn’s disease is very heterogeneous in its clinical expression, working groups have developed an evolving classification scheme such as the Montreal classification. An important goal has been to enumerate different phenotypic characteristics so that more homogeneous sub groups can be explored.

**Methods:** This was a retrospective study. Patients, followed up for at least 5 years, were classified by the Montreal classification for behaviour and location at diagnosis and five years later. The evolution of these characteristics and the need for surgery and immunosuppressive drugs were evaluated.

**Results:** 122 consecutive patients were recruited from 1998 to 2003 (70 male and 52 female), at diagnosis 68% of patients belongs to A2 as determined by the MC. Disease was most often localized in the colon. The disease location in Crohn’s disease remains relatively stable over time, with 93.4% of patients showing no change in disease location. Crohn’s disease behaviour changed during follow up, with an increase in stricturing and penetrating phenotypes from 6% to 11% after 5 years. The only predictive factor for behaviour change was the small bowel involvement: HR = 3.4. During follow-up, 82% of patients have presented a severe disease as attested by the use of immunosuppressive drugs or surgery. The factors associated with the disease severity were: small bowel involvement (L1 location), the stricturing B2 and the penetrating B3 behaviour (OR = 17.3, 12.3 respectively), without association with age, sex or smoking habits.

**Conclusion:** CD evolves with time: inflammatory diseases progress to more agressive stricturing and penetrating phenotypes. Stratifying patients according to the Montreal Classification may prove useful in identifying different phenotypes with different therapies and severity.
Early versus late surgery for ileocecal Crohn’s disease

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In spite of the important role of conservative treatment, up to 90% of all patients with Crohn's disease will undergo an operation during the course of their disease course.

**Purpose:** The purpose of this study was: to compare the evolution of patients who had an early ileocecal resection compared to those with a resection during the course of Crohn’s disease and to assess the severity of the disease in the 2 groups, as attested by the use of immunosuppressive drugs or surgery.

**Patients and methods:** A retrospective comparative study, including all patients who underwent an ileocecal resection between January 2000 and December 2008, and who were bleached at the time of surgery. It was excluded patients on preventive medical treatment of relapse (5-ASA, azathioprine, methotrexate or infliximab).

**Results:** 47 patients were included. Of these, 32 (68%) underwent early surgery (at diagnosis) (Gr 1) and 15 (32%) during the evolution of their disease (Gr 2). In group 1, the main indication for surgery was intestinal obstruction of the small bowel (65.6%) and abscess of the right iliac fossa (34.4%). The duration of remission was 43.8 months with a relapse rate of 34.4% after a median period of follow up of 17 months. The need for corticosteroids was in 18.2% cases, for salicylates in 18.2% of cases, for a second surgery in 54.5% of cases and infliximab in 9.1% of cases.

In the 2nd group, the delay between the diagnosis of Crohn’s disease and surgery was 47 months on average (4–144 months). The median follow up period was 51.5 months during which the duration of remission was 26 months with a relapse rate of 40% requiring the use of corticosteroids in 33% of cases, surgery in 33% of cases and corticosteroid with Immunosuppressant in 33% cases. The indications of surgery were: an occlusion in 65.6%; pseudoappendicitis (25%), intraabdominal abscess in 9.4%. The difference was significant between the 2 groups regarding the duration of remission but not the recurrence rate.

**Conclusion:** Early surgery improves the duration of remission of Crohn compared to surgery performed throughout evolution, but without change of the natural history of disease.
Allele frequency of inosine triphosphate pyrophosphohydrolase and thiopurine-S-methyltransferase gene in patients with inflammatory bowel disease

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Mutation in the thiopurine-S-methyltransferase (TPMT) and inosine triphosphate pyrophosphohydrolase (ITPA) have been associated with the occurrence of azathioprine related toxicity. It has previously been reported polymorphisms in the gene encoding the TPMT and ITPA, the major azathioprine/6-mercaptopurine metabolizing enzymes. In this study, we examine the frequencies of TPMT and ITPA polymorphisms and compared it with allele frequencies in others populations.

ITPA (94C>A, IVS2+21A>C) and TPMT (719A>G, 460G>A and 238G>C) genotypes were assessed in 208 Tunisian patients with inflammatory bowel disease (IBD) (88 males, 120 females) by polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) and allele specific PCR methods. Concerning ITPA, the allele frequency of the 94C>A variant in our patients was of 0.06 and that of IVS2+21A>C polymorphism was of 0.079. About TPMT, allele frequencies of the 460G>A, 719A>G polymorphisms were respectively of 0.0024 and 0.0168. The 238G>C and 460G>A + 719A>G mutations were not found in our studied population.
Adalimumab therapy in luminal and perianal Crohn’s disease in real practice: A long-term multicenter study of effectiveness, safety and predictors of response

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Background: Effectiveness of adalimumab in Crohn’s disease (CD) showed by randomized controlled trials must be confirmed in clinical practice.

Objective: To evaluate effectiveness and safety of adalimumab in CD patients of the Madrid area (Spain) and identify clinical predictors of response.

Methods: Multicenter retrospective survey of all CD patients treated with adalimumab in 9 hospitals of the Madrid area (Spain). To evaluate effectiveness we distinguished luminal from perianal fistulizing disease. Univariate and multivariate analysis of predictors of response was performed.

Results: 174 patients were included (50% males, mean age at diagnosis of the disease 28 years SD 12 years) with a median follow-up of 40 weeks. The median duration of the disease was 9 years (range 1–37). 65% were non-smokers. The most frequent location and behaviour of the disease were ileocolonic (50%) and inflammatory (50%) respectively. 30% had active perianal fistulizing disease at the beginning of the therapy with adalimumab. 60% had had previous surgeries related to CD (27% intestinal resection, 10% perianal surgery, 13% a combination of both and in 10% it was not specified). 59% had been previously treated with infliximab, being the lost of response (42.2%) the most frequent cause of withdrawal of the drug. Adalimumab was given as a first line drug in 39% of the patients. The indications of adalimumab were refractory luminal disease (69.5%), perianal fistulizing disease (19%) and a combination of both (11.5%). The majority of them (93.7%) had an induction dose of 160 mg at week 0 and 80 mg at week 2. 33% of patients needed dose escalation from every-other week to every week. The median time for this dose escalation was 33 weeks (range 2–120). 64% had concomitant therapy, being azathioprine the most common drug (26%). The percentages of complete response at 4 weeks, 6 months and end of follow-up were 63, 70 and 63% in luminal disease and 45, 45 and 41% in perianal disease respectively. As far as predictors of response were concerned we only found that those who needed a dose escalation
had a worse response (p = 0.017). It is worth mentioning that we did not find any difference in effectiveness between those who had adalimumab as first line treatment and those who had been previously on infliximab therapy. The prevalence of adverse events was 18% (most frequent being abscess in 2.9% of patients) causing the withdrawal of the drug in 21% of them.

Conclusions: Adalimumab is effective and safe for the management of CD, even in refractory cases to infliximab. In order to maintain this effectiveness it is necessary a dose escalation in a third of the patients, although with less satisfactory results.
The evolution of nutritional status in patients with severe forms of Crohn’s disease treated with infliximab

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Introduction: The majority of Crohn’s disease (CD) patients with moderate to severe flares of activity present with weight loss, sometimes important, malnutrition being observed frequently in this group of patients. The aim of our study was to determine the evolution of nutritional status in patients which necessitated infliximab treatment for the control of disease activity.

Methods: Patients with moderate-severe CD with remission of disease obtained and maintained with infliximab were followed prospectively. Weight was monitored before and during the biologic treatment. Patients were classified as normal if BMI > 20, with mild malnutrition if BMI 19–20, moderate if BMI 18–19 and severe malnutrition if BMI < 18.

Results: 18 patients were included in the study, 8 women and 10 men, with a mean age of 37 ± 3.26 years, with severe CD. At the beginning of treatment all patients presented with weight loss and 13 (72.2%) of them were malnourished (8 mild, 3 moderate and 2 severe malnutrition). After induction of remission a slow increase in weight was observed, after one year of remission all patients having a normal nutritional status. The mean weight gain was of 5.8 ± 1.75 (2–7.8) kg.

Discussion/Conclusion: The nutritional status of patients with severe forms of CD normalizes in all cases when infliximab treatment determines the induction and long term maintenance of disease remission. The correction of nutritional status is an important benefit of infliximab treatment for this group of patients, frequently malnourished.
Maintenance treatment with infliximab versus azathioprine in Crohn’s disease: A prospective study

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Introduction: Crohn’s disease is characterized by flares of inflammatory activity which alternate with periods of remission. To avoid the disease’s relapses a maintenance treatment is mandatory. The aim of our study was to evaluate the efficacy of periodic administration of infliximab (IFX) as compared with azathioprine (AZA) in the maintenance of remission in patients with Crohn’s disease.

Methods: All patients with severe flares of Crohn’s disease in whom remission was obtained after IFX induction treatment were included in a prospective study. Two maintenance treatments were compared: AZA (2.5 mg/kg) daily and IFX (5 mg/kg) at 8 weeks interval. Patients were followed by clinical (CDAI) and biological evaluation every 8 weeks and colonoscopy was performed every 24 weeks. Clinical remission was defined as CDAI < 150 and endoscopic remission was defined as the absence of ulcers.

Results: 23 patients received maintenance treatment with IFX and 14 patients received AZA. Patients were followed for a mean of 36.48 ± 25.21 (12–96) months. At one year from the induction treatment with infliximab there were no statistical significant differences between the patients in clinical remission in the two groups. The difference reached statistical significance at two years (p = 0.03) when significant more patients were in clinical remission in IFX group as compared with AZA group. The most important difference between the two groups was the endoscopic remission: for IFX group mucosal healing was obtained more rapidly: the mean time to remission was 8.83 ± 4.62 (6–18) months, significantly less than for AZA group in which the mean time needed was of 15.42 ± 5.85 (12–24) months and remission was maintained in a larger number of patients (p < 0.01) in IFX group.

Discussion/Conclusion: The treatment with infliximab is highly effective in maintaining the remission of Crohn’s disease and determines mucosal healing in a shorter period of time as compared with azathioprine. Sustained endoscopic remission is the most important benefit of infliximab treatment compared with azathioprine treatment.
Screening patients initiating anti-TNF agents for mycobacterial infection using interferon-gamma release assays (IGRA): The experience of a large inflammatory bowel disease service

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Introduction: Screening and treatment for latent tuberculosis infection (LTBI) is recommended by the BTS prior to initiation anti-TNF agents. Conventional screening involves assessment of risk factors, chest radiograph, and tuberculin skin testing (TST) – which can be difficult to interpret in immunosuppressed subjects, IGRA may detect *M. tuberculosis* (*M*.tb) infection with greater specificity and possibly sensitivity compared to TST. Here we review our experience of blood IGRA in patients with inflammatory bowel disease (IBD) initiating anti-TNF therapy.

Methods: A retrospective single-centre review was undertaken of IBD patients either considered for, or using, anti-TNF agents assessed for evidence of *M*.tb infection with IGRA testing as part of their screening protocol. T SPOT-TB was the IGRA selected. Baseline assessment was undertaken by the IBD team, with onward referral to the TB service as needed.

Results: Since 2008, 77 patients (43 anti-TNFα naïve, 34 established on anti-TNFα) have been screened for LTBI using IGRA. All subjects had normal chest radiographs and negative clinical assessment. Eighteen (23%) had risk factors for tuberculosis. Sixteen (21%) patients were on no immunosuppression at the time of testing while 61 (79%) were taking either azathioprine, prednisolone, mercaptopurine or anti-TNFα. Seventy one (92%) patients had a non-reactive Elispot result, three (4%) had reactive result and three (4%) had an indeterminate Elispot result. Thirty (70%) of the anti-TNF naïve group went on to have either infliximab or Humira. Median follow-up of anti-TNFα naïve group is 5 months (IQR 2–7) and established Anti-TNFα group 25 months (IQR 17–44 months). No cases of active TB have occurred.

Discussion/Conclusion: The use of a simple screening protocol for LTBI incorporating T SPOT-TB IGRA in place of TST appears to work well in our IBD service. Our detection rate for *M*.tb infection is consistent with other data. Longer term follow up will indicate whether we have missed any LTBI using this assessment.
A paediatric and adult gastroenterology team collaboration to design an innovative adolescent IBD transition service – Exploring the attitudes and experiences of adolescent’s pre and post transition

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Introduction: Around 30% of all IBD cases are diagnosed in childhood. There is an increasing need for specialised transitional care to adult services. In the UK, the National Standards Framework for children and adolescents (2004) recommended these services to be multidisciplinary and tailored to the adolescents’ and their parents’ needs. Our recent audit of the previously existing IBD handover clinic (one single appointment) found that 80% of both patients and parents felt that they were not ready for handover. They also felt that transition should occur as multiple joint clinics.

Methods: A newly designed joint adolescent IBD transition service was delivered in the paediatric setting. Each clinic was attended by both paediatric and adult gastroenterologists and specialist nurses. Anonymous questionnaires were handed out to 25 patients attending their first transition clinic appointment between March 2008 and March 2009. Questions included knowledge of disease/medication, perception/actual effect of disease on daily living, sources of support/advice, readiness/adequacy for transition and anxiety surrounding it.

Results: We had an 84% response rate (21/25 patients), mean age was 16, (62% CD, 38% UC). 100% of patients knew their medications and 57% had some understanding of how the medications worked. 27% admitted non-compliance with drugs, with the main reason cited being forgetfulness. All the patients felt confident at recognising flare-ups. Body image, mobility and education were the main perceived adverse effects of IBD. Most patients used friends or parents for advice, with only 24% seeing advice from the hospital. Half of all patients had concerns regarding transferring to the adult service (losing close contact, new staff and different treatments & investigations). We will repeat the questionnaire post transition to assess patients’ knowledge and independence of managing their disease.

Discussion/Conclusion: Adolescents with IBD are generally well informed about their disease and medications. They still rely on their parents to make contact with the medical team during flare-ups and transition to adult services is a source of anxiety. A structured transition service tailored to the adolescents’ needs could improve self-confidence and self awareness, ultimately resulting in a smoother transition to the adult gastroenterology services.
Urinary neopterin is a marker of a clinical activity in patients with inflammatory bowel disease

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Background: The aim of this study was to investigate the relation between urinary neopterin and inflammatory bowel disease (IBD) compared to controls, and to assess its ability to discriminate active versus inactive IBD.

Methods: We conducted a cross sectional study including 44 IBD patients (27 with Crohn's disease and 17 with ulcerative colitis), of a mean age 35 years (17–56) and 25 healthy controls of a mean age 39 years (15–94). In all subjects, urinary samples for neopterin measurement were obtained. Clinical parameters were recorded and blood samples for CRP were collected as well.

Results: Patients with inactive IBD showed similar levels of urinary neopterin excretion than healthy volunteers 74 (14–199) nmol/mol of creatinine versus 67 (17.6–201) nmol/mol of creatinine, respectively; p = 0.1. In contrast, urinary neopterin excretion from active IBD was significantly higher 392 (32–1193) nmol/mol of creatinine; p = 0.001. Moreover, urinary neopterin excretion was positively correlates to CRP levels, (r = 0.026, p = 0.035) but was not associated with age, sex, IBD subtypes or duration.

Based on the cutoff of 150 nmol/mol of creatinine for urinary neopterin, the sensitivity and specificity of urinary neopterin to discriminate between active and inactive CD were 80% and 83%, respectively.

Conclusions: Urinary neopterin excretion is an objective, valuable and noninvasive biomarker to discriminate between active and inactive IBD patients. Further work is warranted to study its clinical value and relation to mucosal healing.
Lymphotoxin alpha-expressing lymphoid-tissue inducer cells are required for the development of intestinal Th17 cells

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Introduction: Naturally-occurring IL-17-producing CD4+ T (Th17) cells reside in the intestinal mucosa of healthy mice under specific-pathogen-free conditions. It has been reported that mice lacking RORγt defect the Th17 cells and lymphoid-tissue inducer (LTi) cells that are essential for the formation of gut lymphoid organs. Thus, it remains unknown whether the function of RORγt, the presence of LTi cells, or the formation of lymphoid organs is crucial for the development of Th17 cells.

Methods: To determine this, we analyzed lymphotoxin alpha-deficient (LTα−/−) mice, which lack gut lymphoid organs, but retain normal RORγt gene.

Results: The ratio of intestinal Th17 cells in LTα−/− mice was significantly reduced as compared to that in age-matched wild type (WT) mice. Surprisingly, the ratio of intestinal IL-17-producing CD3−CD4+NK1.1−CD11c−IL-7RαhighCCR6+ LTi-like cells was conversely increased in LTα−/− mice, but not in RORγt−/−mice. To assess a reciprocal regulation of Th17 cells and LTi cells, we compared LTα−/− x RAG-2−/− mice to RAG-2−/− mice. We confirmed that both mice lack intestinal Th17 cells, but the absolute number and the ratio of intestinal LTi cells in LTα−/− x RAG-2−/− mice were significantly greater than those in RAG-2−/− mice, suggesting that intestinal LTi cells are negatively regulated by LTα signaling pathway, but are produced independently of intestinal Th17 cells. To clarify a necessity of lymphoid tissues for the development of intestinal Th17 and LTi cells, we next conducted a parabiosis system between Ly5.1+ WT mice and Ly5.2+ LTα−/− mice. Four weeks after parabiosis surgery, substantial number of Th17 cells irrespective host or donor cells emerged in intestinal mucosa of LTα−/− mice, whereas substantial number of host-derived LTi cells persisted in intestinal mucosa of LTα−/− mice.

Discussion/Conclusion: Collectively, all the present results suggest that the development of intestinal Th17 cells is regulated by LTα-LTβR signaling pathway via LTα-expressing LTi cells in physiological conditions.
Administration of biological therapy to IBD patients in the Czech Republic

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Introduction: In the Czech Republic, there are centres for biological treatment (CBT) for gastroenterology, rheumatology and dermatology. For gastroenterology – i.e. treatment of inflammatory bowel diseases (IBD) – biological treatment (BT) includes infliximab and adalimumab. Since 2006, there are 26 CBTs in the Czech Republic with more than 1000 patients. More than 150 patients with IBD have been treated of BT at the University Hospital in Olomouc.

Methods: 32 patients with IBD underwent BT before the establishment of CBT and continue to undergo BT to date. We have examined these patients’ satisfaction with application of BT before and after the CBT establishment using a questionnaire survey. The questionnaire featured 9 questions and patient’s satisfaction was graded at the scale 0–5. Doctors care, nurses care, monitoring of adverse effects, providing information on BT, support from auxiliary staff, waiting time, informed consent, recommendations and overall satisfaction. The quantitative differences were evaluated by CHI quadrate test and qualitative differences by Student T-test.

Results: Statistically non-significant difference (p = 0.88) before and after the establishment of CBT was only found in evaluation of the level of doctor’s care. In all other monitored items showed statistically significant difference – nurses care (p < 0.05), monitoring of adverse effects (p < 0.05), providing information on BT (p < 0.05), support from auxiliary staff (p < 0.05), waiting time (p < 0.05), informed consent (p < 0.05), recommendation and overall satisfaction (p < 0.05).

Discussion/Conclusion: Establishing CBT for IBD patients in majority of cases significantly improved the standard of medical care for IBD patients.
Mesenchymal stem cells: From lab to clinical trials in Crohn’s disease

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Introduction: Studies trying to find new approaches for non-responding Crohn’s disease patients are currently underway. Attractive sources for cellular therapy in autoimmune diseases, including Crohn’s disease, are mesenchymal stem/stromal cells.

Methods: Mesenchymal stromal cells (MSCs) are an attractive tool for cell therapy and tissue engineering. However, investigators report studies using different methods of isolation and expansion, and different approaches to characterize the cells. The International Society for Cellular Therapy recently proposed minimal criteria to define human MSCs: MSCs must be plastic-adherent, have a phenotype of CD105+, CD73+, CD90+, CD45-, CD34-, CD14-, HLA-DR-, and have the capacity to undergo in vitro differentiation to at least three different cell lineages: osteoblasts, adipocytes, and chondrocytes.

MSCs can be obtained from bone marrow, umbilical cord blood, adipose tissue, peripheral blood, amniotic fluid and other various sources. We optimized protocol for preparation of clinically applicable MSCs from bone marrow (BM MSCs) and adipose tissue (AT-MSCs).

Results: Cells isolated from both sources exhibited typical fibroblastoid morphology, the formation of CFU-F, a multipotential differentiation capability, and the expression of a typical set of surface proteins.

Discussion/Conclusion: Autoimmune diseases, including Crohn’s disease, are characterised by immune dysregulation with activation of autoreactive immune clones of both T and B lymphocyte lineages and insufficient function of immunoregulatory cells. The effect of MSCs was already described in some studies in patients with Crohn’s disease and the future of this treatment seems to be promising.

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The analysis of colorectal cancer and other neoplasia origin in the families of probands with inflammatory bowel diseases

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Introduction: Despite numerous data about genetic aspects of the pathogenesis of ulcerative colitis (UC) and Crohn's disease (CD), the significance of the heredity in the origin of colorectal cancer (CRC) on the ground of these diseases are not widely studied. Our aim was to analyze the origin of CRC and cancers of other localizations in probands with UC and CD and their relatives for the oncopathology risk group formation for early diagnosis of cancer in families with IBD.

Methods: It was carried out the genealogical analysis of 91 families with IBD and 31 families of control group. Among these UC was diagnosed in 57 probands, CD – in 34 probands. The diagnosis was confirmed using clinical, endoscopical and laboratory analysis.

Results: It was shown that in 3 (8.82%) probands with CD and in 1 (1.75%) probands with UC developed CRC. It was accessed the frequency of CRC in I and II degree relatives. 12 (1.90%) persons had CRC among all relatives of probands with CD (630 persons). 9 (0.62%) persons had CRC among all relatives of probands with UC (1453 persons). In the control group (559 persons) CRC had 3 (0.53%) persons. The similar counting of cases of others localization cancers was carried out in relatives of probands with IBD. It was shown that 40 (6.34%) persons – relatives of probands with CD, have cancers of other localization. 29 (1.99%) relatives of probands with UC have other oncological diseases than CRC. Cancer of digestive tract dominated in these families. In comparison to the relatives of probands with IBD the cancers of other localization was diagnosed in 16 (2.96%) persons of control group.

Discussion/Conclusion: This study showed that oncological diseases, especially CRC, most frequently developed in families of probands with CD in comparison with families of probands with UC and control group. It should not be excluded that some common factor exists, leading to the origin of CD and CRC. The presence of sporadic CRC in some relatives of probands with IBD leads to the higher risk of malignancy in probands.
Comparison of colonoscopy results and morphological changes in biopsies in IBD in children

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Introduction: Colonoscopy is the method of choice for the diagnosis of inflammatory bowel diseases (IBD) in children. The aim of the present study was to find out, how well the endoscopic findings correlate with the biopsy findings.

Methods: We have carried out a retrospective analysis of the reports of colonoscopy performed in children from 2 to 16 years old for inflammatory diarrhea. The data were compared with the results of a morphological study of colon biopsies obtained in the same procedure. In total 42 endoscopy reports have been studied. During the procedure, biopsies were obtained from the most involved areas of the colon. The number of biopsies varied from one patient to another between 1 to 6 with an average of 4.2. A total of 176 biopsies were examined.

Results: A diagnosis of IBD was established by colonoscopy in 22 of 42 patients. The endoscopical aspect was characterized by hyperemia, granularity, erosion and ulcers. In 14 cases the pattern corresponded to ulcerative colitis (UC) and in 5 cases to Crohn’s disease (CD). In 3 cases endoscopic changes were regarded as exsudative and follicular and highly suspicious for IBD. Histology confirmed the diagnosis of IBD in 11 cases (5 UC, including one case with atypical presentation without rectal involvement; 2 cases of CD and 4 cases classified as IBD unclassified). The diagnosis of CD was established mainly by the presence of changes in the ileum. In 8 cases mild inflammatory changes and follicular hyperplasia were found, not being diagnostic for IBD.

Discussion/Conclusion: Colonoscopy with biopsy study is very important for the diagnosis of colitis in children. Morphological changes in biopsies not always confirm the diagnosis of IBD. The best results are obtained in patients with erosive and ulcerative lesions in rectum and distal parts of colon. For a precise diagnosis of CD it is useful to find ileal involvement and the subsequent morphological confirmation of ileitis is extremely important.
Ask the doctor about inflammatory bowel disease on the Internet: Experiences after more than one thousand questions

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The Internet has become an important source of medical information for patients with inflammatory bowel disease (IBD). The “Ask the doctor” topic makes it possible to get free and quick medical consultation with a specialist. Our aim was to evaluate the most commonly discussed topics among the patients and the Internet doctor at a frequently visited Hungarian IBD website (www.crohn-colitis.hu).

Patients and methods: Questions, asked by the visitors at the Hungarian IBD website were assessed retrospectively. IBD-specific problems were analyzed statistically.

Results: 58% of the total 1204 questions concerned IBD. 67% of the IBD questioners were females and 20.2% (p < 0.001) were males. 39.4% of the questioners were diagnosed with Crohn's disease (CD), and 36.1% with ulcerative colitis (UC). Ask for therapeutic advice (27.8%), and concern about the patients’ symptoms (17%) composed the most common questions, although the interest of medication use was more significant among females and patients with UC (p = 0.05 and p = 0.029) compared to males CD. Questions about fistulas and extraintestinal manifestations occurred only among patients with CD (p < 0.001), however, pregnancy, ask for the explanation of different findings and concern about colorectal cancer were generally UC-related topics (p < 0.001).

Discussion: According to our results, the majority of the questions asked by the IBD patients were related to the medication use, indicating the lack of information about the therapy in the practice. Our study revealed significant differences in the questions of UC and CD patients and highlighted the importance of taking enough time for detailed introduction and discussion of the disease.
Conception outcomes and opinions about pregnancy for men with inflammatory bowel disease

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Background and aims: Patients with inflammatory bowel disease (IBD) who want to have children are anxious to receive medical treatment. The consensus regarding pregnancy has not been surveyed for male IBD patients. The present study was investigated opinions among male IBD patients about pregnancy, conception and neonatal outcomes for partners.

Methods: Subjects comprised 364 of 386 patients enrolled (94.3%). Subjects received a questionnaire regarding their opinions and thoughts about pregnancy. The course of partner’s conceptions and presence of neonatal malformations was also surveyed.

Results: The rate of live births for partners of male IBD patients was 91.6% (219/239). Most patients with CD (29/33; 88%) had their children after surgery had been performed. The rate of expressing hopes to have a child tended to be higher for patients with UC (93/128; 73%) than for patients with CD (61/97; 63%; p = 0.21). Furthermore, the rate of hesitation was significantly higher in CD patients (34/107; 32%) than in UC patients (38/188; 20%; p = 0.03). Patients considered that safety of medication (51%) and maintenance of remission (41%) was more important than receiving no treatment for IBD (19%) when planning to conceive. Mesalamine and infliximab were more favorable at conception than sulfasalazine and immunomodulators.

Conclusions: This is the first report to survey the thinking of male IBD patients regarding pregnancy. Most male IBD patients considered “maintaining remission” as important at conception. Our study provides important information for IBD patients and for the treating physician when planning to conceive.
Usefulness of oral beclometasone dipropionate to induce remission in active ulcerative colitis patients: Results from the RECLICU Study


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Introduction: New steroid formulations, with less systemic effects, have been added to the IBD armamentarium in recent years. Oral beclometasone dipropionate (BDP) is available in Spain to treat mild to moderately active ulcerative colitis (UC) patients. We estimate that 20.000 patients have received this treatment in our country in the last two years.

Objectives: To evaluate the efficacy and safety of oral BDP to treat active UC patients, in clinical practice.

Methods: This is a retrospective, multicenter study that included 434 patients with active UC treated with BDP, recruited at 34 Spanish hospitals. Since endoscopy was not performed before and after BDP treatment in most patients, the Mayo Clinic score (MS, 0–9), including number of bowel movements, presence of blood in stools and physician global assessment, was used to measure disease activity. Patients in which pre- and/or post-treatment MS could not be calculated (n = 20) and patients with pre-treatment MS < 3 (n = 20) were excluded, leaving a total of 394 evaluable patients. Remission was defined as post-treatment MS of 0 or 1. Response was defined as a decrease in MS of 3 points or 2 points and > 30%. Failure was defined as lack of remission or response.

Results: There were 197 women and 197 men, with a mean age 43.7 years, mean disease duration 72 months and UC extension E1 (11.4%), E2 (48%) and E3 (40.6%). Some patients were on oral 5-ASA (81.7%), rectal 5-ASA (39.8%), azathioprine (18.8%) and rectal steroids (9.4%) treatment before BDP therapy. BDP
dose was 5 mg/day in 81.7% and 10 mg/day in 18.3% of patients. Mean treatment duration was 6.2 weeks. BDP achieved remission in 44.4%, response in 22.3% and failed in 33.2% of patients. The mean MS decreased from 4.9 ± 1.3 to 2.4 ± 2.3 (p < 0.0001). The remission rate was higher in mild and moderate UC than in severe UC (p < 0.043). There was also a trend towards a higher remission rate in left-sided and extensive UC than in proctitis (p < 0.06). Mild adverse events were reported in 7.6% of patients (headache and nausea the most frequently found). Some patients required hospitalization (6.6%) or colectomy (1%).

Discussion/Conclusion: Oral BDP induces response or remission in two thirds of the active UC patients with a good safety profile. Patients with mild to moderately active left sided or extensive UC are most likely to benefit from oral BDP.
Microsomal epoxide hydrolase *3 and *4 polymorphism associated with increased risk of ulcerative colitis in Turkish population

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Introduction: Ulcerative colitis is an inflammatory disorder of the colon of unknown etiology. Patients with chronic ulcerative colitis are at increased risk of developing colon cancer. Ulcerative colitis is believed that environmental factors and genetic polymorphism of the some enzymes are involved in developing this disease. The aim of this study is to determine association of ulcerative colitis with the genetic polymorphisms of microsomal epoxide hydrolase (mEPHX) *3 (Tyr113His) and mEPHX*4 (His139Arg) polymorphisms, known to be involved in carcinogenesis in Turkish population.

Methods: The genotypes were determined with use of PCR/RFLP techniques on 120 healthy controls and 76 ulcerative colitis patients.

Results: The homozygous mutant of mEPHX*3 (His/His) were more common in ulcerative colitis patients than the controls (OR: 3.0896; 95%CI: 0.9941–9.6023). These results suggested that, the genotypes of mEPHX*3 is possible factor for risk of incidence of ulcerative colitis since we found that these variant genotypes had a 3.09 fold higher risks of developing ulcerative colitis than those the wild type genotype. On the other hand, we found that mEPHX*4 polymorphisms have not associated with developing ulcerative colitis (OR: 0.918; 95% CI 0.1634–5.1567).

Conclusion: The present study suggested the involvement mEPHX*3 codon 113 polymorphism in the genetic predisposition to ulcerative colitis among Turkish populations.
Psychological profile, level of neuropeptide Y and serotonin in inflammatory bowel disease

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Introduction: Inflammatory bowel disease (IBD) is associated with increased risk of psychological disorders. Neuropeptide Y (NPY) and serotonin are suspected to play a role in the pathogenesis of IBD. Also, NPY regulates mood, has antidepressive effect, it is elevated in stress due to sympathetic activation, too. Altered serotonin secretion is observed in depression.

Methods: 46 individuals were included – 15 healthy controls, 31 patients with exacerbated IBD (16 with Crohn’s disease and 15 with ulcerative colitis). Psychological profile was evaluated with Minnesota Multiphasic Personality Inventory-2 (MMPI-2). NPY and serotonin were measured in serum using ELISA.

Results: According to MMPI-2 38.7% of the patients suffer from clinically significant hypochondria, depression and hysteria. The other 61.3% are emotionally imbalanced, also, at higher risk of developing depression. NPY was significantly elevated in IBD patients compared to the control group. There was no statistical difference in NPY level in patients with psychological deviation compared to the other patients. All individuals showed normal serum serotonin.

Discussion/Conclusion: Patients with exacerbated IBD have clinically significant psychological deviation or are prone to depression. Elevated NPY in the sera of active IBD is probably due to sympathetic nervous system activation, caused by the stress from the disease. Nevertheless, further investigations have to be made. Serotonin level in sera of IBD-patients can not be used as marker of psychological deviation.
Comparison expression of Bcl-xL in ulcerative colitis and Crohn’s disease

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Introduction: Ulcerative colitis and Crohn's disease are risk factors for colon cancer. Patients with colorectal Crohn's disease have a less risk of colorectal cancer than that of patients with ulcerative colitis. Literature describes a significant role of apoptosis in the evolution of pathogenesis of ulcerative colitis and Crohn’s disease. Moreover, overexpression of Bcl-xL protein, causing increased survival of cancer cells, results in tumor progression and metastasis formation. Apoptosis in physiological condition plays an essential role by controlling and allowing elimination of damaged or neoplastically transformed cells. Our study objective was the immunohistochemical assessment of the expressions of the apoptosis-regulating protein Bcl-xL in ulcerative colitis and Crohn’s disease.

Methods: The 55 patients with ulcerative colitis, 21 patients with Crohn’s disease, and 15 patients without any inflammatory pathology were analysed in this study. The protein expression was evaluated by immunohistochemical reaction using antibodies for Bcl-xL.

Results: Cytoplasmic reaction in every case was observed. Expression of Bcl-xL in unchanged epithelium (in control group) was the lowest, greater in Crohn’s disease and the strongest was observed in ulcerative colitis, particularly in altered dysplastic crypts.

Conclusion: These investigations suggest that expression of anti-apoptotic Bcl-xL is associated in formation of dysplastic changes in colorectal glands. Elevated expression of Bcl-xL protein in ulcerative colitis, by protecting damaged cells from apoptosis, may lead to malignant transformation and tumor formation greater than in Crohn’s disease.

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Morphological peculiarities of intestinal amoebiasis during the epidemiological outbreak in Tbilisi

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Amebiasis is characterized by clinical polymorphisms. In spite of the appendix and ascendance colon are often damaged at first, not too seldom arise the intestinal ulceration which is the result of the secondary haematogenic spreading.

We studied 124 patients (females – 98, males – 26). The goal of our research was to connect the clinical manifestations with pathomorphological changes, which are accompanied with above mentioned disorder. For this aim there were investigated postoperative histomorphological materials.

There were operated 19 patients. Indication for surgical intervention was acute peritonitis. In all cases there was found free liquor in abdominal cavity. In 11 (9%) patients were damaged pelvic colon, in 5 (4%) – all intestine, and in 3 cases – colon and intestinal part simultaneously.

Postoperative materials of 19 patients were revealed the following disturbance: colono-intestinal ulceration without ulcer edging which penetrated with wedge-shaped form throw the colon and intestinal walls. The mucosal membrane between ulcers wasn't changed. In 37 cases were noted necrotic regions, in 4 (2%) – manifested amebomas, which were estimated as tumors before the operation.

The received data are important for endemic regions because for corrective diagnosis in cases of ulceration of esophagus, colon and intestine.
Protein tyrosine phosphatase N2 regulates TNFα-induced signalling and cytokine secretion in T84 intestinal epithelial cells

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Background: We have previously shown that the Crohn’s disease (CD) candidate gene, protein tyrosine phosphatase N2 (PTPN2), regulates interferon gamma (IFNγ)-induced signalling and epithelial barrier function in T84 intestinal epithelial cells (IEC). Studies in fibroblasts showed that PTPN2 regulates tumor necrosis factor alpha (TNFα)-induced mitogen activated protein kinase (MAPK) signalling. The aim of this study was to investigate whether PTPN2 is regulated by TNFα and if PTPN2 controls TNFα-induced signalling and effects in IEC.

Methods: T84 IEC were used for all studies. Protein analysis was performed by Western blotting, mRNA analysis by RT-PCR. PTPN2 knock-down was induced by siRNA and cytokine levels were measured by ELISA.

Results: TNFα treatment (100 ng/ml) elevated PTPN2 mRNA (6 h and 48 h; p < 0.05; n = 4) as well as nuclear (24 h; p < 0.001; n = 4) and cytoplasmic (72 h; p < 0.001; n = 4) protein levels. Immunofluorescence studies further indicated that TNFα causes cytoplasmic accumulation of PTPN2 by 72 h treatment. Inhibition of nuclear factor κB (NFκB) by the pharmacological inhibitor, BMS-345541 (p < 0.001; n = 3), completely prevented the TNFα-induced rise in PTPN2 protein (24 h; p < 0.001; n = 3). In contrast, though the MAPK/extracellular signal-regulated protein kinase (ERK) kinase (MEK) inhibitor, U0126, which also inhibits the activator protein-1 (AP-1) transcription factor, blocked TNFα-induced ERK1/2 phosphorylation (p < 0.01; n = 3), it had no effect on PTPN2 protein (n = 3). Knock-down of PTPN2 by siRNA revealed that the phosphatase downregulates TNFα-induced ERK1/2 (24 h; p < 0.01; n = 3) and p38 (24 h; p < 0.05; n = 3) activity, without affecting c-Jun N-terminal kinase (JNK; n = 3), inhibitor of κB (IκB; n = 3), or NFκB (n = 3) activity. On a functional level, loss of PTPN2 potentiated TNFα-induced secretion of interleukin (IL)-6 (p < 0.01; n = 5) and IL-8 (p < 0.001; n = 3) after 24 h. In TNFα (100 ng/ml; 24 h) and IFNγ (1000 U/ml; 24 h) co-treated cells, loss of PTPN2 enhanced the expression of inducible nitric oxide synthase (iNOS) (p < 0.05; n = 3), and apoptosis as assessed by the amount of cleaved caspase-3 (p < 0.05; n = 3) and the number of fragmented nuclei in DAPI-stained cells.

Conclusions: Our data demonstrate that TNFα induces PTPN2 expression in T84 IEC via NFκB. Loss of PTPN2 promotes TNFα-induced MAPK signalling and expression of inflammatory mediators. We show that PTPN2 plays a key role in the regulation of TNFα-induced pro-inflammatory events in IEC, and thus PTPN2 activity may play an important role in the establishment of chronic inflammatory conditions in the intestine, such as CD.

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BRA101, a novel small molecule with profound efficacy in murine DSS-colitis

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Introduction: While recent advances in the treatment of inflammatory bowel disease have commonly revolved around monoclonal antibody therapies there has been little progress in developing effective small molecules despite their inherent advantages. We report for the first time, preliminary results of experiments on a novel heterocyclic compound, BRA101 with a M.W. of 337, in the dextran sulfate sodium (DSS) colitis model.

Methods: Acute colitis was induced with 5% DSS, administered in drinking water, in BALB/C mice over a period of 8 days. A disease activity index (DAI) was calculated for individual mice each day based on weight loss, occult blood and stool consistency as described previously [1]. Histological damage was assessed by an arbitrary scoring system [2]. Colon myeloperoxidase (MPO) was determined as described elsewhere [3]. Cytokines in colon supernatants were analysed by ELISA. Levels of cytokines and MPO are expressed relative to colon protein. Values are expressed as a mean ± SEM, n = 8 and significance is taken at p < 0.05 using 1 way ANOVA and Dunnett Multiple Comparison Test.

Results: DSS, at 5%, caused significant colitis in BALB/C mice; by day 8 the DSS mice had lost up to 10% of their body weight and had rectal bleeding: DAI was raised to 7.4 ± 0.75 in the vehicle control group. In contrast, treatment with BRA101 at 10 mg/kg i.p. and administered as a suspension in carboxymethylcellulose reduced the DAI score by more than 60% to 2.86 ± 0.38.

Histologically, non-DSS (only drinking water) colons were scored at 0.14 ± 0.14 and DSS resulted in histological damage with a score of 5.14 ± 0.63. BRA101-treated colons were scored at 0.71 ± 0.28; this value was not significantly different from non-DSS values and represented an 86% reduction. MPO was raised from 6.8 ± 0.37 U/mg colon protein to 10.74 ± 0.37 in DSS-mice administered vehicle only. BRA101 reduced MPO activity to 6.02 ± 0.31; this value was not significantly different from non-DSS mice.

Mean colon length in non-DSS mice was 86.37 ± 2.03 mm and this was reduced to 65.71 ± 2.94 mm by DSS. In contrast, colon length in PH-5-treated mice was 78.57 ± 1.68 mm, representing more than a 2-fold improvement.

DSS induced a significantly elevated level of IL1-β at day 8, while other cytokines tested (IL-2, IL-6, IL-10 and TNF-α) were significantly reduced; BRA101 blocked every change in colon cytokine levels to a substantial degree (see Table). In fact, the values of every cytokine with the exception of IL2, tested in BRA101-treated DSS mice, were not significantly different from non-DSS mice.

In summary, BRA101 is highly effective in preventing 5% DSS murine colitis; the effects were observed in every variable measured, and in many cases, BRA101-treated DSS-mice were indistinguishable from non-DSS mice. BRA101 represents a potential first-in-class therapy for the treatment of inflammatory bowel disease.
Colon cytokines

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Non-DSS</th>
<th>Vehicle-control</th>
<th>BRA101-treated</th>
<th>BRA101-vs-Non-DSS</th>
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</thead>
<tbody>
<tr>
<td>IL1-β</td>
<td>111.70 ± 13.23</td>
<td>225.47 ± 25.05</td>
<td>104.76 ± 7.40</td>
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<tr>
<td>TNF-α</td>
<td>81.92 ± 19.93</td>
<td>5.08 ± 3.38</td>
<td>88.18 ± 40.0</td>
<td>ns</td>
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<tr>
<td>IL6</td>
<td>356.0 ± 16.53</td>
<td>41.60 ± 8.24</td>
<td>376.93 ± 16.53</td>
<td>ns</td>
</tr>
<tr>
<td>IL10</td>
<td>181.43 ± 49.38</td>
<td>49.20 ± 68.52</td>
<td>226.91 ± 36.73</td>
<td>ns</td>
</tr>
<tr>
<td>IL2</td>
<td>34.91 ± 1.68</td>
<td>5.98 ± 1.548</td>
<td>26.81 ± 2.67</td>
<td>p &lt; 0.05</td>
</tr>
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</table>

Discussion/Conclusion: In summary, BRA101 is highly effective in preventing 5% DSS murine colitis; the effects were observed in every variable measured, and in many cases, BRA101-treated DSS-mice were indistinguishable from non-DSS mice. BRA101 represents a potential first-in-class therapy for the treatment of inflammatory bowel disease.

References:

Morphological diagnostic features of inflammatory bowel diseases in children

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**Introduction:** Over the last years there an increased rate of inflammatory bowel disease (IBD) in children and teenagers was reported in many countries including Russia. Colonoscopy with biopsy is an important diagnostic procedure for establishing the correct diagnosis. Therefore pathologists must approach diagnostic statements carefully.

**Methods:** We have studied the morphological features of colon biopsies from 22 patients for whom a diagnosis of IBD has been proposed on the basis of clinical, laboratory and instrumental data. The material has been reviewed without the information of the proposed diagnosis and previous treatment.

**Results:** Diagnosis of IBD was confirmed in 11 cases (5 ulcerative colitis [UC], including one case with atypical presentation without rectal involvement; 2 cases of Crohn’s disease (CD) and 4 cases in which morphological changes were not obvious and therefore classified in a group of IBD unclassified (previously called indeterminate). All children in this group were more than 10 years old (middle age of 13.1 years). In one patient, a boy of 3 years old, the diagnosis of pseudomembranous colitis has been established. Morphological signs of minimal colitis, not diagnostic for IBD, were found in 4 patients and regarded as residual changes of colitis of unknown etiology. Absence of inflammatory changes but with presence of prominent follicular hyperplasia and marked edema of the mucosa have been found in 4 patients. Morphological changes within normal limits were observed in 2 patients.

**Discussion/Conclusion:** The morphological diagnosis of IBD in children implies knowledge of the age of the patient and a detailed clinical situation (duration of disease, medication). Furthermore, information on the immune status of the patient, and also on previous therapy is extremely important. It could be difficult to establish a definite diagnosis since treatment can restore the morphological picture completely.
Clinical pattern in the ulcerative colitis patients with surgery

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Medical treatment, generally with medications taken orally or rectally, is the first therapeutic option for people with ulcerative colitis (UC). However, about 25 to 40\% of patients with UC will eventually require surgery.

The aim of this study is to relate the clinical pattern of history disease and relate the risk factor predictors for surgery.

Patients and methods: A total number of 15 (10.3\%) patients, (13 male, 2 female, median age 43.27 ± 8.83 years) out of 143 patients with UC seen and followed-up for a mean period of 7.98 years, had undergone ileorectal anastomosis 8 patients (53.3\%), 4 patients (26.6\%) total proctocolectomy, one patient (6.7\%) with permanent ileostomy, ileo pouch anastomosis 2 patients (13.4\%), mainly for bad response to conservative treatment 60\%, toxic megacolon 14\%, large bowel cancer 13\%, perforation 13\%, stenosis 6\%.

Results: A number of statistically highly significant differences between the operated and non-operated group of patients were noticed. The patients operated on had more extensive and severe diseases in comparison with non-operated ones and were younger at the time of diagnosis. 75\% patients operated had extraintestinal manifestation, 45\% patients with family history disease and 63\% patients had positive pANCA test. For all patients the medical treatment included also immunomodulator drugs. Post operator the quality of life improved for all the patients expected on patient who needed more surgery for complications occur post operator. Mortality range in the patient group is zero.

Conclusion: Although the frequency at the UC patients who needed surgery is low it is concluded that the clinical pattern of the patients operated with UC have similarities from other countries of the world taking into consideration the fact that in this area the frequency of UC is low.

Key words: ulcerative colitis, surgery, and clinical pattern
The effect of vitamin D on inflammatory bowel disease-related colon cancer

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Introduction: Inflammatory bowel diseases (IBD) including ulcerative colitis and Crohn's disease increase the risk of colon cancer development. Since screening for colorectal cancer in IBD patients and treatment of such cases have logistic and financial limitations, primary prevention strategies are sought. Vitamin D is known to inhibit development of sporadic adenomas and colorectal cancer through regulating cell proliferation and differentiation. In this current study we evaluated the effect of vitamin D on IBD related colon cancer.

Materials and methods: Five weeks old 16 mice were included in this study. Mice were given a first i.p. injection of azoxymethane (AOM: 10 mg/kg) on day 0. Seven days after the AOM injection, the mice were given 3% dextran sulfate sodium in the drinking water for 3 cycles (every cycle: 3 weeks). Starting from the first day mice were divided into two groups; first group received vitamin D (10 IU/mg, three times a week) and second group received placebo throughout the study. At the end of the study mice were sacrificed and colons were dissected for histopathological and immunohistochemical examinations.

Results: During the study period, group who received placebo seemed to be more sick and they gained less weight when compared to the group who received vitamin D. In placebo group, 50% of the animals developed any grade of dysplasia (low/high) in their colon. On the other hand, in animals treated with vitamin D, no dysplasia was observed during histopathological examination.

Discussion: Vitamin D treatment seems to prevent development of colitis associated colorectal neoplasia. The underlying mechanism of this protective effect should be further elucidated.
Endoscopical method for stopping rectorrhagia in ulcerative colitis and advancer rectal cancers

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Introduction: In the last 30 years colorectal cancer frequency increased from 7% to 33%.
The purpose of our study is to improve the patients with rectorrhagia in ulcerative colitis and advancer rectal cancer.

Methods: For ten years' periods we have diagnosed 200 colorectal cancers and 220 ulcerative colitis. All patients were endoscopicaly and double-contrast enemas examined and histological confirmed. We treated our patients with Tissucol-two-component fibrin sealent.
75% of patients with application of Tissucol-Kit were with ulcerative colitis and 25% with lower inoperative cancer.

Results: In 75% of patients treated with Tissucol-Kit were found clearly Tiseel clot, after first application and stopping the bleeding, but in 20% the same effects were found after the second application-on, 5%-effect after more application. All patients were examined endoscopicaly and clinically after treatment. In endoscopical examination we found the typical milky white, clearly visible Tisseel clot cover the rectal ulceration and cancers’ surface. Blood in stool was disappeared.

Discussion/Conclusion:

1. Tissucol's applications are effective in 75% of patients with ulcerative colitis and rectal cancers for stopping haemorrhage.

2. This method improve anaemic syndrom in patients with rectorrhagia.

3. Tissucol-Kit is suitable in cases with rectorrhagia.
Pyloric metaplasia in ileal pouches in Crohn’s disease

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Background: Although colonic resection with ileoanal pouch anastomosis is not the treatment of choice for Crohn’s disease and is generally avoided if possible, it may be chosen in selected cases. Histopathologic findings in these pouches in Crohn’s patients have not been documented in detail. Epithelial transformation into colonic-type mucosa with or without metaplasia is of interest in the understanding of the pathophysiology of pouchitis, recurrence of Crohn’s disease and the dysplasia-carcinoma cascade.

Methods: We searched the database of the Department of Pathology at the University of North Carolina at Chapel Hill for cases of ileal pouches in Crohn’s disease with biopsy specimens in a twenty year time frame from 1989–2009. Slide review revealed pyloric metaplasia in three cases.

Results: Pyloric metaplasia was identified in a minority of ileal pouch biopsies in patients with Crohn’s disease. There were two women and one man ranging in age from 21–47 years who had undergone ileal pouch anastomosis 3–12 months prior. No concomitant or subsequent dysplasia or carcinoma was identified (mean follow-up of 61 months). There was mild to moderate chronic inflammation and villous blunting without significant active inflammation or granulomata in all cases.

Conclusions: Pyloric metaplasia occurs in some ileal pouches in Crohn’s disease even without active pouchitis, but it does not appear to indicate an increased risk of development of dysplasia or carcinoma in the pouch. Whether pyloric metaplasia is a hitherto less appreciated feature of the postulated ileal to colonic epithelial transformation that may occur in pouches warrants additional investigation.
Fc fragment of infliximab modulates its inhibitory activity in fibroblasts and monocytes via interaction with Fc receptors

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Background and aims: One of the most important cytokines in the pathogenesis of inflammatory bowel disease (IBD) is tumor necrosis factor alpha (TNFα) – which stimulates inflammatory reactions in various cell types. Recently, antibodies targeted against this cytokine, namely infliximab, adalimumab, and certolizumab pegol have been successfully implemented in IBD therapy. The aim of this project was to evaluate the efficiency of these drugs in blocking the TNFα-mediating pro-inflammatory responses in different cell types of the intestinal wall.

Methods: As a model system we used cultures of intestinal epithelial (Caco-2/BBE), intestinal myofibroblastic (CCD-18Co), and monocytic/macrophagic (THP-1) cell lines. To stimulate the pro-inflammatory signaling pathways TNFα, IFNγ and IL-1β were used. Specificity of signal transduction and transcription factor activation was investigated by Western Blot and EMSA. mRNA expression levels were quantified by RT-PCR. Interaction of therapeutic antibodies with cells was studied by fluorescent microscopy. The contribution of Fc fragments of the therapeutic antibodies in the inhibitory activity was assessed by combinatory approach of proteolytic digestion and immunoprecipitation followed by RT-PCR and Agilent protein chips analysis.

Results: TNF stimulation induced phosphorylation of STAT1, p38 MAPK and activation of NFκB. TNFα increased mRNA expression of pro-inflammatory cytokines such as TNFα and IL-8 in all cell lines tested. All three drugs prevented TNFα-specific responses in intestinal epithelial cells. However, infliximab had a limited inhibitory capacity in fibroblasts and monocytes, most likely due to the interaction with Fc receptor(s), which are abundantly expressed on the surface of both cell types. Fluorescently labeled infliximab, but not adalimumab, accumulated at the surface of fibroblasts. Blocking Fc fragments and isolation of Fab fragments of infliximab restored partially its inhibitory capacity in fibroblasts.

Conclusions: Anti-TNFα drugs effectively prevent TNFα-mediated pro-inflammatory responses in intestinal epithelial cells. Infliximab has limited inhibitory capacity in fibroblasts and monocytes, most likely due to the interaction with Fc receptor(s) expressed on the surface of these cell types. This mechanism may modulate the bioavailability and effectiveness of anti-TNF antibodies when administrated in IBD patients.
Prevalence and associated factors in hepatitis B and C virus infection in patients with inflammatory bowel disease

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Introduction: Hepatitis B and C are the main causes of chronic hepatitis, cirrhosis and hepatocellular carcinoma. Patients with inflammatory bowel disease (IBD) are at higher risk of hepatitis C (HCV) and B virus (HBV) infection, because of surgical and/or endoscopic procedures and blood transfusions. The aims of this study were to investigate the prevalence of HCV and HBV, and to determine associated risk factors in a population of patients with inflammatory bowel disease.

Methods: This comparative study was an attempt to evaluate the presence of HBV and HCV infection in patients with IBD. 286 IBD patients, 202 with ulcerative colitis (UC), and 84 with Crohn’s disease (CD) were tested for the presence of antibodies to HCV and antibodies and antigens to HBV. Also included was a control group consisting 170 healthy individuals. The number of blood transfusions, surgical and endoscopic procedures was also noted.

Results: A total of 286 IBD patients were included. There were 202 (70%) CD patients and 86 (30%) UC patients. There was no significant difference between baseline characteristics of the patients (n = 268, 128 women; mean age: 41.3 years) compared to control group (n = 170, 74 women; mean age: 45.8 years). Nine IBD patients was found to be positive for HBsAg (3.1%), none of them was positive for HBV DNA. 100 (34.9%) patients were positive for anti-HBs antibody. Anti-HBc was evaluated only in 129 patients. Among the 129 patients, 29 patients (22.4%) had positive for anti-HBc. Only one patient was positive for anti-HCV (0.03%). Four (2.2%) out of 170 healthy subjects were positive for HBsAg. Other serologic markers for the control group were as follows: anti-HBs: 52 (30.5%), antiHBc: 32 (18.8%), anti-HCV: 1 (0.05%). Nor the patients neither the control group were positive for anti-HIV.

Discussion/Conclusion: The seroprevalences of HBsAg and anti-HCV in IBD patients was not high from control group and the overall population. It was observed that sex, endoscopic procedures, surgery, dialysis and blood transfusions were not considered probable risk factors in HBV and HCV infection in patients with IBD.
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